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12. Preventive Therapy for Tuberculosis in HIV Infected Individuals

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The HIV pandemic has had a major impact on the epidemiological dynamics of tuberculosis. In countries with a severe HIV epidemic, there has been a dramatic rise in the notification rates for tuberculosis (TB). The results of various studies[1,2,3] have documented that persons co infected with *Mycobacterium tuberculosis* and HIV have a 5.8% annual risk and a 30% or greater life time risk of developing active TB, The mechanisms include reactivation of latent infection; rapid progression of primary infection[3] or reinfection with *Mycobacterium tubercuiosis*[4].

UNAIDS estimates that of the global total of 37.8 million people living with HIV at the end of 2003,70.1% are in sub-Saharan Africa and 16.1% are in South East Asia[5]. About a third of the people living with HIV worldwide are co infected with *Mycobacterium tuberculois*[6]. Since 68% of those co infected live in Sub Saharan Africa, this region caries the overwhelming burden of global epidemic of HIV associated tuberculosis. In sub Saharan Africa 20 to 67% of patients with pulmonary tuberculosis have been reported to be HIV seropositive[7] However, with 22% of those co infected living in this region, South East Asia also bears a considerable burden of HIV associated TB. In other regions with a high number of AIDS cases. an increased HIV prevalence rate has been noted among TB patients[8,9,10].

HIV is the major cause of the large increase over the last decade in the incidence of tuberculosis in populations with a high prevalence of HIV infection. In South India. one of the early observations in 1992 has shown that a significant proportion of AIDS cases detected, had active tuberculosis[11]. The increased risk of developing TB disease among those infected with HIV has prompted a need to reconsider institution of preventive measures to enable HIV seropositive patients to avoid the risk of progression to clinical TB. Four types of intervention are available for TB control, namely, case finding and treatment, preventive therapy use of BCG vaccination and environmental measures[12]. Emphasis in developing countries has been on case finding and treatment and on provision of BCG vaccination to infants. Preventive therapy was not recommended except for breastfeeding infants of mothers with pulmonary tuberculosis or other children under 5 years of age living with infectious persons[13].

Preventive therapy (PT) or chemoprophylaxis against tubercuiosis is the use of one or more anti- tuberculosis drugs (AT) given to persons with latent infection with *Mycobacterium tuberculosis* in order stop or prevent the progression to active disease Prior to the HIV epidemic, its use in countries with a high prevalence of tuberculosis was limited to childhood

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contacts of active cases since these children have a higher risk of progression to disseminated and severe forms of disease. Evaluation of preventive therapy, before the emergence of AIDS, involving over 100,000 participants in a placebo-controlled trial demonstrated a reduction of tuberculosis of 25-92%[14]. Several studies have now demonstrated that preventive therapy is effective in preventing progression of ruberculosis infection in individuals dually infected with HIV and *M.tuberculosis,* although the efficacy is not 100% (ranges from 60-90%). In addition, there is a suggestion that chemoprophylaxis may delay HIV disease progression amongst asymptomatic HIV infected individuals[15].

The increased risk of developing active disease associated with HIV infection has provoked a number of questions, regarding who should receive prophylactic therapy, how long it should be continued. whether isoniazid alone is the most effective agents role of secondary prophylaxis etc. Clinical trials are ongoing in these areas and some data are available,

Table I: Efficacy of Isoniazid preventive therapy; results from three meta analyses

Author	Country	Rate ratio or odds ratio for INH compared to no INH (95% CI)		
		PPD+	PPD-	Total
Wilkinson[23]	Haiti, Kenya	OR 0.46 (0.2 to 1.07)	OR 1.02 (0.49 to 2.13)	OR 0.86 (0.51 to 1.44)
Bucher[17]	Haiti, Mexico, Zambia, USA, Uganda, Kenya	RR 0.41 (0.24 to 0.71)	RR 0.94 (0.52 to 1.38)	RR 0.58 (0.39 to 0.87)
Woldehanna S[18]		RR 0.38 (0.25-0.57)	RR 0.83 . (0.58 to 1.18)	RR 0.64 (0.51 to 0.81)

