Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of HIV and Tuberculosis:
What Every GP Should Know

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Abstract

Tuberculosis (TB) is the leading cause of morbidity and mortality in people living with HIV (PLWH). The epidemiologic link between HIV and TB is strong even in a low HIV prevalence country such as India – hence all Indian physicians that see patients with suspected or confirmed TB should understand how to approach TB diagnosis and treatment among PLWH, even if they are not working in a community where HIV infection is common. This article provides general practitioners with a concise and practical overview of TB screening, prevention, diagnosis and treatment, in PLWH.

Key words: HIV/AIDS, TB screening and prevention, antiretrovirals, treatment

INTRODUCTION

Tuberculosis (TB) remains the leading cause of morbidity and mortality in people living with HIV (PLWH).[1] In 2013, 13% of all cases of TB in the world occurred in PLWH, and this group accounted for 27% of TB deaths.[2]

India is home to 2.1 million PLWH—the third largest population of HIV-infected persons in the world. While the overall prevalence of HIV in India is estimated to be 0.27%,[3] PLWH account for 5.7% of incident TB cases.[2] In India, any general practitioner that sees patients with suspected or confirmed TB should have a solid understanding of how the presence of HIV infection affects the clinical presentation, diagnosis, and treatment of TB. This is true even for physicians who primarily practice in a low HIV prevalence community. Indian general practitioners working with subpopulations where HIV infection is common should also have a firm grasp on how to approach TB screening and prevention in PLWH.

This review article provides a concise overview of the critical aspects of TB management in PLWH. The keys to successful TB screening, prevention, diagnosis and treatment in PLWH can be found in the Standards for Tuberculosis Care in India (STCI)[4] and various World Health Organization guidelines,[5-10] and the reader is referred to these documents for more detailed guidance.

HIV-TB BASICS

There are two clinical forms of TB infection: latent and active. In people with latent TB infection, bacilli are in a "dormant" state – kept in check by the host's immune system, the bacilli are essentially not replicating, and are not causing tissue destruction.[11] People with latent TB infection are not contagious. In contrast to latent infection, active TB is a disease state in which the bacilli are actively replicating and inducing immune-mediated tissue destruction.

While active TB can occur in a number of anatomical locations, the most common are the lungs—i.e., pulmonary TB. People with active pulmonary TB, and also those with TB of the upper airways, can transmit infection to others. Without treatment, active TB can be fatal. Once someone has acquired latent TB infection, the probability that they will subsequently develop ac-

tive TB depends on a number of factors, such as how recently the person was infected and the presence of co-morbid conditions.[11]

THE IMPACT OF HIV ON PROGRESSION FROM LATENT TB INFECTION TO ACTIVE TB

HIV infection is one of the strongest risk factors for progression from latent to active TB.[12-15] A common misunderstanding is that the risk of progression from latent to active TB only increases in PLWH if the CD4 count has fallen below 200 cells/mm^3. In fact, the risk of active TB starts to increase within months of becoming infected with HIV, before the CD4 cell count has fallen below 200 cells/mm^3.[14] If HIV infection continues to weaken the immune system— i.e., in the absence of effective antiretroviral therapy (ART) — the risk of progression from latent to active TB will continue to rise.[14] It should be noted that while ART greatly lowers the risk of progression from latent to active TB in PLWH,[16] the risk of TB remains elevated compared to the risk in non-HIV infected populations.[17] This is why TB screening and prevention are important for all PLWH, regardless of their CD4 count and whether or not they are on ART.

THE IMPACT OF HIV ON THE CLINICAL MANIFESTATIONS OF ACTIVE TB

Clinical manifestations of active TB in PLWH depend on the degree of immunosuppression.[18,19] In PLWH, active TB can present with classic symptoms – fevers, cough, sputum production, hemoptysis, weight loss, and night sweats. However, with advanced immunosuppression, active TB can be minimally symptomatic. Hence, the presence of any of these classic symptoms should trigger further diagnostic evaluation of TB—even if the symptoms are mild—in a high TB incidence setting such as India. While pulmonary TB is the most common form of active TB in PLWH, in patients with advanced immunosuppression, extrapulmonary disease is also common.[20,21] Extrapulmonary TB can occur in almost any organ system; common sites include lymph nodes, the pleural space, CNS, abdomen, bones/joints, and genitourinary system.

