

# Let's Talk TB

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

## Monitoring and Improving Adherence to Tuberculosis Medications

Ramnath Subbaraman, MD, MSc, FACP<sup>1,2</sup> and Amrita Daftary, PhD, MPH<sup>3</sup>

<sup>1</sup>Department of Public Health and Community Medicine, Tufts University School of Medicine,

<sup>2</sup>Division of Infectious Diseases, Brigham and Women's Hospital and Harvard Medical School,

<sup>3</sup>McGill International TB Centre, McGill University, Canada

### Abstract

*Today, about 10% to 50% of all TB patients in India fail to complete treatment, depending on the type of TB the patient has. The consequences of poor adherence to TB treatment are disastrous, increasing the risk of patient morbidity and mortality, disease relapse, drug-resistance, and transmission of TB. While the Revised National TB Control Programme (RNTCP) has long relied upon direct observation of therapy (DOT) for TB patients, this monitoring strategy requires greater resources than are available to most GPs. New technologies for monitoring medication adherence—including cellphone-based strategies and electronic pillboxes—may soon become available to GPs in parts of India and provide alternative strategies for monitoring pill-taking by patients in real time. Once a GP identifies medication non-adherence, she or he should screen for and address toxicities from TB medications, poor nutrition and other comorbidities (e.g., HIV, diabetes), psychosocial barriers (e.g., depression, stigma, substance use disorders) and poor treatment literacy that could be contributing to non-adherence. Improving TB medication adherence therefore requires an interdisciplinary approach.*

with more in her life than just TB. But you know that the only way she can be cured is if she adheres to the full course of treatment. You will see her once a month for about 10 minutes. How are you going to monitor her medication adherence and support her in achieving this outcome?

Today, about 10% to 50% of all TB patients in India fail to complete treatment, depending on the type of TB the patient has.<sup>1</sup> The consequences of poor adherence to TB treatment are disastrous, increasing the risk of patient morbidity and mortality, disease relapse, drug-resistance, and transmission of TB.<sup>2,3</sup> In this chapter, we discuss strategies for GPs to monitor and improve a TB patient's medication adherence.

### MONITORING ADHERENCE TO TB MEDICATIONS

For more than a decade, India's Revised National TB Control Programme (RNTCP) has relied upon direct observation of therapy (DOT) to monitor medication adherence. DOT may be conducted at the health facility level or outsourced to family members or individuals in the community. Either way, DOT requires a trained individual to observe a TB patient take every dose of medication, which demands greater resources and supervision than are available to most GPs.

### INTRODUCTION

You have just informed your patient that she is to start TB treatment immediately. She has to take 4 drugs for 2 months, and continue to take 2 or 3 drugs for another 4 months. You know that this is a long and tedious regimen. You know that she will probably develop some side effects. You hope that she will not develop drug-resistance. You know that she is probably dealing

# Let's Talk TB

Monitoring and Improving Adherence to Tuberculosis Medications

## Table 1 — Examples of questions to ask tuberculosis patients at routine visits to identify non-adherence

### Single screening question<sup>8</sup>

Have you missed any of your TB pills in the past week?

### Morisky Questions<sup>8-10</sup> (any positive answer suggests significant non-adherence)

1. Do you ever forget to take your medications?
2. Are you careless at times about taking your medicine?
3. When you feel better, do you sometimes stop taking your medications?
4. Sometimes when you feel worse, do you stop taking your medicine?

In addition, it is unclear that DOT results in better treatment outcomes when compared to self-administered therapy (i.e., patients taking pills at home without observation).<sup>4,5</sup> DOT may result in loss of time, autonomy, and privacy; regular travel to a health facility may also lead to loss of money and employment.<sup>6,7</sup>

For most GPs, the only opportunity to evaluate TB medication non-adherence may be at brief monthly clinic visits. Single questions<sup>8</sup> or brief structured questionnaires, such as the Morisky scale<sup>9</sup> have been shown to have some value in detecting non-adherence in TB patients (Table 1).<sup>10</sup>

In addition, new technologies for monitoring TB medication

adherence are emerging in the public and private sector in India that record patients' pill-taking history via computer or cellphone applications. For example, the cellphone-based adherence monitoring strategy 99DOTS entails patients calling a phone number dispensed with each day's TB pills to report taking every dose (Figure 1).<sup>11</sup> Electronic pillboxes can record when the box containing TB drugs is opened and closed to indicate doses taken (Figure 2).<sup>12</sup> While these technologies do not guarantee pill intake, they can be useful proxies of adherence. As pill-taking records are continually updated in "real-time" and may be remotely accessed, GPs can rapidly identify non-adher-

ent patients and contact them to intervene early, before the next clinic appointment. Electronic pill-taking histories can also be used as longer-term records to help GPs to better counsel patients during monthly clinic visits. These novel technologies are currently being tested in India. Research is needed to determine how they can be best used by GPs and to understand whether they positively impact patient care.