Ideal candidate for chemoprophylaxis

The risk of developing active tuberculosis in HIV infected persons with positive tuberculin (PPD), skin test reactions may be as high as 7.9% per year, in a study by Selwyn and colleagues[2] in a methadone maintenance programme in NewYork. All of these cases occurred in patients who did not take prophylactic isoniazid and occurred among those with a positive PPD, Swaminathan et al[16] reported an incidence rate of 7.1 per 100 person years in PPD Positive and 6.9 per 100 person years in PPD negative HIV positive individuals in South India. A meta analysis[17] of 7 randomized controlled clinical trials to determine the efficacy of isoniazid (INH) for the prevention of TB in tuberculin skin test positive and negative individuals with HIV infection was carried out which revealed that in groups of tuberculin skin test positive and negative persons, the risk ratio of TB was 0.40 (95% CI, 0.24-0.65) and 0.84 (95% CI. 0.54-1.30), respectively and the difference in the effectiveness of INH versus placebo between these groups was statistically significant (P=0.03); consistency of results was found across

trials for all comparisons. Another meta analysis[18], on the effectiveness of tuberculosis preventive therapy in reducing the risk of active tuberculosis and death in HIV infected persons, analyzed 11 different preventive therapy trials with a total of 8,130 randomized participants. The result of this meta analysis shows that the benefit was more in individuals with a positive tuberculin skin test (RR 0.38, 95% CI 0.25 to 0.57) than in those who had a negative test (RR 0.83.95% CI 0.58 to 1.18). A positive tuberculin skin test is defined as an induration of ≥ 5mm in HIV-1 seropositive persons. These observations have led to the recommendation that all HIV infected patients should undergo tuberculin skin testing and persons with a positive tuberculin skin test be offered preventive therapy with isoniazid (INH), after ruling out active tuberculosis.

A study among injecting drug users in Baltimore, Maryland[19] found that there was a considerable change in the delayed type hypersensitivity (DTH) status over time. particularly among HIV infected persons with lower CD4 cell counts. Some have suggested that establishing the likelihood of *Mycobacterium tuberculosis* infection on grounds other than skin testing is a more useful means for determining who should receive prophylactic therapy[20]. However, at present, there is no surrogate test for *M. tuberculosis* latent infection that is consistently better than the tuberculin skin test. Factors such as community rates of infection and active disease, demographic information, history of exposure and abnormalities on chest radiographs can all be used to identify those HIV infected patients at highest risk. These individuals may be considered for prophylactic therapy regardless of skin test results

The CDC has recommended that preventive therapy for anergic HIV infected persons be considered if the patient has had known contact with an active TB case or belongs to a group in which the prevalence of TB infection is at least 10%[21]. In areas endemic for TB and HIV, PPD or tuberculin test may not be helpful in identifying persons who could benefit from INH prophylaxis. Among TB patients with HIV infection, upto 40% could be anergic[22]. This further complicates the issue of tuberculosis preventive therapy among individuals infected with HIV.

Chemoprophylaxis in tuberculin negative HIV infected persons

Tuberculin skin test negative, HIV infected persons from high-risk groups or from areas with a high prevalence of *Mycobacterium tuberculosis* infection may be at increased risk of primary or reactivation tuberculosis. Some experts recommend preventive therapy for persons in this category. The efficacy of preventive therapy in Mantoux or PPD negative HIV positive persons has not been clearly established, most studies showing it to be of limited value. In a meta analysis[23] combining the various studies on efficacy of preventive therapy in subjects with a negative PPD test, INH was found to be significantly better than placebo with a rate ratio of 0.57 (95% CI 0.41 to 0.79). Hence in HIV seropositive individuals with negative Mantoux or in situations where mantoux cannot be performed living in a high prevalence TB region, chemoprophylaxis with INH will reduce the risk of developing active TB in the short term to around 60% of what it would have been without such treatment. Hence the target population for preventive therapy among HIV seropositives should be

All PPD positive HIV infected individuals who donot have active tuberculosis

When PPD testing is not feasibie -

those living in areas with a high prevalence of TB infection (>30%)

health care workers

household contacts of TB patients

prisoners and miners

other selected groups at high risk of acquisition or transmission of TB.

