Management of Latent Tuberculosis Infection in People Living with Human Immunodeficiency Virus

Latent Tuberculosis Infection Working Group

Tuberculosis Control Coordinating Committee of

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Management of latent TB infection (LTBI) in people living with HIV (PLHIV)

Introduction

Global data in 2018 showed that PLHIV were 20 times (95% confidence interval 16-27) more likely to develop TB than those without HIV infection.[1] In Hong Kong, a retrospective cohort study showed that the TB incidence was substantially higher in PLHIV tested positive for LTBI at baseline in comparison with those tested negative (1.43 vs. 0.21 per 100 person-years), and the TB incidence from HIV diagnosis was substantially lower in PLHIV with treatment of LTBI than those without treatment (0.48 vs. 6.12 per 100 person-years).[2]

Both international and local guidelines have recommended systematically screening for and treating LTBI in PLHIV.[1,3] In Hong Kong, the Scientific Committee on AIDS and STI (SCAS) (Centre for Health Protection, Department of Health) has recommended annual testing for LTBI with TST using 2 units of PPD-RT23 and a 5mm induration as cutoff for defining positive results, and offering preventive treatment of TB to those tested positive after ruling out TB disease.[3] With significant recent exposure to an infectious source of TB, preventive treatment of TB is indicated for PLHIV regardless of TST results.[3] Dual testing by TST and IGRA was advised for improving detection of LTBI in PLHIV with CD4 < 100/uL.[3] In light of new insights and findings in recent years, the SCAS updated its recommendations recently particularly with regard to testing strategies and treatment options of LTBI.[4]

Guideline statements

PLHIV should be routinely screened for LTBI.

Either TST (using 5 mm induration as cutoff for defining positive results) or IGRA could be used for testing of LTBI. At a low CD4 count <100/μL, dual testing by TST and IGRA could be employed to increase case finding.

Testing should be repeated among those without additional risk factors for TB upon achieving immune reconstitution and virological suppression with antiretroviral treatment and then repeated as and when necessary, e.g. subsequent to virological failure.

Re-screen should be offered to those with potential exposure. For those with potential ongoing exposure, e.g. healthcare providers working in high risk settings, regular screening should be offered.

A positive LTBI result with either test is an indication for treatment of LTBI after ruling out active TB disease according to a clinical algorithm. With significant recent exposure to an infectious source of TB, preventive treatment of TB is indicated for PLHIV regardless of LTBI test results

Nine months of isoniazid given at 300 mg daily remains the standard treatment of LTBI. Alternative treatment options include twelve doses of once-weekly isoniazid and rifapentine taken under observation, and four months of daily rifampin (when isoniazid resistance or intolerance is of concern, after checking for potential drug-drug interactions with specific antiretrovirals). The two-month regimen of rifampin and pyrazinamide is not recommended because of excessive hepatotoxicity. Neither is continuous isoniazid preventive treatment beyond 12 months recommended when the risk of TB reinfection is low.

Rationale

Neither TST nor IGRA have high accuracy for the prediction of active TB in PLHIV in low risk settings.[5-7] A systematic review with meta-analysis involving 7 studies in low/middle income areas showed that neither IGRA nor TST performed very well in predicting TB (as evaluated by the TB incidence rate ratio) although IGRA was marginally better. [5] Modest performance might be partly explained by reinfection. Another systematic review of comparative data did not find robust evidence for demonstrating the superiority of IGRAs over TST for the diagnosis of TB in PLHIV.[8] One systematic review with meta-analysis showed that the pooled positive and negative predictive values for progression from LTBI to TB disease were significantly better for IGRA than TST especially when performed in high-risk persons, but the pooled positive predictive value for IGRA was only 6.8% (95% CI 5.6% to 8.3%) in high-risk groups. [9]

