The following questions were submitted by participants in the above Clinical Conundrums in Latent Tuberculosis Infection (LTBI) Treatment Webinar. The responses have been provided by the faculty members and CITC staff and relate to information presented during the training. To view the archived recording of the 12/18/12 training, please visit the following website: [http://www.currytbcenter.ucsf.edu/training/webarchive/conundrum/arch_ltbiconundrum.cfm](http://www.currytbcenter.ucsf.edu/training/webarchive/conundrum/arch_ltbiconundrum.cfm)

1. If someone has a negative interferon gamma release assay (IGRA) test, do they need a chest x-ray (CXR)?

   There may be circumstances where a CXR may be requested for person with negative IGRA (e.g., if person were a close contact and symptomatic).

2. Question re: when to get 2 view CXR for asymptomatic positive tuberculin skin test (TST) or IGRA- I thought that 2 views are used if chest not near adult size (mid to late teens depending on body size and maturity). Children >5 present primarily with adult-type pulmonary TB, or is there more of a mix?

   In general, two views are recommended for children <5. Certainly if there is question from PA view on an older child being evaluated for TB, other view(s) may be needed. Clinical judgment.

3. Can 6 months of INH be used in Asian refugees for LTBI treatment or is 9 months required?

   Yes, 9 months gives greater protection but 6 months INH (meaning 180 daily doses completed within 9 months) is considered an acceptable regimen.

4. What does 3HP stand for?

   3 months of isoniazid plus rifapentine taken once weekly by directly observed therapy.
5. We almost exclusively do LTBI in refugee populations. Often they come in for LTBI treatment for 6-8 months, then won't come in for 2 or 3 months. Would you look at them being completed at 6 months? Many times we cannot get the doses in within 9-12 months and have to restart LTBI treatment.

If 6 months of INH completed within 9 months timeframe, you could consider this completed treatment for LTBI. See the CDC MMWR on Targeted Tuberculin Testing and Treatment of Latent TB Infection. We have a link to this in our resources document.

6. Is anyone too old for LTBI treatment?

The age limit has been removed. Approach now is to assess risk - benefit.

7. Do you have any literature to support the practice of obtaining a CXR within the past 3 months of starting LTBI treatment?

The CDC guidelines do not specify a timeframe. The recommendation is a CXR be obtained for all persons being considered for LTBI treatment to exclude active pulmonary TB. Timeframes as to how recent may vary by jurisdiction. Depends on the comfort of the clinician treating as to how long from time of chest radiography to treatment initiation that would be considered safe.

8. In high risk category what is the definition for low body weight? A specific BMI?

See guidance contained within the CDC Targeted Tuberculin Testing and Treatment of LTBI.

9. Are there many TB programs who are using Skype for DOT?

Yes, some programs are using Skype. Some concerns have been raised about confidentiality with use of Skype. This form of observation is commonly referred to as 'video DOT'. Most jurisdictions that have included this approach have established local protocols for use.
10. After completing LTBI therapy, when would you do another CXR, i.e., in place of TST testing?

Typically the patient would only need another CXR if they become symptomatic for tuberculosis disease.

11. Are there some instances that you would recommend doing a repeat CXR well after the initial LTBI diagnosis is made? For example, I had an asymptomatic pregnant 30-y/o Ukrainian woman who worked in a TB hospital in the Ukraine. She had some abnormalities on her initial CXR 5 years earlier. Would it be worthwhile to repeat her CXR? Or are there other scenarios based on the prior CXR and epidemiology when repeating the CXR would be a good idea?

In the situation you described, whether or not a repeat CXR was warranted would depend upon the type of abnormalities found in her CXR and whether treatment for LTBI is now being considered. Typically you would want to establish that the CXR is stable and there is no disease process occurring prior to initiating treatment for LTBI. This process could require more than one CXR. Once you’ve determined the CXR is stable, repeat CXRs at regular intervals would not be required unless the person developed symptoms of TB disease.

In general, we do not repeat CXRs once it has been determined that the film is stable unless the individual becomes symptomatic for TB disease. When treating active disease, some jurisdictions have patients return to clinic 6-12 months after treatment completion for reassessment and a repeat CXR. This may be required for all patients or just those with high disease burden; it really depends upon the treating clinician and the local protocol.

12. In high risk category what is the definition for low body weight? A specific BMI?

We use this resource from Heartland to determine low body weight: http://www.heartlandntbc.org/products/bmi_card_oct_2008.pdf

13. Clients with the BCG immunization that test positive on a TST and their CXR is negative CDC recommends LTBI treatment, any ideas to get higher compliance? They start out well but are hard to get to finish the 9 month regimen.

It can be useful to instead use an IGRA to test those who’ve been BCG vaccinated.
14. For a client unknown to you, documentation of +IGRA, normal CXR history, client refuses preventive treatment: how often repeat CXR when screening tool for symptoms is normal?

A repeat CXR is not needed unless the person develops symptoms of TB disease in the future.

15. For B1 immigrants who report having prior undocumented treatment for TB disease and current disease is ruled out, do you treat for LTBI?