Prerequisites to initiate Preventive therapy

Prior to starting an individual on preventive treatment for tuberculosis, it is essential to ensure that he/she does not have active tuberculosis. This is done by a complete clinical examination along with a chest x-ray and sputum smear examination for acid-fast bacilli (AFB). It is advisable that chest x-ray is done for every individual before considering preventive therapy. Any HIV infected patient with fever, cough or abnormal chest x-ray should not be given preventive treatment until a full evaluation has been done and it is confirmed that active TB disease is not present. At times, it is difficult to exclude TB even when the chest radiograph is normal and three sputum smears are negative for AFB[24]. Therefore preventive therapy should only be used in settings where it is possible to exclude active TB cases and to ensure appropriate monitoring and follow up.

Duration of preventive therapy

A multicentric trial conducted in the U.S.A.. Mexico, Brazil and Haiti[25] demonstrated that the magnitude of protection obtained from a regimen of isoniazid administered daily for 12 months was similar to that obtained from a regimen of rifampicin and pyrazinamide administered daily for 2 months. Moreover, it was noted that persons taking rifampin and pyrazinamide for 2 months were significantly more likely (80%) to complete therapy than those persons taking isoniazid for 12 months (69%). However, due to several cases of fatal hepatoxicity reported among HIV-negative individuals on this regimen, it is no longer recommended for preventive therapy. A study amongst HIV infected persons in Uganda[26] evaluated a 6-month regimen with a placebo comparison group and demonstrated a 70% reduction in the incidence of tuberculosis among persons in the treatment group

In another trial by Halsey et al[27] researchers found similar overall protection against tuberculosis in 2 groups of Mantoux positive, HIV infected persons: those who took partially supervised isoniazid twice weekly for 6 months and those who took rifampin and pyrazinamide twice weekly for 2 months. There was no significant difference in total mortality rates at any time between both the groups.

Table II : Studies of Rifampicin containing regimens for Preventive therapy in HIV+

Study reference	Country	Regimen	Comments	Relative Risk
Whalen[28]	Uganda	3RH, 3RHZ 6H, Placebo 3 drugs	Side effects higher with	0.41, 0.51, 0.33. All significantly lower compared to placebo
Gordin[25]	USA, Mexico Haiti, Brazil	12H, 2RZ	Equivalent, better adherence with 2RZ	Breakdown rate 3.3% vs 2.4% at 37 months follow up
Mwinga[30]	Zambia	$3RZ_2$, $6H_2$ placebo	Equivalent, no effect after 18 months, no effect on mortality	0.58 and 0.62 compared to placebo
Halsey[27]	Haiti	$6H_2$, $2RZ_2$	H better in earlier months no *difference later*	Breakdown rate 3.8% vs 5.0% at 4 years follow up
Hanvanich	Thailand	4RH, 12H	Equivalent	-
Narita M[36]	Florida	2RZ, 12H	Higher adherence *and side effects* with 2RZ	

Another trial in Ugandan adults[28] infected with human immunodeficiency virus studied three regimens namely isoniazid daily for 6 months versus isoniazid with rifampicin daily for 3 months and isoniazid with rifampicin and pyrazinamide daily for 3 months along with a placebo group. 80-89% of different groups completed treatment and the mean follow up duration was 15 months. This study demonstrated an 83% reduction in the incidence of tuberculosis among persons in the treatment groups as compared to the placebo group. It was also noted that the advantage of shorter regimens was better patient compliance and earlier sterilization of any lesions, however, the risk of drug toxicity was higher.

