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Preventive therapy for tuberculosis in HIV infected individuals

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The increased risk of developing tuberculosis (TB) among those infected with HIV has prompted a need to reconsider the institution of preventive therapy/chemoprophylaxis with one or more antituberculosis drugs. Prior to the initiation of preventive therapy for tuberculosis, it is essential to rule out active TB. The target population for chemoprophylaxis among HIV seropositives includes all Mantoux (PPD) positive individuals who do not have active tuberculosis and could include all PPD negative individuals living in high prevalence region for TB. The optimal duration of preventive therapy with single drug isoniazid, daily or twice weekly, should be greater than six months to provide the maximum degree of protection against tuberculosis. The effectiveness of preventive therapy should be evaluated at regular intervals by monitoring patients for drug adherence, drug toxicity and for the development of tuberculosis. Though the impact of preventive therapy on an individual basis may be rather small, widespread implementation would have substantial impact on morbidity due to tuberculosis and some impact on mortality. Till the vast majority of HIV positive individuals in the world can access antiretroviral therapy, preventive therapy for tuberculosis should be offered at voluntary counselling and testing centres, as part of a package of care that includes prophylaxis and treatment of opportunistic infections, nutritional support and counselling.

Key words Chemoprophylaxis - drug monitoring - drug toxicity - HIV - preventive therapy - tuberculosis

The HIV pandemic has had a major impact on the epidemiological dynamics of tuberculosis (TB). In countries with a severe HIV epidemic, there has been a dramatic rise in the notification rates for TB. Various studies¹⁻³ have demonstrated that persons co infected with *Mycobacterium tuberculosis* and HIV have a 5-8 per cent annual risk and a 30 per cent or greater life time risk of developing active TB. The mechanisms include reactivation of latent infection², rapid progression of primary infection³ or re-infection with *Mycobacterium tuberculosis*⁴.

The Joint United National Programme on HIV/AIDS (UNAIDS) estimates that of the global total of 37.8 million people living with HIV at the end of

2003, 70.1 per cent are in sub-Saharan Africa and 16.1 per cent are in South East Asia⁵. About one third of those living with HIV worldwide are co-infected with *M. tuberculosis*⁶. Since 68 per cent of those co-infected live in sub-Saharan Africa, this region carries the overwhelming burden of global epidemic of HIV associated tuberculosis. In sub-Saharan Africa 20 to 67 per cent of patients with pulmonary tuberculosis have been reported to be HIV seropositive⁷. However, with 22 per cent of co-infected individuals, 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 patients⁸⁻¹⁰.

Over the last decade HIV has been the major cause for the large increase 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 tuberculosis¹¹. The increased risk of developing TB 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 measures¹². 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 infants being breastfed by mothers with pulmonary tuberculosis or other children under 5 yr of age living with infectious persons¹³.

Preventive therapy (PT) or chemoprophylaxis against TB is the use of one or more antituberculous drugs (ATT) given to persons with latent infection with *M. tuberculosis* in order to 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 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 25-92 per cent in tuberculosis¹⁴. Several studies have now demonstrated that PT is effective in preventing progression of TB infection in individuals dually infected with HIV and *M. tuberculosis*, although the efficacy is not 100 per cent (ranges from 60-90%). In addition, there is a suggestion that chemoprophylaxis may delay HIV disease progression amongst asymptomatic HIV infected individuals¹⁵.

The increased risk of developing active disease associated with HIV infection has provoked a number of questions, like who should receive prophylactic therapy, how long to continue, whether isoniazid alone is the most effective agents, role of secondary prophylaxis, *etc.* Clinical trials are ongoing in these areas.

