

**Prevention and Management
of Tuberculosis in HIV infected Patients
in Hong Kong**

- an information paper

Scientific Committee of the Advisory Council on AIDS

Hong Kong

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Prevention and Management of Tuberculosis in HIV infected patients in Hong Kong is an information paper prepared by the Scientific Committee on AIDS, one of the three committees of the Governor-appointed Advisory Council on AIDS. The paper summarises the current understanding of the problem of tuberculosis as it relates to HIV infection in the local setting. No specific guidelines have been formulated yet because of the scarcity of relevant information in the subject. Health care workers are advised to take note of the information and analysis contained herein. The situation will be kept under review by the Committee, taking into consideration local as well as international development in AIDS and tuberculosis research.

Scientific Committee on AIDS
April 1995

Scientific Committee on AIDS 1994/95

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1. Introduction

In Hong Kong, the incidence of tuberculosis (TB) is high with a yearly notification rate of about 110 per 100,000 population. HIV infection, on the other hand, is relatively uncommon, but WHO has predicted that Asia will be the next focus of the epidemic. Locally, about 10% of all reported AIDS cases presented with tuberculosis as the primary AIDS-defining illness. Infection with *Mycobacterium tuberculosis* and HIV would soon become an important health issue because:-

- HIV is one potential factor for promoting development of clinical tuberculosis. Worldwide, the estimated annual risk of TB in patients with HIV is 5-8%, while the life time risk can be as high as 50% or more.
- Tuberculosis may result in immune activation, thereby leading to a more rapid progression to AIDS.
- Clinical presentation of TB in HIV-infected persons is usually atypical, particularly in the advanced stages.
- TB often presents earlier than other HIV-related opportunistic infections.
- Outbreaks of multi-drug resistant tuberculosis have been reported from HIV-infected patients due to nosocomial transmission.

In spite of the potential threat posed by TB/HIV, tuberculosis is largely preventable and is amenable to treatment. Early recognition, prompt treatment and assurance of compliance are the crucial steps for controlling the disease(s) in Hong Kong.

2. Recognition of TB in HIV-infected Patients

Diagnosis is based on (a) clinical features, (b) radiological findings and (c) bacteriological & histological examinations. The role of tuberculin skin test is also discussed.

2.1 Clinical Features

Clinical manifestations of TB occurring in HIV-infected patients vary considerably according to the degree of immunosuppression. The earlier TB occurs (when cell-mediated

Immunity is relatively preserved) the more usual its clinical presentation. The later it develops, the more atypical are its features e.g. extrapulmonary TB with frequent involvement of lymphatic organs or dissemination, as well as such involvement in the central nervous system, bone, pericardium, gastrointestinal tract, bone marrow etc.

Because of the likely atypical presentation, diagnosis requires a high index of suspicion and an aggressive diagnostic approach. Even if pulmonary TB is diagnosed, there is a need to look out for possible co-existence of extrapulmonary TB. On the other hand, atypical clinical presentation of TB should certainly alert clinicians to look for the presence of an underlying HIV infection.

2.2 Radiological Findings

Chest radiograph can be normal while sputum is positive for acid-fast bacilli (AFB), which suggests endobronchial involvement. A patient may appear relatively well for the degree of abnormality seen on X-ray.

Atypical findings can occur, particularly in the advanced stage of HIV infection:

- Lower lung zone/diffuse or miliary shadowing (rather than the usual upper lobe involvement);
- Intrathoracic adenopathy;
- Pleural effusion (can be more common);
- Cavitation which occurs unusually.

2.3 Tuberculin Skin Testing

The Mantoux Technique is generally recommended. In Hong Kong, all the tuberculin supplied by the government is PPD-RT23, and 1 unit of PPD-RT23 is used routinely for tuberculin testing. Because of the high prevalence of TB in the community and that BCG is almost universally administered to newborns, the result of a Mantoux should always be interpreted with caution. Its limitation is acknowledged if used as a diagnostic tool, especially when therapeutic consideration is involved.

(a) *Negative Results*

Tuberculin skin testing commonly shows little or no reaction in persons with advanced HIV infection. In general, anergy occurs in less than 10% of individuals with CD4 cell count >500/ul, but in about 80% with CD4 <50/ul. It may therefore be considered as an investigative tool for anergy instead of tuberculous infection. To determine if a negative result is caused by immunosuppression or is truly negative, other recall antigens

may need to be applied: such as Candida, tetanus toxoid to which most persons with intact cell-mediated immunity will respond (multi-test is commercially available). Thus,

- a negative tuberculin test in the presence of positive reactions to one or more of the other recall antigens: true negative.
- a negative tuberculin test and no reactions to other antigen: may or may not be truly negative.