The evidence to date suggests that preventive therapy is efficacious in HIV positive persons with tuberculin reactions > 5mm, and that optimal duration of isoniazid preventive therapy (using a single drug) should be greater than six months to provide the maximum degree of protection against TB. Although the American Thoracic Society[29] has recommended that

isoniazid therapy be continued for 12 months in persons with HIV infection, there are only few studies comparing the efficacy of this approach with that of either shorter or longer courses. There has been some suggestion that the effect of prophylaxis tends to wane, as time passes". However, no long-term follow-up studies are available to confirm this.

Rhythm of administration of preventive therapy

HIV seropositive patients in Haiti[27], who received either isoniazid twice weekly for six months or rifampicin with pyrazinamide twice weekly for 2 months were studied, the rate of development of activeTB was similar in the two groups after 3 years; but patient who received rifampicin and pyrazinamide had significantly more cases of activeTB during the first 10 months.

In another study in which isoniazid was administered twice a week (10-15mg/kg, with a maximum dose of 900mg) to a cohort of injecting drug users under Directly Observed Preventive Therapy (DOPT), the findings support the efficacy of twice weekly isoniazid preventive therapy[31]. Twice weekly regimens with DOP were used in the study with the hope that supervised delivery of therapy would enhance adherence with preventive therapy regimen. Thus the available data suggests that the protection obtained from preventive therapy regimens may be the same whether the drug is administered daily or twice a week.

Monitoring

a) Adherence

Patients on preventive therapy should be monitored during routine visits and by means of surprise checks for adherence to the preventive therapy. Pili counts, self-report and estimation of urinary acetyl INH may be useful in assessing adherence. Patients who interrupt therapy should be counseled about reasons for stopping treatment. Preventive therapy should only be restarted if the obstacles to adherence have been removed. The aim is to provide at least 6 months of INH therapy during a 1-year period.

b) Drug Toxicity

Patients with symptoms suggestive of toxicity to medication should be evaluated immediately. Patients should be carefully educated about symptoms of hepatitis and instructed to attend the ciinic/OPD promptly should these occur, No toxicity from isoniazid was encountered in the Haitian study[15]. In the study from Spain[32] 9 of 86 (11 %) patients who started therapy had to discontinue it, in 6 cases because of hepatotoxicity. But in our experience at Tuberculosis Research Centre[33]preventive therapy with isoniazid can be safely employed in HIV infected patients, if baseline liver function tests are within normal limits. Another review article suggests an overall risk of death of 0.001% among subjects of all ages taking isoniazid for preventive therapy[34]. Data on rates of adverse effects in HIV infected individuals are not available: although experience suggests that toxicity from ATT drugs in advanced HIV disease is frequent[35]. In a community based programme in Florida[36], of the 135 HIV infected patients who received RMP with PYZ for 2 months under DOT for latent TB infection, 5 patients had to discontinue treatment due to side effects and allergic skin reaction (n=4) and hepatitis (n=1). In the Ugandan HIV infected adults trial[28], it was noted that side effects were higher in the 3

drugs group. In a recent meta analysis[17] that compared INH monotherapy to short course multi drug regimen, it was noted that compared to INH monotherapy short course multi drug regimens were much more likely to require discontinuation of treatment due to adverse effects.

c) Development of TB

Preventive therapy should not be continued if the patient develops signs or symptoms of TB. The suspected cases must be properly evaluated for active TB and referred for treatment

Drug Resistance

Several studiescarried out in India show that primary drug resistance to isoniazid varies from 6 to 13%[37,38,39]. Studies done at the Tuberculosis Research Centre[40], Chennai from 1956 to 1995 have shown that there is a gradual increase in the prevalence of primary drug resistance to INH from 3 to 13%. Hence, preventive therapy with INH alone may not be successful in such situations. Preventive treatment with INH (or other drugs) does not induce drug resistance if active tuberculosis is ruled out. In situations where there is a high default rate for anti-TB drugs, there is likely to be high default rate for the prophylaxis regimen as well.