Ideal candidate for chemoprophylaxis: In a study under a methadone maintenance programme in New York the risk of developing active tuberculosis in HIV infected persons with positive tuberculin (PPD) skin test reactions was shown to be as high as 7.9 per cent per year². All 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-analysis¹⁷ 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 revealed that in groups of tuberculin skin test positive and negative persons, the risk ratio of TB was 0.41 (95% CI, 0.24-0.71) and 0.94 (95% CI, 0.52-1.38), respectively and the difference in the effectiveness of INH versus placebo between these groups was statistically significant; consistency of results was found across trials for all comparisons. Another meta-analysis¹⁸, 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 showed 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 with a negative test (RR 0.83, 95% CI 0.58 to 1.18) (Table I). A positive tuberculin skin test is defined as an induration of >5 mm 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 test be offered preventive therapy with INH, after ruling out active tuberculosis.

A study among injecting drug users in Baltimore, Maryland¹⁹ 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. Another study²⁰ suggested that establishing the likelihood of *M. tuberculosis* infection on grounds other than skin testing is a more useful means for determining who should receive prophylactic therapy. Recently, the detection of interferon-gamma (IFN- γ) production by

peripheral blood mononuclear cells (PBMCs) in response to TB antigens like ESAT-6 and Cfp 10 has been suggested as a test for latent TB infection²¹. However, its utility in HIV infected persons has not been established. 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 the HIV infected patients at highest risk. These individuals may be considered for prophylactic therapy regardless of skin test results.

The Centers for Disease Control and Prevention (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 high²². 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, up to 40 per cent could be anergic. 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 *M. 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-analysis²³ 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 0.82 (95% CI 0.50 to 1.36). Hence in HIV seropositive individuals, living in a high prevalence TB region, with negative PPD or in situations where tuberculin test cannot be performed, chemoprophylaxis with INH will reduce the risk of developing active TB in the short term to around 60 per cent of what it would have been without such treatment. Hence the target population for

preventive therapy among HIV seropositives includes all PPD positive HIV infected individuals who do not have active tuberculosis and when PPD testing is not feasible like those living in areas with a high prevalence of TB infection (>30%), among health care workers, household contacts of TB patients, among prisoners and miners and other selected groups at high risk of acquisition or transmission of TB.

Prerequisite 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 is done to confirm 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. Where mycobacterial culture facilities are available, sputum culture can be used to definitively diagnose TB²⁴. In general, it is safe to presume that completely asymptomatic individuals are unlikely to have TB.

Duration of preventive therapy

A multicentric trial conducted in the USA, Mexico, Brazil and Haiti²⁵ demonstrated that the magnitude of protection obtained from a regimen of isoniazid (H) administered daily for 12 months was similar to that obtained from a regimen of rifampicin (R) and pyrazinamide (Z) administered daily for 2 months. Moreover, it was noted that persons taking R and Z for 2 months were significantly more likely (80%) to complete therapy than those taking H for 12 months (69%). However, due to several cases of fatal hepatotoxicity reported among HIV-negative individuals on the RZ regimen, it is no longer recommended for preventive therapy. A study amongst HIV infected persons in Uganda²⁶ evaluated a 6-month regimen with a placebo comparison group and demonstrated a 70 per cent reduction in the incidence of tuberculosis among persons in the treatment group.

Another trial by Halsey *et al*²⁷ found similar overall protection against tuberculosis in 2 groups of Mantoux positive, HIV infected persons: those who took partially supervised H twice weekly for 6 months and those who took R and Z twice weekly for 2 months. There was no significant difference in total mortality rates at any time between both the groups (Table II).

Another trial in Ugandan adults infected with HIV²⁸ studied three regimens namely H daily for 6 months versus H with R daily for 3 months and H with R and Z daily for 3 months along with a placebo group; 80-89 per cent of different groups completed treatment and the mean follow up duration was 15 months. This study²⁸ demonstrated a 83 per cent 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.

There is evidence to suggest that preventive therapy is efficacious in HIV positive persons with tuberculin reactions >5 mm, 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 Society²⁹ 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 passes³⁰. A randomized clinical trial is currently underway at the Tuberculosis Research Centre, Chennai to investigate a 6-month regimen of ethambutol and isoniazid compared to a 3-yr regimen of isoniazid alone (in lieu of lifelong therapy). The results of this trial should provide information on the need for long-term prophylaxis.