(b) Positive Results

In Hong Kong, the use of 10mm as the cutting point is more appropriate to be indicative of TB infection (In low prevalence countries like USA, a reaction of >5mm induration to 5 units of PPD-S which is equivalent to 2 units of PPD-RT23, is often regarded as indicative of TB infection). When the response is between 5 and 10mm, other clinical factors e.g. household contact with a TB patient, have to be taken into consideration. Two-step tuberculin test may be required.

2.4 Bacteriological & Histological Examination

Bacteriological investigation remains the primary approach in making a definitive diagnosis of mycobacterial infection. Development of new technology should, therefore, be prioritized in hastening the diagnostic procedure and in improving its accuracy.

(a) TB Smear & Culture

Most reported series indicate that the frequency of positive sputum smears & culture in patients with pulmonary TB is the same irrespective of a person's HIV status. In some instances, sputum induction (e.g. by aerosolized hypertonic saline) or bronchoscopic procedures are required to facilitate the diagnosis of pulmonary TB.

Specimens from other sites of clinical abnormality in patients with or suspected of having HIV infection should be examined for Mycobacterium tuberculosis by smear & culture. For cases presenting with PUO or other unexplained systemic symptoms, there is the need to search for mycobacteria in blood, urine, stool bone marrow and biopsy tissues (e.g. liver). In some cases culture is positive in the absence of evidence on AFB smear. In the presence of pulmonary TB, co-existing extra-pulmonary TB should also be excluded. Finally, the presence of AFB smear on stool examination is usually more indicative of pulmonary TB (with organisms in swallowed sputum) than gastrointestinal TB.

(b) *Newer Techniques*

Standard techniques for detection of growth & speciation of mycobacteria requires 6-10 weeks.

The use of newer techniques, especially in combination, can provide faster results. The bactec radiometric culture technique, which has become more readily available worldwide, can speed up both the process of detection and the drug sensitivity test. Other useful new techniques which are not widely available include the use of nucleic acid probes and polymerase chain reaction (PCR).

(c) *Histopathology*

A high index of suspicion for mycobacterial disease is necessary when handling specimens from HIV-infected individuals. Other points of relevance are:-

- Classic granulomas are not produced in advanced HIV infection.
- Co-infection with non-mycobacterial pathogens may occur.
- Granuloma, if present, is more indicative of TB than non-TB mycobacterial diseases.
- Other organisms (including pneumocystis carinii) may also cause granuloma formation.

3. Treatment

Despite their immunosuppressed state, patients with TB and HIV infection usually have a good response to anti-TB treatment. In a patient with proven or suspected HIV infection, therapy should be started empirically if TB is a likely diagnosis, even before bacteriological confirmation is available. Whenever positive AFB smear is found, treatment should be promptly initiated, and it can be subsequently changed or discontinued if the culture reveals presence of non-TB mycobacteria.

3.1 Current Recommendation

In adults with HIV infection, treatment for pulmonary TB should include the following drugs in the initial 2 months:

- Isoniazid 300mg/day
- Rifampicin 600mg/day (450mg/day if body weight <50kg)
- Pyrazinamide 2g/day (1.5g/day if body weight <50Kg)
- Ethambutol 25mg/kg/day

Treatment with isoniazid and rifampicin should then be continued for a total of 9 months, or for 6 months after documented culture conversion, whichever is longer.

Treatment with the same regimen (same 4 drugs followed by same 2 drugs) but with the drugs given thrice weekly is very useful in HIV-non infected persons, and it is probably also effective in the HIV-infected individuals. It is more suitable for full supervision. Dosages are:

- Isoniazid 15mg/kg/day
- Rifampicin 600mg/day (same of those above & below 50kg body weight)
- Pyrazinamide 2.5g/day (2g/day if body weight <50Kg)
- Ethambutol 25mg/kg/day

Streptomycin has not been included in the regimens as the drug requires regular intramuscular injection, and may thus affect a patient's acceptance. If used, infection control measures should be strictly observed.