THE IMPACT OF HIV ON THE DIAGNOSIS OF ACTIVE TB

In patients with advanced immunosuppression, most microbiologic tests for active TB are less sensitive (i.e., will have a higher false-negative rate). This is true for sputum smear microscopy,[22, 23] and also for more advanced PCR-based tests, such as GeneXpert (Xpert MTB/RIF).[24] In general, sputum smear microscopy is not an adequate test for ruling out pulmonary TB in PLWH because the rate of false-negative results is high—even when more than one smear has been performed[23]—and the risk of mortality from untreated TB is very elevated in PLWH.

Figure 1 – Xpert MTB/RIF (GeneXpert) is the recommended TB test for people living with HIV/AIDS

The GeneXpert (Xpert MTB/RIF) assay is a much more sensitive test than sputum smear microscopy, hence, the STCI recommend GeneXpert as the front-line test for TB in PLWH (**Figure 1**). However, a false-negative GeneXpert result is seen in ~20% of PLWH who have active TB;[24] hence, if the first GeneXpert result is negative (i.e. "MTB not detected"), and TB is still suspected, it is reasonable to perform GeneXpert on a second sputum sample in order to lower the likelihood of missing a case of active TB in PLWH. The STCI also recommends that all persons in whom pulmonary TB is suspected should have two sputa submitted for microbiologic analysis, at least one of which should be an early morning sample.[4] Ideally these should be sent for both smear microscopy and TB culture. Even though it can take several weeks before cultures confirm or exclude TB, specimens should always be sent for culture—as it is the most sensitive and specific test for TB, even in PLWH.

Chest x-ray (CXR) is a sensitive test for identifying active pulmonary TB in PLWH—even in patients with minimal symptoms. In PLWH, the presence of any CXR abnormality—including those that are not "classic" for TB—should raise the possibility that active TB is present; this is particularly true in patients with advanced immunosuppression.[25,26] When a CXR abnormality is present, all efforts should be made to send sputum for microbiologic evaluation for TB (as described above), but consideration should also be given to other pulmonary infections seen in PLWH. In patients with "classic"

CXR findings of pulmonary TB, it may be reasonable to empirically start treatment for active TB while awaiting results of confirmatory testing. In PLWH with very advanced immunosuppression, active pulmonary TB can be present even if the CXR is normal in appearance[27,28]—hence, in such patients, a normal radiograph should not preclude microbiologic analysis of sputum as described above.

Microbiologic confirmation of extrapulmonary TB is challenging for two reasons. First, it is often difficult to obtain specimens. Second, when tissue or fluid is obtained, the rate of false-negative microbiology results is high – especially for smear microscopy. Nevertheless, all efforts should be made to obtain specimens for TB cultures and GeneXpert to confirm the diagnosis when extrapulmonary TB is suspected.[10] When TB meningitis is suspected, the WHO recommends cerebrospinal fluid analysis by the GeneXpert assay as the preferred front-line test.[10] GeneXpert can also be used to test fluid obtained from other sites (e.g., lymph node aspirates, gastric lavage).[10] Empiric treatment for extrapulmonary TB may be reasonable—and should not be delayed, particularly when TB meningitis is suspected—in PLWH with advanced immunosuppression in whom diagnostic confirmation may be difficult.

THE IMPACT OF HIV ON ACTIVE TB OUTCOMES

As compared to their HIV-negative counterparts, PLWH who have active TB are more likely to experience poor TB treatment outcomes. In particular, HIV infection greatly increases the risk of mortality,[29-32] and acquisition of resistance to anti-TB medications.[32-35] Additionally, PLWH who are cured of active TB are at increased risk of TB relapse. By providing appropriate medical management—including early diagnosis and institution of effective HIV and TB treatment—general practitioners can help mitigate many of these risks and give their patients with active TB and HIV infection the best chance of survival and relapse-free TB cure, and also prevent the devastating consequences of acquired TB drug-resistance.