## ADDRESSING TB MEDICATION NON-ADHERENCE: A FOUR-PRONGED APPROACH

The Standards for TB Care in India states, "[TB] treatment adherence goes beyond the realm of DOTS to a larger concept of treatment support system developed with mutual trust and respect between the patient, family, providers, treatment supporters and the health system at large to promptly identify and address all possible factors that could lead to treatment interruptions. This includes not only medical factors such as promptly addressing comorbidities, substance use, adverse drug reactions and emergencies but also spans out to addressing various social, vocational, nutritional, economic, psychological stress experienced by the patient "throughout the course of treatment" (p.55).<sup>13</sup> In other words, in order to support patients with treatment completion, we must tackle the clinical and social determinants of non-adherence.

When a patient with poor adherence to TB medications is identified, we suggest that GPs should screen for, and address, four major issues: (1) toxicities from TB medications, (2) poor nutrition; (3) medical comorbidities, and (4) psychosocial barriers (Figure 2).



Figure 1 — 99DOTS, a cellphone based strategy used to monitor TB medication adherence, in which patients dial a unique phone number dispensed with each day's doses to report pill-taking. (Photo with permission from Everwell Health Solutions)

# Let's Talk TB

Monitoring and Improving Adherence to Tuberculosis Medications

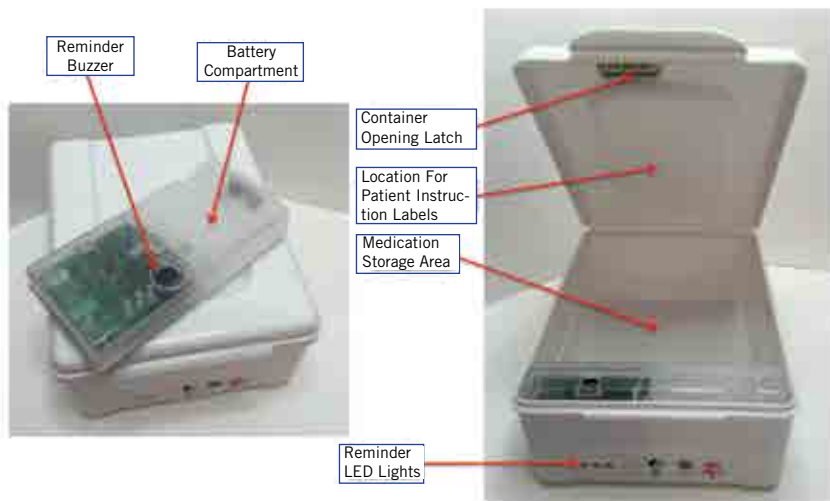


Figure 2 – The Medication Event Reminder Monitor, an electronic pillbox used to monitor TB medication adherence. The device contains an optional reminder audio buzzer and LED lights that glow everyday when the patient is scheduled to take his or her medication. Opening and closing the pillbox lid is recorded as a “dose taken” by the patient. (Photo with permission from the Arcady Group)

## TOXICITIES OF TB MEDICATIONS

Medication adverse effects may be a major cause of TB treatment interruption or poor medication adherence,<sup>14</sup> especially for patients with multidrug-resistant TB.<sup>15</sup> Patients with drug-susceptible TB should be educated about common

adverse effects of standard four-drug anti-tuberculosis therapy at the time of starting treatment. Early education will help ensure that harmless effects (e.g., orange-red discoloration of body fluids from rifampicin) and self-limited side effects that occur soon after starting treatment (e.g., mild

gastrointestinal symptoms such as nausea without liver function abnormalities) do not result in treatment interruption. Pyridoxine (vitamin B6) supplementation at a dose of 25mg to 50mg by mouth daily should be considered for all patients with risk factors for developing peripheral neuropathy (diabetes, HIV, malnutrition, and alcohol use), since prevention of isoniazid-related peripheral neuropathy will also prevent treatment interruptions.