If either isoniazid or rifampicin is not included in the treatment regimen because of resistance or intolerance, therapy should be continued with rifampicin and ethambutol for a total of 18 months (if isoniazid cannot be used) or with isoniazid and ethambutol for a total of 18 to 24 months (if rifampicin cannot be used). Both drug regimens should include pyrazinamide for at least the first 2 months and should be continued for 12 months after culture conversion. Some authorities would extend the use of pyrazinamide from the first 2 months to the full 18 to 24 months when drug regimens are used that do not include both isoniazid and rifampicin. The dosage of ethambutol has to be reduced from 25mg/kg to 15mg/kg after the first 2 months of therapy. However, the efficacy and toxicity of these recommended 18 to 24 months drug regimens (without isoniazid or rifampicin) are unknown in the setting of immunosuppression arising from HIV infection. The optimal duration of treatment to prevent relapse after anti-TB drugs are stopped is unclear.

For paediatric patients, the use of regimen similar to that for adults is recommended except that ethambutol is not generally prescribed because symptomatic visual symptoms cannot be reported accurately. A total of three (isoniazid, rifampicin and pyrazinamide) or four drugs (plus streptomycin) may be considered in the initial two months, followed by two (isoniazid and rifampicin) for a total duration of at least 9 months: :

	<i>Daily doses</i>	<i>Thrice weekly doses</i>
Isoniazid	5 mg/Kg (max 300mg)	15 mg/Kg/day (max 300mg)
Rifampicin	10 mg/Kg (max 450mg)	15 mg/Kg/day (max 600mg)
Pyrazinamide	35 mg.kg (max 1.5g)	50 mg/Kg/day (max 2g)
Streptomycin	15-20 mg/Kg (max 0.75g)	20 mg/Kg/day (max 1g)

Extrapulmonary TB may coexist. If TB meningitis, miliary TB and TB involving bone and joint is present, four drugs should be used initially for two months, and the total duration of two drugs (isoniazid and rifampicin) should be at least 12 months – similar for both children and adults.

3.2 Monitoring

(a) *Response to Therapy*

The response to therapy should be monitored with:

- clinical evaluation, including the possible emergence of drug interaction
- bacteriological examination of sputum (for pulmonary TB) – pre-treatment and then monthly till culture conversion, then three-monthly till end of treatment
- radiographic examination

Drug susceptibility tests should be done routinely and treatment regimen revised, if resistance to any of the drugs used is found.

(b) *Ensuring Compliance*

Compliance is an important problem which can easily affect treatment outcome. Directly observed therapy (DOT) or fully supervised therapy is strongly recommended. This can be done on an outpatient basis by designated health personnel. For those who cannot attend clinics frequently, DOT may have to be provided through the patient's caring relatives, friends, community nurses or other helpers in the community.

After completion of treatment, frequent (say thrice to six-monthly) follow up for life is required, with mycobacterial examination repeated if necessary.

(C) Adverse Reactions to Anti-TB Drugs

Usually the drugs are reasonably well-tolerated. However, the incidence of adverse reactions is higher among immunocompromised patients. These reactions may sometimes be difficult to be recognized as they may be simulated by:-

- TB itself
- Multiple & recurrent non-TB infection
- Effects due to concurrent use of other drugs

Specifically, concurrent therapy with zidovudine and anti-TB medications is usually well tolerated. The anti-fungal agents ketoconazole & fluconazole both have interaction with isoniazid and rifampicin, resulting in reduced serum concentration of the anti-fungal agents, making anti-fungal treatment ineffective. In addition, ketoconazole tends to interfere with absorption of rifampicin and may cause treatment failure.

3.3 Secondary Prophylaxis

Life-long secondary prophylaxis with isoniazid has been given by some groups after completion of treatment. Its usefulness as a routine recommendation remains to be established.

4. Multi-drug Resistant TB (MDR-TB)

4.1 Epidemiology

Multiple drug resistant tuberculosis (MRD-TB) is particularly important when organisms show resistance to isoniazid and rifampicin with or without other drugs. MDR-TB has occurred in HIV infected person in Hong Kong but its prevalence is not exactly known. Outbreaks of MDR-TB have been reported overseas due to nosocomial transmission. Many victims are HIV-infected patients, and health-care workers, both HIV-seropositive and negative, have been infected. The nosocomial transmission has been documented with substantial epidemiological and laboratory (Restriction fragment length polymorphism, RFLP analysis) data.

MDR-TB is associated with a high fatality rate, ranging from 72% to 89% in certain reported series, within a period ranging from 4 to 16 weeks.

Suggested reasons for the increasing prevalence of MDR-TB:

- Insufficient attention and resources devoted to TB control.
- Poor compliance of treatment.
- Inappropriate management of TB.
- Rapid progression of TB in the HIV-infected persons leading to rapid transmission of infection.
- Lack of effective means of control of airborne infections in the health-care facilities.