Rhythm of administration of preventive therapy

HIV seropositive patients in Haiti²⁷, 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 active TB was similar in the two groups after 3 yr;

but in group receiving rifampicin and pyrazinamide had significantly more cases of active TB during the first 10 months.

In another study in which isoniazid was administered twice a week (10-15 mg/kg, with a maximum dose of 900 mg) to a cohort of injecting drug users under directly observed preventive therapy (DOPT), support the efficacy of twice weekly isoniazid preventive therapy³¹. Twice weekly regimens with DOPT were used in the study with the hope that supervised delivery of therapy would enhance adherence with preventive therapy regimen. Thus, the available data suggest that the protection obtained from isoniazid preventive therapy regimens may be the same whether the drug is administered daily or twice a week.

Drug monitoring

(i) *Adherence*: Patients on preventive therapy should be monitored during routine visits and by means of surprise checks for adherence to the preventive therapy, for drug toxicity and signs and symptoms of developing active TB. Pill counts, self-report and estimation of urinary acetyl INH may be useful in assessing adherence. Patients who interrupt therapy should be counselled 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 one year period.

(ii) *Drug toxicity*: Patients with symptoms suggestive of toxicity to medication should be evaluated immediately. Patients should be educated about symptoms of hepatitis and instructed to attend the clinic/OPD promptly should these occur. No toxicity from isoniazid was encountered in the Haitian study¹⁵. In the study from Spain³², 9 of 86 (11%) patients who started therapy had to discontinue it, in 6 cases because of hepatotoxicity. In our experience at Tuberculosis Research Centre preventive therapy with isoniazid can be safely employed in HIV infected patients, if baseline liver function tests are within normal limits (unpublished observations). Another study suggested an overall risk of death of 0.001 per cent among subjects of all ages taking isoniazid for preventive therapy³³. Data on rates of adverse effects

in HIV infected individuals are not available; although experience suggests that toxicity from anti-tuberculosis drugs in advanced HIV disease is frequent³⁴. In a community based programme in Florida³⁵, of the 135 HIV infected patients who received R with Z for 2 months under DOT for latent TB infection, five had to discontinue treatment due to side effects and allergic skin reaction (n=4) and hepatitis (n=1). In the Ugandan HIV infected adults trial²⁸, it was noted that side effects were higher in the 3 drugs group. In a meta-analysis¹⁷, it was noted that compared to INH monotherapy short course multidrug regimens were much more likely to require discontinuation of treatment due to adverse effects.

(iii) *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.

Contraindication 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 women, who have a history of exposure to active tuberculosis or after active TB has been ruled out. INH with pyridoxine (to reduce the risk of neurotoxicity) is the prophylactic agent of choice³⁶. Some 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 yr³⁶. Children exposed to those with 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 with 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 recurrences³⁷. A trial was conducted in Haiti³⁸ to determine whether post treatment INH prophylaxis 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 (RR0.18, 95% CI 0.04-0.83). Another trial conducted in South Africa³⁹ 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 per cent 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 absolute impact of secondary preventive therapy to reduce TB recurrence was highest 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. The impact of preventive therapy on the prevalence of tuberculosis in HIV infected persons in contemporary sub-Saharan Africa⁴⁰ showed that giving preventive therapy to 25 per cent of HIV-positive individuals with latent tuberculosis infection leads to a 3.9 per cent reduction in the prevalence of tuberculosis in 10 yr and a 5.1 per cent reduction in 20 yr. Doubling the preventive therapy coverage to 50 per cent approximately doubles the effect size, suggesting a linear relationship within the 20-yr 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 a meta-analysis²³ showed some 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 (95% CI 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 study²⁸ 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 Centres that offer preventive therapy should assess its effectiveness 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 for regular reports, which may be used in the TB programme to estimate future drug requirements.

Current recommendations for preventive therapy against TB in HIV infected persons

(i) *WHO recommendation*: Isoniazid is the recommended drug (5 mg/kg - maximum 300 mg) as daily, self-administered therapy for 6 months. Individuals should be seen monthly and given only one month's supply of medication at each visit¹³.