At follow-up visits, GPs should routinely ask about concerning symptoms associated with serious adverse effects (e.g., loss of visual acuity as a sign of optic neuritis). Early identification of potential toxicities of TB medications may help to build patients’ confidence in their care providers, thereby improving adherence to medications. Detailed recommendations for screening for and managing drug toxicities are available in the chapter titled “Adverse Drug Events with Anti Tuberculosis Therapy.”

## NUTRITION

Nutrition and TB are closely intertwined, and undernutrition may adversely impact adherence to TB medications. Poor nutrition not only compromises the immune system and puts people at risk for developing TB, it makes diagnosed TB patients more susceptible to poorer clinical outcomes, lower quality of life, and death.<sup>16,17</sup> Undernutrition is also a major risk factor for drug-induced hepatitis from TB medications, which could lead to treatment interruption.<sup>18,19</sup>

Comprehensive nutritional support of TB patients has not been shown to reduce mortality, and as such is not recommended as a standard package of care to enable adherence to TB treatment. However, nutritional supplementation may

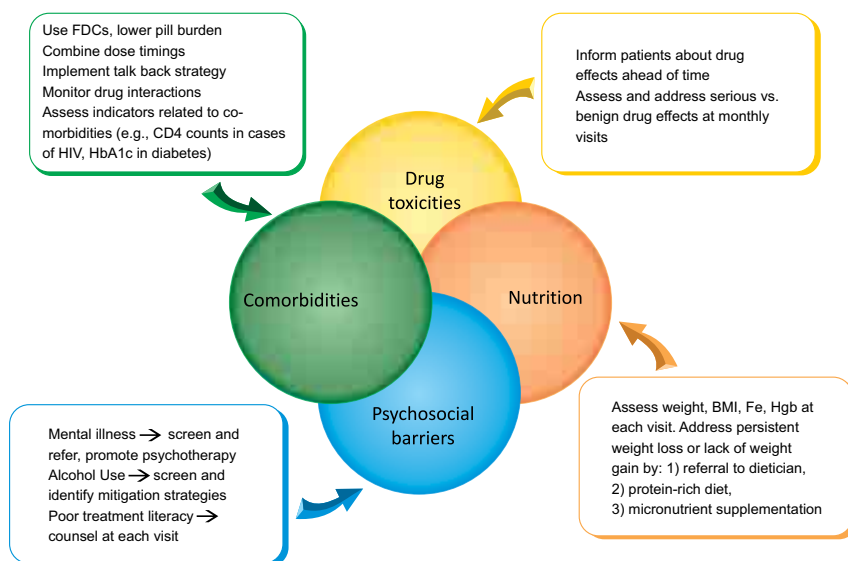


Figure 3 – Multi-pronged approach to addressing non-adherence

# Let's Talk TB

Monitoring and Improving Adherence to Tuberculosis Medications

**Table 2 — Strategies to promote medication adherence in TB patients with comorbidities**

1. Reduce the number of tablets by using fixed dose combinations wherever possible and eliminate unnecessary auxiliary medications
2. Simplify dose timings by combining medication doses for TB and other medical comorbidities when safe and appropriate
3. Implement a “talk-back” strategy at each visit by having the patient repeat back to you his or her understanding of the medications for each of his or her medical conditions
4. Monitor potential drug interactions and reactions, such as hypo or hyperglycemia in TB patients with diabetes (e.g., activity of sulfonylureas may be reduced with rifampicin and increased with isoniazid)

have positive impacts on patients' quality of life, including their capacity to continue to work and/or serve as caregivers. While the data are mixed, two small Indian studies suggest that provision of nutritional supplements may improve treatment completion rates<sup>20,21</sup> and other studies highlight improvements in physical functioning (measured using grip strength),<sup>21,22</sup> which could improve patients' overall participation in their TB care.