HIV AND DRUG-RESISTANT TB

PLWH are at increased risk of developing drug-resistant forms of TB—in particular, rifampicin resistance.[32-35] The reasons for this are unclear—interactions with other medications and malabsorption may contribute. Drug-resistant TB and HIV are a deadly combination—particularly in the presence of multidrug-resistant (MDR) or extensively drug resistant (XDR) strains. A recent hospital-based outbreak of XDR-TB in PLWH was associated with a mortality rate of close to 100%.[36] Because of this, drug susceptibility testing should be performed for all PLWH who have active TB at the start of therapy—even in those that have never before received anti-TB medications—in order to reduce delays in the diagnosis of drug-resistance. Drug susceptibility tests should be repeated for patients on treatment if there is suspected failure, or lack of improvement. The STCI recommends that all PLWH who have active TB be tested for drug-resistance to isoniazid and rifampin with rapid molecular drug-susceptibility tests as the method of choice.[4]

MANAGEMENT OF HIV-TB CO-INFECTION: FREQUENTLY ASKED QUESTIONS

I am seeing a patient and I suspect they have active TB. Should I test them for HIV infection?

Yes. Because of the strong epidemiologic link between HIV and TB, all patients in whom TB is suspected should be tested for HIV infection, even before the diagnosis of TB has been confirmed. In fact, in high TB burden areas, active TB is often the presenting manifestation of HIV-infection.

My patient has been diagnosed with active TB. Should I test them for HIV infection?

Yes. As stated earlier—all patients with active TB should be tested for HIV infection.[4]

Is there anything I can do to lower the risk of infection by *Mycobacterium tuberculosis* in my patients that are PLWH?

Yes. Many people become infected with TB in healthcare settings—including hospitals and clinics—because they are more likely to encounter people with undiagnosed active TB in these locations. Simple TB infection control measures can substantially reduce the risk that TB transmission will occur in such settings.[5] Administrative measures that you can institute in your clinic to reduce the risk of TB transmission include: having a clinic attendant monitor all people in the waiting room for cough, ensuring that anyone who is coughing wears a simple mask, or covers their mouth and nose with a cloth. Environmental measures can include ensuring that windows are kept open to maximize ventilation.

Should I screen PLWH for active TB? If so, how?

Yes! The WHO recommendation, echoed in the STCI, is that all PLWH should be screened for active TB using a symptom-based questionnaire, and, if resources permit, a CXR.[4,9] The screening should be performed at the time the patient is enrolled into care and repeated at every clinical visit. For symptom-based TB screening, the WHO recommends assessing for the presence of

the following: fevers, night sweats, cough, and weight loss. The presence of at least one symptom means that active TB should be suspected and further diagnostic evaluation is required. If you work in a clinic or region where TB prevalence amongst PLWH is very elevated (e.g., greater than 5%), then all efforts should be made to ensure that a CXR is obtained for TB screening in addition to the symptom assessment.[9] Under such circumstances, CXR should be performed regardless of the presence or absence of symptoms in order to lower the likelihood of missing a case of active TB in someone that is asymptomatic (e.g., early in the course of active TB). If a CXR is performed in addition to the symptom-based questionnaire, then the presence of any abnormality means that active TB should be suspected and further diagnostic testing is warranted—this is true even if the person being screened is asymptomatic. Once a PLWH has been identified as a presumed TB case, all efforts should be made to confirm or exclude active TB using a microbiologic test (**see below**).

If my patient has HIV-infection, and is showing symptoms of active TB, which test should I order?

In addition to CXR, a GeneXpert test is the best microbiological test to order in those with HIV-infection. According to WHO, Xpert MTB/RIF should be used as the initial diagnostic test in adults and children presumed to have HIV-associated TB.[4,10]

How can I prevent the development of active TB in PLWH?

The two most important and highly effective interventions that lower the risk of active TB in PLWH are ART—which has been shown to reduce the risk of TB in PLWH regardless of their CD4 count[16,37]—and isoniazid preventive therapy (IPT).[16,37] Prior to starting IPT, patients must be screened to rule out active TB—this is because the provision of isoniazid alone to someone with active TB will result in the development of isoniazid-resistant TB. Hence IPT initiation is typically closely tied to TB screening: first, PLWH are screened to rule out active TB (as described above), and if the screening is negative, they initiate IPT. IPT should be given for at least 6 to 9 months.[4]

Apart from choosing the right drugs for TB and HIV—are there other things I can do to improve TB outcomes in my co-infected patients?