Contraindications to Preventive therapy

Preventive therapy is contraindicated in patients with active tuberculosis and in patients with active (chronic or acute) hepatitis. Isoniazid should be given with caution to individuals who consume alcohol daily. Active tuberculosis must be excluded before beginning preventive therapy.

Chemoprophylaxis in special situations

Chemoprophylaxis in Pregnancy- Chemoprophylaxis for tuberculosis is recommended during pregnancy for HIV infected patients, who have a history of exposure to active tuberculosis, after active TB has been ruled out. In the absence of exposure to drug resistant TB. INH with pyridoxine (to reduce the risk of neurotoxcity) is the prophylactic agent of choice[41]. Some providers may choose to initiate prophylaxis after the first trimester to avoid teratogenicity.

Chemoprophylaxis in children- Infants born to HIV infected mothers should have a Mantoux test (5-TU PPD or 1-TU PPD RT23 with Tween 80) at or before age of 9-12 months and should be retested at least every 2-3 years[41]. Children exposed to persons who have active TB, should be administered preventive therapy after active TB has been ruled out. However, there have been no clinical trials of preventive therapy in HIV positive children

Chemoprophylaxis in developing countries- In many of the developing countries, where there is a high prevalence of HIV and TB, many HIV infected individuals are likely to develop active TB. The first priority of National TB control Programme in such settings, is to treat all active cases of TB, render them non infectious and achieve a high cure rate. Although it could be accepted that preventive therapy should be offered to individuals who are diagnosed to be infected with both HIV and latent TB, such preventive therapy programme should not

compromise or undermine the priority of the TB control programme of diagnosing and curing patients with infectious tuberculosis.

Secondary prophylaxis

The rate of recurrent TB is higher in HIV-1 positive individuals than in HIV negative individuals with both re-activation and new infections contributing to recurrences[42]. A trial was conducted in Haiti[43] to determine whether post treatment INH prophylaxls decreases the risk of recurrent TB. The rate of recurrent TB among patients who had completed a short course regimen was found to be 4.8 per 100 person years in HIV-1 infected individuals and 0.4 per 100 person years in uninfected individuals (RR=10.7, 95% CI 1.4-81.6). Among HIV-1 positive patients receiving INH for 6 months after TB treatment the TB recurrence rate was 1.4 per 100 person years and among HIV-1 positive patients receiving placebo, it was 7.8 per 100 person years (0.18 (0.04-0.83). Another trial conducted in South Africa[14] to determine the efficacy of secondary preventive therapy against TB among gold miners, concluded that the overall incidence of recurrent TB was reduced by 55% among men who received preventive therapy compared with those who did not (RR = 0.45,95% CI 0.26-0.78). It also showed that the impact of secondary preventive therapy to reduce TB recurrence was greatest among individuals with low CD4 cell counts.

Cost Efficacy

Studies are being conducted to consider not just the efficacy but the feasibility and cost efficacy of preventive therapy in HIV infected people in countries with a high prevalence of TB. The unit cost to prevent future TB disease should be evaluated against the cost of successful treatment of TB cases under programme conditions. The need for and provision of preventive therapy should therefore depend on the HIV situation and local resources. A model-based analysis to assess the impact of preventive therapy on the prevalence of tuberculosis in HIV infected persons in contemporary Sub-Saharan Africa was carried out[45]. The model implementation showed that giving preventive therapy to 25% of HIV positive individuals with latent tuberculosis infection leads to a 3.9% reduction in the prevalence of tuberculosis in 10 years and a 5.1% reduction in 20 years. Doubling the preventive therapy coverage to 50% approximately doubles the effect size, suggesting a linear relationship within the 20-year period. This model-based analysis suggests that the impact of preventive therapy on tuberculosis in the population is likely to be small contrary to general belief.

Effect of Preventive therapy on Mortality

The combined estimate provided by the largest meta analysis[23] shows a modest reduction in death rates in those subjects with a positive tuberculin skin test who took INH rather than placebo (RR=0.73 95% CI 0.57-0.95). In those with a negative tuberculin test the pooled relative risk for mortality was 1.02 (0.89 to 1.17). The overall estimate for all subjects in the trial did not differ significantly from unity, confirming that no substantial protection was conferred by interventions.