Guidance on assessing and managing nutritional status for TB patients is provided in a recent report from the Central TB Division.<sup>23</sup> GPs should assess patients' nutritional status at baseline and at monthly follow-up visits through clinical examination (e.g., evidence of temporal wasting), anthropometrics (e.g., height and weight to assess body mass index, mid-upper arm circumference), and labs (e.g., hemoglobin

and albumin).<sup>23</sup> GPs should provide nutritional counseling and support in the case of any patient who fails to regain normal BMI after 2 months of treatment or who loses weight during TB treatment, with particular attention to pregnant or breastfeeding women, children under the age of 5 years, and patients with MDR-TB or HIV coinfection.<sup>23</sup> In these cases, GPs should consider referral to a dietician and encourage increased daily protein intake, daily micronutrient supplementation (e.g., with a multivitamin), and ensure that these patients are taking pyridoxine to prevent development of peripheral neuropathy from isoniazid.<sup>23</sup> Locally available nutrient-rich or fortified supplementary foods may be prescribed on a case-by-case basis. Persisting malnutrition in TB patients on treatment should raise concern for poor medication adherence or drug-resistance.

**Table 3 — Screening questions to identify alcohol use disorder and depression in tuberculosis patients with poor adherence to medication**

**Alcohol use screening<sup>34</sup>** (answer of >0 to second question suggests alcohol use disorder)

1. Do you sometimes drink alcoholic beverages? (If the answer is yes, ask second question)
2. How many times in the last year have you had five (four for women) or more drinks in a day?

**Depression screening<sup>35</sup>** (any positive answer suggests possible clinical depression)

1. During the last month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?

## MEDICAL COMORBIDITIES

Diabetes and HIV are the most common comorbidities facing TB patients in India. TB patients who are also taking medications for diabetes or HIV may experience additional challenges in adhering to their TB treatment regimens due to a higher pill burden, drug-drug interactions, medical complications, as well as psychosocial issues. By discussing these comorbidities at each visit, and guiding patients through their multiple complex drug-regimens, GPs have the potential to improve adherence (Table 2). Issues specific to HIV comorbidity are discussed in the chapter “Management of HIV and TB: What Every GP Should Know.”

## PSYCHOSOCIAL BARRIERS TO ADHERENCE

Common psychosocial barriers that may impede patients' healthcare seeking behaviors and trigger non-adherence include poor treatment literacy,<sup>24</sup> alcohol use disorder,<sup>25</sup> stigma from TB or comorbid conditions,<sup>26</sup> and mental illness (especially depression and anxiety).<sup>27,28</sup>

Establishing basic TB treatment literacy is an important first step to promoting medication adherence.<sup>24</sup> Many GPs will not have counseling staff on-site or the time to deliver comprehensive patient counseling and education. Nonetheless, we recommend they cover at least 3 fundamental topics at the time of starting TB treatment: (1) explain TB disease, including potential consequences, and strategies for infection control; (2) explain the treatment regimen, including drugs, treatment duration, potential adverse effects; and (3) discuss the importance of adherence and consequences of non-adherence (i.e., mortality, transmission, relapse, drug-resistance). The chapter, “What Counselling and

Support Do Patients With Tuberculosis Need?" offers a more comprehensive framework for counseling patients with TB.

Alcohol use is common among TB patients in India and has been associated with poor treatment outcomes.<sup>29,30</sup> One study from South India found that 29% of TB patients currently used alcohol and 15% had alcohol use disorder (i.e., dependence or hazardous drinking behavior).<sup>25</sup> GPs can easily screen for alcohol disorder using brief questionnaires such as the AUDIT-C (**Table 3**). Peer-delivered psychotherapy has been shown to be helpful in alleviating alcohol use disorders in India.<sup>31</sup> An alcohol use intervention manual by the National Institute for Research in TB in Chennai is available online to guide GPs (<http://www.nirt.res.in/pdf/AlcoholManual.pdf>).<sup>32</sup> This intervention was recently found to increase TB treatment completion rates in a pilot study.<sup>33</sup> When tackling heavy drinking among TB patients, GPs can refer patients to mental health specialists and advise patients to eat before drinking, switch to low-alcohol beverages, pace the rate of drinking, and identify triggers such as peer pressure, so they may be avoided or proactively addressed.<sup>32</sup>

The social exclusion and stigma facing many TB patients may result in depression and contribute to poor medication adherence.<sup>27,28,36</sup> GPs should therefore evaluate for mental illness, especially depression, using simple screening questions (**Table 3**). GPs should consider referring TB patients with depression to a mental health specialist. However, access to mental health specialists is difficult in many parts of India. In these settings, GPs can implement psychotherapy interventions themselves or with the help of lay

counselors, as these interventions have been shown to reduce depressive symptoms in a number of communities in India.<sup>37-39</sup> GPs may also avail of mental health cell-phone applications, developed to assist care providers in providing evidence-based mental health care related to stress and depression.<sup>40</sup> Psychotherapy has been shown to improve medication adherence and treatment completion in Indian TB patients.<sup>41</sup> ■