(ii) *CDC recommendation*: Isoniazid is chosen for prevention of tuberculosis in persons with HIV infection, 9 months is recommended rather than 6 months⁴¹. Rifampicin and pyrazinamide may be offered daily for 2 months to contacts of patients with INH resistant, rifampicin susceptible TB.

(iii) *American Thoracic Society*: Isoniazid is recommended for 12 months as prophylaxis in person infected with HIV infection²⁹.

Implementation of preventive therapy in India

In order to make an impact on the incidence of tuberculosis in India, preventive therapy has to be administered to a large number of people. Delivery of preventive therapy will be limited by the number of sites where a sufficient number of people know their HIV status, or where there is sufficient demand for and capacity of voluntary counselling and testing (VCT) services. 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 counselling 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.

Table I. Efficacy of isoniazid (INH) preventive therapy: results from three meta-analyses

Author	Country	Rate ratio (RR) or odds ratio (OR) for INH compared to no INH (95% CI)		
		PPD positive	PPD negative	Total
Wilkinson <i>et al</i> ²³	Haiti, Kenya, Uganda & U.S.	OR 0.32 (0.19 to 0.51)	OR 0.82 (0.50 to 1.36)	OR 0.57 (0.41 to 0.79)
Bucher <i>et al</i> 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 & Volmink ¹⁸	11 trials	RR 0.38 (0.25-0.57)	RR 0.83 (0.58 to 1.18)	RR 0.64 (0.51 to 0.81)

PPD, Purified protein derivative
Superscript numerals represent reference numbers

Table II. Studies of rifampicin containing regimens for Preventive therapy in HIV seropositive persons

Study reference	Country	Regimen	Comments	Relative Risk
Whalen <i>et al</i> ²⁸	Uganda	3RH, 3RHZ, 6H, Placebo	Side effects higher with 3 drugs	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 <i>et al</i> ³⁰	Zambia	3RZ ₂ , 6H ₂ , placebo	Equivalent, No protective 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
Narita <i>et al</i> ³⁵	Florida	2RZ, 12H	RZ higher adherence rate. Side effects higher with 2 drugs	

Superscript numerals represent reference numbers
R, Rifampicin; H, isoniazid; Z, pyrazinamide

In India, collaboration between the National AIDS Control Programme (NACP) and Revised National Tuberculosis Control Programme (RNTCP) is being strengthened. All symptomatic persons diagnosed to have HIV infection VCT centres are referred to the nearest microscopy centre to rule out tuberculosis. In this setting, it would be feasible to offer preventive therapy to those individuals who are found not to have TB. Both isoniazid and co-trimoxazole prophylaxis can be given in the same clinic under close monitoring. If symptoms of TB develop at any time, patients can be promptly investigated and treated.

Following issues need to be clarified through future research: (i) Ideal duration of preventative therapy in TB-endemic areas: need for life-long prevention? (ii) Operational research to identify ideal setting, method of delivery, monitoring for exclusion of active TB and adherence; and (iii) Preventive therapy for TB in the era of highly active antiretroviral therapy (HAART).

Conclusion

The evidence to date indicates that preventive therapy for TB in HIV infected persons reduces the incidence of TB by 50-60 per cent. The efficacy is

higher in those who are tuberculin test positive. Challenges to implementation in resource-constrained settings include the exclusion of active TB disease and monitoring for adherence and toxicity.

Recommendations for duration of preventive therapy range from 6-12 months of isoniazid daily to short term (2 or 3 months) regimens. The efficacy of long-term (>12 months) regimens is currently being investigated. In India, preventive therapy can be offered to HIV positive persons detected at VCT centres, who are referred to the nearest TB clinic. It should be included in the package of care for HIV positive persons, which would include ongoing counselling and provision of prophylaxis and treatment for opportunistic infections. Till the vast majority of HIV positive individuals in the world can access antiretroviral therapy, preventive therapy for TB will continue to play a role in reducing the incidence of TB thereby decreasing mortality and morbidity in this population.

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