The Uganda efficacy study[28] showed that survival did not differ among the different groups but subjects with anergy had a higher mortality rate than the PPD positive subjects. Although the individual benefits may be rather small, widespread implementation of preventive therapy would have some impact on mortality.

Evaluation of Outcome of Preventive therapy

Programmes or centers that offer PT should assess the effectiveness of PT regularly. This assessment should include attendance at scheduled appointments, adherence (number of persons started on preventive therapy and number completed), toxicity and withdrawals from therapy due to toxicity, number of suspected TB cases found by screening, and monitoring of therapy. Individual records should be maintained to document use of PT Individual information will be aggregated tor regular reports, which may be used by the TB programme to estimate future drug requirements.

Current Recommendations for preventive therapy

1) WHO recommendation of preventive therapy against TB for PLWHA- Isoniazid is the recommended drug (5mg/kg - maximum 300mg) as daily, self-administered therapy for 6 months. Individuals should be seen monthly and given only one month's supply of medication at each visit.

2) CDC recommendation ofpreventive therapy against JB - Isoniazid is chosen for prevention of tuberculosis in persons with HIV infection, 9 months is recommended rather than 6 months[46]. Rifampicin and Pyrazinamide may be offered daily for 2 months to contacts of patients with H resistant, Rifampicin susceptible TB.

3) American Thoracic Society–Isoniazid is recommended for 12 months in persons infected with HIV infection.

Implementation of preventive therapy in India

In order to make an impact on the incidence of tuberculosis, preventive therapy has to be administered to a large number of people. The number of sites where a sufficient number of people know their HIV status, or where there is sufficient demand for and capacity of VCT services will limit delivery of preventive therapy. Preventive therapy should therefore be promoted as an intervention for those living with HIV, rather than as a primary strategy to control the public health burden of tuberculosis.

Before a developing country can implement a preventive therapy programme it should be able to readily identify HIV infected persons through counseling services and there should be good collaboration between the TB and AIDS programmes.

Most importantly, preventive therapy should be organized and integrated into health services and the cost of prevention must be affordable or fully supported by state/district health service.

Preventive therapy should not distract from the top priority goal for health services of preventing HIV infection and successfully treating infectious TB cases using the DOT strategy. Mass or indiscriminate use of chemoprophylaxis against TB in developing countries not only entails an enormous cost for drugs for millions of people but could also increase the chance of developing drug resistance among unscreened TB cases. Therefore assessing the cost effectiveness and feasibility of such a programme is the first requisite to instituting preventive therapy services in developing countries like India.

Research Issues

Trials evaluating the long-term effects of anti-tuberculosis chemoprophylaxis

Influence of level of immunocompromise on effectiveness

Operational research to identify ideal setting, method of delivery, monitoring for exclusion of active TB and adherence.

Summary

Treatment of latent tuberculosis infection reduces the risk of active TB in HIV positive individuals with a positive tuberculin skin test. The choice of regimen will depend on factors such as cost, adverse effects, adherence and drug resistance. Decisions about preventive therapy require a balance between the needs of the individual and those of TB control at a public health level. The challenge in resource limited countries will be to provide voluntary HIV testing and counseling, tuberculin skin testing and preventive therapy in a supervised fashion to benefit as many people as possible without endangering public health through undisciplined use of antituberculosis drugs. Preventive therapy is not an alternative to the DOT strategy for controlling TB, even in areas with a high prevalence of HIV. Preventive therapy should be part of the package of care available to persons living with HIV/AIDS. The next step should be to develop systems that greatly increase the accessibility of preventive therapy to people living with HIV in settings of high TB prevalence, while ensuring that the efficiency of TB control programmes are not compromised. This will require greater collaboration between those fighting TB and those fighting HIV/AIDS.

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