## REFERENCES:

1. Central TB Division. TB India 2017: Revised National TB Control Programme annual status report. New Delhi: Ministry of Health and Family Welfare, 2017.
2. Thomas A, Gopi PG, Santha T, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. *International Journal of Tuberculosis and Lung Disease* 2005;9(5):556-61.
3. Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk factors associated with default among new smear positive TB patients treated under DOTS in India. *PLoS One* 2010;5(4): e10043.
4. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2015; (5):Cd003343.
5. Tian JH, Lu ZX, Bachmann MO, Song FJ. Effectiveness of directly observed treatment of tuberculosis: a systematic review of controlled studies. *International Journal of Tuberculosis and Lung Disease* 2014;18(9):1092-8.
6. Yellappa V, Lefevre P, Battaglioli T, Narayanan D, Van der Stuyft P. Coping with tuberculosis and directly observed treatment: a qualitative study among patients from South India. *BMC Health Services Research* 2016;16:283.
7. Sagbakken M, Frich JC, Bjune GA, Porter JD. Ethical aspects of directly observed treatment for tuberculosis: a cross-cultural comparison. *BMC Medical Ethics* 2013;14:25.
8. Stephenson B, Rowe B, Brian Haynes R, Macharia W, Leon G. Is this patient taking the treatment as prescribed? In: Simel D, Drummond R, eds. *Rational Clinical Examination*. New York: McGraw-Hill Publishing; 2008:173-82.
9. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care* 1986;24(1): 67-74.
10. van den Boogaard J, Lyimo RA, Boeree MJ, Kibiki GS, Aarnoutse RE. Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study. *Bulletin of the World Health Organization* 2011;89(9):632-9.
11. Cross A, Kumar M, Soren P, et al. 99DOTS: monitoring and improving TB medication adherence using mobile phones and augmented packaging [OA-414-05]. *Union World Conference on Lung Health*; 2015; Cape Town; 2015.
12. Liu X, Lewis JJ, Zhang H, et al. Effectiveness

of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. *PLoS Medicine* 2015;12(9): e1001876.

13. WHO Country Office for India. Standards for TB Care in India. New Delhi: World Health Organization, 2014.
14. Breen RA, Miller RF, Gorsuch T, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. *Thorax* 2006; 61(9):791-4.
15. Thomas BE, Shanmugam P, Malaisamy M, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. *PLoS One* 2016;11(1):e0147397.
16. Bhargava A, Chatterjee M, Jain Y, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS One* 2013;8(10):e77979.
17. Andrews J, Subbaraman R. Nutrition and tuberculosis. In: Sharma SK, Mohan A, eds. *Tuberculosis* (2nd edition). New Delhi: Jaypee Brothers Medical Publishers; 2008:646-55.
18. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. *American Journal of Respiratory and Critical Care Medicine* 2002;166(7): 916-9.
19. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996;51(2):132-6.
20. Sudarsanam TD, John J, Kang G, et al. Pilot randomized trial of nutritional supplementation in patients with tuberculosis and HIV-tuberculosis coinfection receiving directly observed short-course chemotherapy for tuberculosis. *Tropical Medicine & International Health* 2011; 16(6):699-706.
21. Jahnavi G, Sudha CH. Randomised controlled trial of food supplements in patients with newly diagnosed tuberculosis and wasting. *Singapore Medical Journal* 2010;51(12):957-62.
22. Paton NI, Chua YK, Earnest A, Chee CB. Randomized controlled trial of nutritional supplementation in patients with newly diagnosed tuberculosis and wasting. *American Journal of Clinical Nutrition* 2004;80(2):460-5.
23. Central TB Division. Guidance Document: Nutritional care and support for patients with tuberculosis in India. New Delhi: World Health Organization Country Office for India, 2017.
24. Achmat Z. Science and social justice: the lessons of HIV/AIDS activism in the struggle to eradicate tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2006;10(12):1312-7.
25. Suhadev M, Thomas BE, Raja Sakthivel M, et al. Alcohol use disorders (AUD) among tuberculosis patients: a study from Chennai, South India. *PLoS One* 2011;6(5):e19485.
26. Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR. Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. *Social Science & Medicine* 2005;60(8):1845-53.
27. Sweetland A, Kritski A, Oquendo M, et al. Addressing the tuberculosis-depression syndemic to end the tuberculosis epidemic. *International Journal of Tuberculosis and Lung Disease* 2017; 21(8): 852-61.
28. Sweetland A, Oquendo M, Wickramaratne P, Weissman M, Wainberg M. Depression: a silent

# Let's Talk TB

Monitoring and Improving Adherence to Tuberculosis Medications

driver of the global tuberculosis epidemic. *World Psychiatry* 2014;13(3):325-6.