Other jurisdictions may do this differently, but we would typically advise questioning the patient on what medication they took, how many pills, for how long, was directly observed therapy done, etc. to try to arrive at a decision as to whether or not we should treat LTBI. You would also take into consideration factors such as the person's age and immune status along with the above. Once we had this additional information we would decide how best to proceed. There is not a standard practice for this particular situation.

16. What are the recommendations for individuals who report having a positive TST in the past and treatment for latent TB but have no records of this and now new employers are requiring documentation? If no documentation is found what would you recommend?

It depends upon what type of employment you are referring to. For health care workers, the employee would be required to have written documentation of the past positive test or treatment for LTBI. If they cannot provide this, a new baseline test result would have to be provided. If acceptable to the health care facility and available, an IGRA could be the best test to use in this situation.

17. To clarify your thoughts on giving credit for meds completed if a change is needed: you suggested counting the percentage of the first med completed and giving the second med LESS that amount. Is that correct? I know you said it's not set in stone, but is that what I'm understanding?

Correct.
18. Do you have to consider the gap between stopping one drug for LTBI treatment and starting another drug in determining length of treatment on the new drug?

I do – if the gap is greater than 2 months, I start over completely.

19. INH and rifapentine 12 doses in 16 weeks is the current recommendation. What is an acceptable gap between doses? What if more than one week gap?

This was not studied but a gap >4 weeks would not allow someone to complete within 16 weeks so should be evaluated carefully to determine the cause and the need to restart treatment or switch to a different regimen.

How do you address missed or late weekly doses? Are there guidelines for missed DOT doses on 3HP regimen?

Missed or late doses can be handled by resuming the regularly scheduled day the following week. The missed dose can be given at any time in the same week as long as 2 doses are at least 3 calendar days apart. This is OK to do for 1 or 2 doses over the course of treatment but it is not recommended to stack doses 3 days apart in order to complete treatment in <12 weeks.

Doses that are missed due to non-adherence or side-effects should be resumed if safe, as soon as possible to allow completion of the regimen on time.

20. Some males in early 30’s on INH/rifapentine have complained of chest pains and shortness of breath. Any thoughts on these symptoms?

I’ve not heard this complaint and can’t think why it might occur physiologically. I’d consider dosing with just the high dose INH one week and just rifapentine the next to see if you can link the symptoms to one particular drug though.
21. Has anyone experienced hypersensitivity reactions with rifapentine?

Hypersensitivity has been reported but appears to be uncommon. Given the lack of a clear definition for this syndrome, it’s difficult to determine the true frequency but severe hypersensitivity reactions are extremely rare.

22. Is there an age limit to use 3HP?

Currently 12 and up but there is data coming on the use in younger children

23. What is the drug interaction of 3HP and methadone?

Rifapentine induces CYP enzymes similar to rifampin and can decrease the effective levels of methadone and other meds

24. Would just like to clarify that 4 months of daily INH and rifampin IS an acceptable regimen in the US? Am I understanding correctly that this regimen is particularly appropriate when there is some degree of uncertainty as to whether a patient may actually have active TB?

This is an acceptable regimen and we use it in people who are culture negative but who have significant fibrosis that is still worrisome for low level active TB even with negative cultures

25. Regarding switching medications mid-treatment: When we perform an IGRA or TST and the result comes back positive we have no way of knowing if the person was exposed to MDR or XDR TB and what type they are infected with. If we start with INH and the person was exposed to MDR TB and let’s say 4 months into treatment we have to discontinue the INH for side effects reasons and start them on rifampin. Don’t we run the risk of them becoming resistant to rifampin if we only have them complete two or three months of treatment?

Resistance occurs through spontaneous mutations in organisms that are dividing. If you have adequately excluded active TB in a patient, the risk of acquired drug resistance from LTBI treatment should be essentially zero. In the scenario described, rifampin would not be an appropriate regimen for treating MDR-LTBI.
26. When diagnosing latent TB in a patient from a MDR TB area (i.e., Southeast Asia), should we worry that INH or rifampin would not be adequate for treating LTBI?

We worry but since the areas with increased rates of MDR TB still have far more drug susceptible disease and our treatments for MDR latent TB are costly and have minimal efficacy data, we go with the odds and treat for drug susceptible LTBI.

27. What would you do with a person who had a negative TST before anti-TNF alpha therapy, then positive TST after treatment? IGRA is positive, CXR unchanged from before treatment with anti-TNF alpha therapy.

Treat for LTBI!

28. What is the basis of the recommendation for INH 9 months for prophylaxis in TNF patients? Is rifampin an acceptable alternative?

The TNF patients are immunosuppressed, so they are more like children under 5 y/o or HIV/AIDS. Rifampin x 6 months would be the alternative.

29. What exactly is the anti-TNF alpha therapy used for? Only rheumatoid arthritis (RA)? Does this help to decrease pain? Does the anti-TNF alpha therapy decrease effectiveness of treatment for LTBI?

Anti-TNF alpha therapy is used for a variety of autoimmune based diseases (RA is just one, but derm uses these drugs to treat psoriatic arthritis, GI uses to treat Crohn's disease), the immunosuppression of anti-TNF alpha therapy makes us worried that a patient's immune system may not be as able to kill the TB. The anti-TNF alpha meds are used to decrease the inflammatory response and thus are really helpful for these disorders.