4.2 Prevention of MDR-TB

The key factor to prevent emergence of MDR-TB is to ensure full compliance with anti-TB treatment. Directly observed therapy (DOT) or fully supervised therapy is an effective measure. Management of patients by physicians experienced in the field is recommended.

4.3 Treatment of MDR-TB

The principle of treatment of MDR-TB is to treat with a combination of previously unused or sensitive drugs, and better results are achieved if 3 to 4 such drugs are available and they are bactericidal. The result will be poor if only 1 or 2 such drugs could be used. The duration of treatment should be 12 to 18 months.

When MDR-TB is suspected during anti-TB Treatment (e.g. with deteriorating clinical condition and/ or radiograph), at least 2 additional bactericidal drugs should be added to the existing regimen (when sensitivity results are still pending).

When the sensitivity results are known, the regimen may need to be modified. At least 2 agents should be used to which the organisms are susceptible. Newer agents such as the fluoroquinolones (ofloxacin, ciprofloxacin), rifabutin, amoxicillin/ clavulanic acid and macrolide compounds are found to have anti-mycobacterial property and can be used in the treatment of MDR-TB in addition to para-aminosalicylic acid, ethionamide, cycloserine, and capreomycin.

In Hong Kong the recent level of initial resistance to isoniazid alone is about 6%, rifampicin alone is about 1%, and isoniazid and rifampicin together is less than 1%. The level of secondary resistance to these drugs is much higher. MDR-TB should be prevented by all means. For previously untreated TB cases, the recommended 4 drug regimen should be very effective.

5. Prevention of TB in HIV-infected Patients

5.1 Chemoprophylaxis

The risk of tuberculosis increases in the presence of immunodeficiency caused by an underlying HIV infection. There exists, therefore, the theoretical advantage of preventing TB from occurring in an HIV infected person by the use of prophylactic drug(s). Some studies conducted overseas have provided data on the protective effect of Isoniazid monotherapy given to HIV infected persons who had positive tuberculin tests. The extrapolation of such data for Hong Kong is doubtful in view of (i) the endemicity of TB locally; and (ii) the difficulty encountered in interpreting the tuberculin tests, given that BCG has been universally administered to babies born in Hong Kong.

Chemoprophylaxis is not recommended for routine use on HIV infected persons in Hong Kong. If given, adequate monitoring is necessary. Clinical studies on the effectiveness of chemoprophylaxis should be encouraged to generate useful data for local use.

(a) Overseas Experiences

In areas with low annual rate of TB, daily isoniazid for 6-12 months decreases the risk of TB in tuberculin positive and HIV non-infected persons at risk of TB. Available information suggests that isoniazid preventive therapy is also effective in preventing TB in HIV-infected individuals. Such therapy may theoretically prolong the survival of HIV-infected patients as TB may hasten progression of HIV diseases. At present, however, there is insufficient evidence to recommend TB preventive therapy for HIV+ people in regular programme settings world-wide.

(b) Some suggested Indications for Isoniazid Chemoprophylaxis

Isoniazid chemoprophylaxis therapy may be considered for HIV positive people:-

- (i) Who are anergic but has a CD4 count below 200/ul with:
 - history of contact with TB
 - history of previous TB
 - radiograph evidence of previous TB
- (ii) Who have been exposed to persons with infectious TB, regardless of results of tuberculin tests

There have been recommendations on the provision of chemoprophylaxis for HIV positive people whose tuberculin test is positive at >10mm. The use of atuberculin test result as the sole criterion for prescribing chemoprophylactic agent should be treated with caution. Under all circumstances, it is crucial to exclude those with active TB who require standard treatment instead. In particular. Old TB scars in chest radiograph should not be confused with active TB lesions. Compliance is another factor which needs to be considered and close monitoring is required. It would be more appropriate and effective that chemoprophylaxis is decided by experienced physicians in the field.

(c) Protocols established overseas

Data is available on the use of isoniazid monotherapy only. Isoniazid is given at 5mg/kg daily up to a maximum of 300mg/day for (6 to)12 months, providing that infection with isoniazid resistant organisms is unlikely. The medication may be given twice weekly at 15mg/kg for those requiing supervision. Otherwise, prescription can be issued at monthly intervals whereas the patient is assessed for compliance, drug toxicity, possible drug interaction and signs of active TB. If, in any case, treatment is interrupted, it should be restarted to provide at least 6 months of preventive therapy during a one-year period. The role of life-long or extended preventive therapy has yet to be established. Another acceptable chemoprophylactic regimen consists of 4 months of isoniazid plus rifampicin. The efficacy of these chemoprophylactic regimens in the Hong Kong setting is unknown. However, in view of the significant level of initial drug resistance in the territory, combination drug regimens for chemoprophylaxis may be more relevant, especially when the sensitivity pattern of the case is unknown. (ref: MMWR 1994, vol 43 no. RR-13)