**29.** Ramachandran G, Agibothu Kupparam HK, Vedhachalam C, et al. Factors Influencing Tuberculosis Treatment Outcome in Adult Patients Treated with Thrice-Weekly Regimens in India. *Antimicrobial Agents and Chemotherapy* 2017;61(5):e02464-16.

**30.** Bagchi S, Ambe G, Sathiakumar N. Determinants of poor adherence to anti-tuberculosis treatment in Mumbai, India. *International Journal of Preventive Medicine* 2010;1(4):223-32.

**31.** Nadkarni A, Weobong B, Weiss HA, et al. Counselling for Alcohol Problems (CAP), a lay counsellor-delivered brief psychological treatment for harmful drinking in men, in primary care in India: a randomised controlled trial. *Lancet* 2017; 389(10065):186-95.

**32.** Department of Social and Behavioral Research at the National Institute for Research in Tuberculosis. Alcohol use intervention manual. Chennai: National Institute for Research in Tuberculosis, 2014.

**33.** Thomas BE, Watson B, Senthil EK, et al. Alcohol intervention strategy among tuberculosis patients: a pilot study from South India. *International Journal of Tuberculosis and Lung Disease* 2017; 21(8):947-52.

**34.** Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. Primary care validation of a single-question alcohol screening test. *Journal of General Internal Medicine* 2009;24(7):783-8.

**35.** Williams J, Steffen D. Is this patient clinically depressed? In: Keitz S, Simel D, Rennie D, eds. *Rational Clinical Examination*. New York: McGraw-Hill Publishing; 2009:247-63.

**36.** Mason PH, Sweetland AC, Fox GJ, Halovic S, Nguyen TA, Marks GB. Tuberculosis and mental health in the Asia-Pacific. *Australasian Psychiatry* 2016;24(6): 553-5.

**37.** Singla DR, Kohrt BA, Murray LK, Anand A, Chorpita BF, Patel V. Psychological Treatments for the World: Lessons from Low- and Middle-Income Countries. *Annual Review of Clinical*

*Psychology* 2017;13:149-81.

**38.** Patel V, Weobong B, Weiss HA, et al. The Healthy Activity Program (HAP), a lay counsellor-delivered brief psychological treatment for severe depression, in primary care in India: a randomised controlled trial. *Lancet* 2017;389(10065): 176-85.

**39.** Shidhaye R, Murhar V, Gangale S, et al. The effect of VISHRAM, a grass-roots community-based mental health programme, on the treatment gap for depression in rural communities in India: a population-based study. *Lancet Psychiatry* 2017;4(2):128-35.

**40.** Maulik PK, Kallakuri S, Devarapalli S, Vadlamani VK, Jha V, Patel A. Increasing use of mental health services in remote areas using mobile technology: a pre-post evaluation of the SMART Mental Health project in rural India. *Journal of Global Health* 2017;7(1):010408.

**41.** Janmeja AK, Das SK, Bhargava R, Chavan BS. Psychotherapy improves compliance with tuberculosis treatment. *Respiration* 2005;72(4):375-80.

# CIS CME—Questions

Monitoring and Improving Adherence to  
Tuberculosis Medications

## Questions

Mohan is a 53 year old man who visits your office with a month of productive cough, 8 kilograms of weight loss, and night sweats. He has type II diabetes, for which he takes glyburide 5mg twice a day. He has a pleasant demeanor and you learn he is an avid cricket fan.

In your initial investigation, you find that a chest X-ray shows a right upper lobe infiltrate, and sputum microscopy shows 2+ acid fast bacilli. He denies ever having had TB previously. You diagnose Mohan with pulmonary tuberculosis (TB) and decide to initiate him on once-daily treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol (AKT-4). He weighs 53 kilograms at the time of your initial evaluation.