30. If a patient is already taking anti-TNF alpha therapy such as enbrel, it would be held for at least 1 month while LTBI treatment is given and then resumed after the month of LTBI completion?

Different people do different things - but waiting for a month at least is what most experts do, and you treat x 9 months. We don't think you need to wait until LTBI treatment is done to re-start anti-TNF alpha therapy.
31. 45 year old Hispanic woman, still traveling to Mexico annually. Before starting anti-TNF alpha therapy for RA, quantiferon was negative. CXR never done. Patient having zero pain at this time, never used steroids. Your advice. Should the provider stop anti-TNF alpha therapy and treat for LTBI? Get CXR now, if no fibrosis, continue?

This is a tricky one - Mexico is a medium risk country. I think I would give her two options - when traveling to Mexico, stop anti-TNF alpha therapy while there, and resume when she comes back and annual screening with TST and IGRA with low threshold to do CXR (or after every trip back to Mexico, do TST/IGRA). Any of these tests are positive with CXR negative, then treat for LTBI. If CXR with finding - need to evaluate for active TB.

32. What is the cost effectiveness of doing IGRA testing vs. TST testing (in LTBI treatment)?

You save money if you avoid CXRs and reduce the number of people you put on LTBI treatment (staff time). If you are doing large annual screening e.g., health care workers, homeless shelters, then the cost does add up. Any time anyone is BCG vaccinated, I think the IGRA is a good value. The trick is to only screen if there has been a new exposure subsequently - it's the serial screening that adds up. For high risk immunosuppression, like anti-TNF - that is a necessary cost to offset the risk of reactivation, new infection.

33. What treatment would you recommend for individuals with chronic hepatitis C virus (HCV) infection who are candidates for treatment of HCV. (Our GI team prefers LTBI be treated prior to treating HCV).

My understanding is that treatment for chronic HCV with interferon gamma is not a significant risk factor for progression to active TB. We don't require that patients go on treatment before HCV treatment – but I would treat with consideration of the degree of cirrhosis or liver disease – good options are rifampin or rifabutin, or the new 3HP regimen. If advanced cirrhosis – (these usually are not candidates for treatment), then fluoroquinolone (FQN).
34. When treating for LTBI are we actually attempting to kill the mycobacterium or are we just reinforcing the wall around the bacterium.

My understanding is that we’re trying to eradicate the small amount of TB in the body so that it cannot reactivate.

35. If a patient was exposed to active TB and treated for LTBI a few years ago, and now has been exposed again to active TB, CXR negative: Do you retreat for LTBI?

Patients previously exposed and treated for LTBI and exposed again with a (-) CXR are generally not retreated. Retreatment may be considered on a case-by-case basis for the following:
- Those recently exposed to drug resistant TB
- Those at risk for rapid progression to TB disease such as <5 yrs. of age, medical risk such as HIV or other immunosuppression, and other medical risks

36. Do any health care organizations require newly diagnosed LTBI employees to complete a regimen in order to continue employment?

I am not aware of any health care facilities or organizations that require newly diagnosed workers with LTBI to complete a course of treatment in order to continue employment. There may, however, be policy in high risk settings (HIV/AIDS units, NICU) that may differ.

37. Is there a maximum age at which you would not recommend LTBI treatment? I have a 95 y/o female resident of a long-term care facility (LTCF) who is 75 pounds and asymptomatic and I am more worried about her quality of life than activated TB in her future.

Most providers would consider risk-benefit when thinking about treating LTBI in the elderly or those with numerous co-morbidities. I doubt that most providers would treat a 95 y/o female weighing 75 pounds in a LTCF.

38. Do you consider low vitamin D levels as a risk category for breakdown?

Difficult to answer this question as definitive research on the association between vitamin D and TB has yet to be done.
39. Who pays for the medications -- public health, or insurance?

Payment for medications probably varies by TB program and jurisdiction. The Alaska TB program pays for all LTBI medications.

40. I am aware of interactions of oral contraceptives and Rifampin. What about other non oral contraception like implants and Depo-Provera? Any interactions with them?

Interactions with RIF and non-oral contraceptives – Any implant that relies upon estrogen or progestin to provide contraceptive effect will also have interactions. RIF is a potent hepatic enzyme inducer and has the potential to negatively affect this entire class of contraceptive methods.

41. I practice in a fairly affluent area & we have had several patients have a positive TST after having a screening required by their children's schools (to help in the classroom). We did get CXRs (all were negative), but there was a resistance to treat. Even the local ID physician & a pulmonologist had different opinions. They used age & living in low risk area as reasons not to treat. Any words of wisdom? I was taught & also using the guidelines, positive TST, negative CXR = LTBI = Treat.

I would agree that a decision to test (TST) should mean a decision to treat (LTBI). Persons with LTBI should be offered treatment once active TB has been ruled out. We cannot, however, mandate LTBI treatment.

42. What about 3HR?

While 3 HR is used in other countries, it is not an approved regimen for LTBI treatment in the US.