Isoniazid-induced hepatotoxicity is the most important adverse reaction, occurring in up to 2% of persons over age 50 receiving the drug. Patients should be carefully educated about the signs and symptoms of hepatitis and instructed to discontinue the drug promptly should these occur. Isoniazid is contraindicated in patients with chronic active hepatitis and should be given with caution to persons with alcohol abuse. Some authorities have reoomended alternative preventive therapy in special situations. However, their efficacy has not yet been shown.

If chemoprophylaxis is not given, close monitoring for TB (e.g., 3-monthly clinical assessment and chest radiograph) should be undertaken for those believed to be at risk.

5.2 BCG Vaccination

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(a) *Newborns*

Currently, BCG is administered to all newborns in Hong Kong. For babies born to HIV-infected mothers, there is the practical difficulty of diagnosing HIV infection at birth as the baby may be seropositive because of circulating maternal antibody, instead of actually harbouring the virus. In the Hong Kong, as has been advocated by World Health Organization, BCG vaccination should be given at birth (or as soon as possible thereafter) to asymptomatic HIV-infected infants, including those born to HIV+ mothers.

(b) **Other Situations**

For HIV-infected children/adults who are symptomatic, BCG should NOT be given because of:

- the risk of disseminated BCG infection.
- The propensity for speeding up progression of HIV disease due to T cell activation.

6. Infection Control in Health Care Settings

TB outbreaks can occur in health-care settings – among HIV-infected patients, health care workers, and other patients in clinics (including AIDS clinics) and wards. Health care workers should be reminded of the importance of infection control to avoid cross infection from occurring. Three basic approaches are considered in the prevention of the transmission of tuberculosis in health-care settings:-

6.1 Control of Source of TB

This can be achieved by :

- Early identification (e.g. regular chest X-Ray for HIV positive people at half-yearly or yearly intervals may be considered) and treatment of persons with active tuberculosis, with particular attention to compliance with treatment.
- Notification of tuberculosis, so that contact tracing can be done.
- Promoting personal hygiene of patients with active pulmonary tuberculosis, e.g., covering mouth during coughing and forbidding spitting.

6.2 Control of Environment

The objectives are to prevent the spread of infectious droplet nuclei into the general air circulation and to reduce the number of infectious droplet nuclei in the air. These are achieved by:-

- Isolation of infectious TB patients (irrespective of HIV status)
- Adequate ventilation developed and maintained in consultation with engineering experts: rooms with negative pressure, > 6 air exchanges/hour, non-recirculated ventilation vented to outside are recommended. This is important especially during cough-inducing procedures and sputum induction. In the case of suspected tuberculosis, aerosolized pentamidine therapy should only be considered as the last resort for prophylaxis against pneumocystis pneumonia.
- Adherence to infection control guidelines for cleaning, decontamination of equipment, disinfection and sterilization.

6.3 Protection of the Host

This can be achieved by:

- conducting surveillance on tuberculosis occurring in the health care setting;
- the use of disposable particulate respirators;
- providing chemoprophylaxis as appropriate.

7. Conclusion

The HIV epidemic is of great concern to the whole population. It is of great importance that preventive measures for the spread of HIV infection be carried out effectively. The prevention of HIV-related TB depends on the ability to control TB as much as HIV infection. Collaboration of Hong Kong's TB and HIV control programmes is therefore vital. For public health surveillance, TB notification can be made to the Department of Health through the format established by the Scientific Working Groups on AIDS (Department of Health temporary circular no. 64/92), while preserving the confidentiality of patients reported.

The basic components of public health control for TB are, in conclusion, (a) case finding, (b) effective chemotherapy, (c) chemoprophylaxis and (d) BCG vaccination. In the development of an effective HIV/TB management programme, the following should be emphasized:-

- (a) Suspected TB cases should be evaluated promptly and then given treatment without delay. It is of utmost importance to ensure compliance with therapy for the best outcome.

- (b) Newer techniques should be available for rapid identification; speciation and drug susceptibility testing of AFB in Hong Kong. Technological development in this regard should be closely monitored.

- (c) For better mobilization of resources and for forward planning in combating the potential increase in TB due to HIV infection, there is the need to monitor the prevalence/incidence of TB, HIV, and co-infection with the 2 pathogens. Guidelines on the prevention and management of TB should be reviewed periodically.