**1 As you start Mohan on TB therapy, what counseling should you provide to counter potential medication adverse effects and to minimize drug-drug interactions, so that he is more likely to adhere and complete therapy?**

- Advise him that he should not worry if his urine or tears turn red-orange color while on therapy
- Tell him that his TB medications should only be taken at bedtime
- Prescribe pyridoxine (vitamin B6) 50mg by mouth daily
- Advise him to visit his diabetes doctor soon after starting TB therapy, due to a risk of poorer blood sugar control while on TB therapy
- Both A and C
- A, C, and D

**2 You see Mohan again more than 6 weeks after starting TB therapy. His weight has dropped from 53kg to 48kg, and he has evidence of temporal wasting. When you talk to him, he endorses ongoing fatigue and night sweats. You worry that he does not seem to be improving clinically after starting TB therapy. What should you do?**

- Order a GeneXpert MTB/Rif test, line probe assay, or other drug susceptibility testing, if not sent already at the time of diagnosis
- Carefully screen for poor medication adherence using questions about his pill-taking
- Empirically add injection streptomycin to his medication regimen
- Inquire about the quality of his diet and refer him to a dietician
- Start a rapid prednisone taper
- A, B, and D
- A, B, and C

**3 You look in his chart and see that a GeneXpert test sent at the start of therapy was negative for rifampicin resistance. You ask the patient about his medication adherence, and he admits to only taking his TB medications twice in the last week. Upon more careful questioning using the Morisky questions, the patient notes that he experienced some clinical improvement after taking his medications regularly for the first 2 weeks, but then he stopped taking his medications as frequently because he was starting to feel better. He also notes that he often forgets to take his medications due to his busy work schedule and confusion with his diabetes medications.**

**What messages can you share with Mohan to ensure that he takes his TB medications every day?**

*(Questions continued on the next page)*

# CIS CME—Questions

Monitoring and Improving Adherence to  
Tuberculosis Medications  
(Continued)

## Questions

- a. Tell Mohan to stop taking his TB medications if he has acid reflux or mild nausea for the hour immediately after taking his medications
- b. Remind Mohan of the consequences of poor medication adherence or stopping TB therapy early, including risk of treatment failure, disease relapse, development of drug-resistant TB, and transmission of TB to family members
- c. Recommend that Mohan set a daily alarm on his phone to remind him to take his pills
- d. Advise him to stop taking his diabetes medications because curing TB is more important in the short term
- e. Advise Mohan to involve his wife or other family members in his care (if he has disclosed his diagnosis to them) to help remind him to take his pills and observe him taking them
- f. Ask him to repeat back your instructions about how and when he should take his TB and diabetes medications
- g. A, B, and D
- h. B, C, E, and F

4

**On follow-up visits for the next two months, Mohan reports improved medication adherence, and his weight increased and symptoms improved. However, he misses his fifth month visit. You call him and Mohan comes into your clinic one week later with his wife. He looks disheveled, does not make eye contact, and provides terse answers during your interview. He smells of alcohol. His wife notes that he becomes intermittently tearful at home and stopped going to work three weeks ago. He stopped taking his TB medications completely at that time.**

**What should you do?**

- a. Tell him that he has finished four and a half months of TB therapy, so it is OK to stop
- b. Screen for clinical depression using simple questions and consider referral to a mental health specialist
- c. Screen for alcohol use disorder using simple questions and consider referral to a mental health specialist
- d. Discuss Mohan's family and social support system with him and his wife
- e. B, C, and D

5

**Before the visit is finished, the patient's wife notes that the patient has started drinking alcohol heavily again (around 7 or 8 drinks a day) after years of sobriety and asks for you to provide advice about the patient's alcohol use disorder. What should you advise?**

- a. Warn the patient about the increased risk of hepatotoxicity of TB medications when taken with alcohol, and encourage him to contact you quickly for any intractable vomiting or jaundice
- b. Identify triggers of his alcohol use (including peer pressure from friends) and recommend strategies for minimizing contacts with these triggers
- c. Tell him that he is at fault for his drinking and state that you will no longer see him at follow-up visits unless he stops drinking
- d. Advise him to eat before drinking to blunt the effects of the alcohol
- e. A, B, and D

(See answers on the next page)



## Answers

- 1** **The correct answer is (F).** Rifampicin often turns body fluids a red-orange color. Alerting patients ahead of time to this benign side effect may help minimize unnecessary concern or interruptions in therapy.