PLHIV may benefit more from treatment of LTBI when LTBI testing result is positive rather than negative. A systematic review of 7 placebo-controlled trials of isoniazid preventive treatment for 6-12 months demonstrated that isoniazid preventive treatment significantly reduced TB risk and TB mortality when TST was positive but not when TST was negative. [10] In a randomized trial in Africa involving PLHIV with relatively high CD4 cell counts, TB incidence rate was much higher among those tested positive

for IGRA than those tested negative (7.7% vs. 2.7%), and TB incidence was significantly reduced by isoniazid preventive treatment given for 6 months.[11] On the other hand, a randomized double-blind placebo-controlled trial conducted in a South African setting with high TB incidence and high false-negative rates due to low CD4 counts showed that isoniazid preventive treatment for 12 months significantly reduced TB risk in PLHIV tested negative for TST or IGRA.[12]

No clear role of repeating LTBI screening on an annual basis has been demonstrated among PLHIV on HAART with good immunological responses and in places where the risk of TB infection is low. A cohort study in Hong Kong that followed the occurrence of TB in PLHIV without previous history of TB or LTBI found major discordance in positive results between TST, T-Spot.TB and QuantiFERON-TB Gold-In Tube, high reversion rates and low TB incidence among test-positive subjects. Given high within-subject test variability and a generally low TB reinfection risk, findings cast doubt on the effectiveness and cost-effectiveness of LTBI screening with TST or IGRA on an annual basis.[6] A Hong Kong longitudinal study on LTBI screening and its association with TB incidence in PLHIV found significant association between active TB disease development and baseline rather than subsequent positive LTBI testing results.[13]

While 6-9 months of daily isoniazid therapy has been recommended by most international guidelines, analysis has found that 9 months of daily isoniazid therapy was perhaps more effective than 6 months but no clinical trial data was available to directly comparing 6 months and 9 months of isoniazid among HIV-positive persons.[1,14,15] Nine months of daily isoniazid therapy remains the standard treatment of LTBI among PLHIV in Hong Kong.

Twelve doses of once-weekly isoniazid and rifapentine taken under observation has been shown to be as effective as isoniazid monotherapy, but with lower risk of hepato-toxicity than the 9-month regimen of isoniazid (0.4% vs. 2.7%, $P<0.001$), and higher completion rates, though it was significantly more likely to cause possible hypersensitivity (3.8% vs. 0.5%, $P<0.001$).[16] It is an alternative option for those requiring shorter course. The 12-dose regimen of once-weekly rifapentine plus isoniazid can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, or raltegravir (safe and well tolerated), but not to people receiving protease inhibitors, nevirapine, rilpivirine, elvitegravir- and bictegravir-based regimen. More information is required to recommend its use with dolutegravir-based regimens.[1] Four months of rifampicin may be considered if isoniazid resistance or intolerance is of concern. Again, due caution should be

exercised against drug-drug interaction were a 4-month rifampicin regimen to be used with concomitant antiretroviral therapy.

While continuous isoniazid given for 36 months in comparison with 6 months of isoniazid significantly reduced TB incidence rate in PLHIV tested positive for TST in Botswana (where the TB reinfection risk was high),[17] another randomized trial in South Africa that randomly assigned PLHIV to different regimens for preventing TB found no significant difference in efficacy between the six-month isoniazid regimen and the other regimens but significantly more common serious adverse reactions for isoniazid continuously given up to 6 years.[18]

One randomized trial of a one-month regimen of rifapentine (300-600 mg daily) plus isoniazid (300 mg daily) in PLHIV demonstrated non-inferiority by efficacy and significantly higher treatment completion rate in comparison with 9 months of isoniazid (300 mg daily).[19] This short-course regimen has recently been recommended by the WHO as an alternative TB preventive treatment option subject to specific conditions,[1] but not in the latest CDC guideline.[14] Further studies evaluating its safety are under way.

Limitations

The predictive value of LTBI tests for TB disease is inevitably constrained by the low risk of progression from LTBI to disease.[9] Treatment of LTBI is not free from harm. The risk of isoniazid-related hepatotoxicity substantially increases with age.[20] A randomized controlled trial published recently showed high rates of adverse events from treatment of LTBI with once-weekly isoniazid and rifapentine among Chinese aged 50-70.[21] Given the limitations of current diagnostic and treatment tools, a targeted approach that focuses on TB risk in specific settings with reference to available scientific data and local epidemiological circumstances is required to optimize cost-effectiveness and individual safety.[7]

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