Absolutely! Minimizing the delay to starting effective TB treatment is crucial—for all patients with active TB, but especially for those co-infected with HIV. It is also important to make all efforts to confirm the diagnosis of TB through microbiologic tests.[4] In order to avoid delays in treatment caused by delays in diagnosis, it may be reasonable to initiate TB treatment before results of your diagnostic evaluation have returned. The GeneXpert assay can be particularly useful in minimizing diagnostic delays as it provides results within a few hours; it has the added advantage of simultaneously testing for active TB and also the presence of resistance to rifampicin (which is a good marker of MDR-TB).

What anti-TB drug regimen should be used to treat active TB in PLWH?

PLWH with active pulmonary TB that are at low-risk of drug-resistant TB should be treated with an intensive phase of two months of isoniazid, rifampin, pyrazinamide and ethambutol (HRZE); followed by a four-month continuation phase of isoniazid and rifampin (HR). During both the intensive and continuation phases, treatment should be given daily (at least five days per week)—this is because intermittent treatment has been associated with increased risks of treatment failure and acquired drug resistance in PLWH.[4] There is some evidence to suggest that prolonging the continuation phase by 2 to 3 months – such that total treatment duration is 8 to 9 months—may reduce the risk of relapse.[38,39] Patients with extrapulmonary TB should be referred to a TB specialist as optimal management will depend on the site of disease—however, such referrals should not delay the initiation of TB treatment as delayed TB treatment increases the risk of mortality, particularly in PLWH.

In PLWH whose ART regimens contain protease inhibitors, rifabutin can be used in lieu of rifampin to minimize drug interactions.

I have just diagnosed active TB in an HIV-infected patient—they are not on ART, should I initiate ART? If so, when?

In general, because of toxicity and drug interactions, it is better for specialists to manage patients who need to be on ART and anti-TB therapy simultaneously. ART is indicated for all PLWH who have active TB, regardless of their CD4 count—as it lowers the risk of death.[4,6] For a number of years, there was clinical equipoise about whether the initiation of ART should be delayed until the end of TB treatment— the concern was that once the immune system started to reconstitute, the inflammatory response elicited by the presence of TB bacilli could result in clinical deterioration. However, a series of randomized controlled trials have addressed this question and provided clear-cut evidence of improved survival in patients that initiate ART within 8 weeks of starting TB treatment.[40,41] Hence the current recommendation is for PLWH with active TB that are not on ART to initiate active TB treatment first, and to subsequently initiate ART as soon as possible and with a maximum delay of 8 weeks from the start of TB treatment.[4,6]

I have just diagnosed active TB in a patient

with HIV infection who is already on ART— what TB treatment should I initiate?

As suggested above, because of the complicated interactions between TB medications and ART, these patients should be referred for urgent assessment by a specialist.

What about co-trimoxazole prophylaxis?

All PLWH who have active TB should receive co-trimoxazole throughout their TB treatment, as this has been shown to lower the risk of mortality.[4,6] Whether co-trimoxazole should be continued after TB treatment has ended will depend on the CD4 count—international or country specific guidelines should be referred to for further guidance.

CONCLUSIONS

As GPs are at the frontline of medical care, it is important for you to have an understanding of the multitude interactions between HIV and TB. The foundations to successful TB screening, prevention and treatment among PLWH are found in the recommendations enumerated in the STCI and WHO guidelines. For your patients that are PLWH who have not yet developed active TB, it is important to regularly screen for active TB and offer IPT for those that eligible. The institution of simple infection control measures in your clinics and hospitals can also protect your patients from acquiring TB infection. In patients that have developed active TB, minimizing diagnostic and treatment delays, testing for drug-resistant TB, using appropriate TB regimens, and initiating ART early on during TB treatment, can all greatly increase their chances of survival and relapse-free TB cure. Ideally, patients with TB and HIV co-infection should be managed by specialists. ■

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