Pyridoxine should be considered for all patients starting TB therapy including isoniazid, but Mohan is at particularly high risk for isoniazid-related peripheral neuropathy due to his diabetes, which can also cause peripheral neuropathy. People living with HIV, malnourished patients, and patients on other medications that can cause peripheral neuropathy (e.g., multidrug resistant TB patients on ethionamide, cycloserine, or linezolid) are also at higher risk for isoniazid-related peripheral neuropathy.

Rifampicin can decrease blood levels of sulfonylureas used to treat diabetes, including glyburide, which can result in worsened blood sugar control in some patients.<sup>1,2</sup> As such, patients on sulfonylurea medications should have their diabetes monitored closely, as they may require modifications of their medications while on TB therapy.

There is no specific requirement that patients should take their TB medications only at bedtime. In general, for patients on standard therapy for drug-susceptible TB, it is important that patients take their medications at the same time every day (whether in the morning or at night). TB medications are best absorbed if taken on an empty stomach; however, for patients with significant gastrointestinal side effects, taking medications with food may be considered to reduce these side effects.

- 2** **The correct answer is (F).** Ongoing weight loss after weeks of TB therapy should raise concern for potential drug-resistance, poor medication adherence, and poor quality of the patient's diet. Per the Standards for TB Care in India, drug susceptibility testing (DST) should be offered to all diagnosed TB patients prior to starting therapy;<sup>3</sup> however, in cases where DST was not done at the initiation of therapy, failure to respond to therapy as evidenced by ongoing weight loss should prompt GPs to send a DST.

Ongoing weight loss may also suggest that a patient is not taking his or her medications, so screening for non-adherence using simple questions (such as the Morisky questions) is important.

Low caloric intake and poor protein intake may blunt replenishment of the patient's nutritional stores, especially in patients with food insecurity, vegetarian patients with poor protein intake, and patients with a high catabolic state from other comorbidities (e.g., HIV cachexia).

Streptomycin alone should not be added empirically to the patient's medication regimen. If there is high concern for drug-resistant TB, DST should be performed, and empiric multidrug-resistant TB therapy (which would involve addition of multiple medications) can be considered in some cases pending the DST result.

While a prednisone taper might briefly increase the patient's weight and temporarily improve symptoms, it would not improve the patient's long-term response to TB therapy.

- 3** **The correct answer is (H).** Unfortunately, evidence-based data about the best approaches for ensuring adherence to TB medications are lacking. However, some common-sense strategies for improving medication adherence include improving

*(Answers continued on the next page)*

# CIS CME—Answers

Monitoring and Improving Adherence to  
Tuberculosis Medications  
*Questions on pages 105 and 106*

## Answers

the patient's treatment literacy (by educating about the consequences of non-adherence), setting daily reminders to facilitate pill-taking, involving close family members in the patient's TB care, and implementing a "talk back" strategy at each visit, in which the patient repeats back your recommendations to confirm his or her understanding.

Patients should not stop TB medications for acid reflux or mild nausea, though they should get in touch with their GP. GPs can then check LFTs to rule out hepatotoxicity and recommend therapies to reduce these GI side effects, such as antacids.

Maintaining good glycemic control is important during TB therapy, and patients should not be advised to stop their diabetes medications while on TB therapy.

- 4** **The correct answer is (E).** Depression and alcohol use disorder are two common barriers to TB medication adherence. Simple questionnaires—such as the Patient Health Questionnaire-2 (for depression) and the AUDIT-C (for alcohol use disorder)—can be easily implemented during brief patient visits to screen for these problems. Ideally, patients should be referred to mental health specialists to help with these problems; however, finding a qualified specialist can be difficult in many areas of India. Encouraging compassionate, non-judgmental involvement from a patient's family members can sometimes provide the social support needed to get through TB therapy.

The patient should not be advised to stop TB therapy, because premature termination of therapy will increase the risk for relapse of TB.

- 5** **The correct answer is (E).** Patients with alcohol use disorder should be reminded about the increased risk of hepatotoxicity from TB medications. Identifying triggers that lead the patient to use alcohol heavily may help patients to reflect upon how they can avoid these triggers and cut down on drinking. For heavy drinkers, eating before drinking may improve nutritional status and blunt the effects of alcohol.

It is important to have a non-judgmental approach to patients with substance use disorders. Patients are more likely to have ongoing engagement with healthcare providers who are open and compassionate. Recent studies suggest that supportive engagement of patients with alcohol use disorder can improve their TB treatment outcomes.<sup>4</sup>