



**A CLINICAL GUIDE FOR HEALTH CARE PROVIDERS
AND PUBLIC HEALTH PROGRAMS**

Testing and Treatment of Latent Tuberculosis Infection in the United States

THIRD EDITION

Formerly titled *Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations – A Guide for Health Care Providers and Public Health Programs*

NTCA NSTC



National Society of
Tuberculosis Clinicians

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Testing and Treatment of Latent Tuberculosis Infection in the United States: A Clinical Guide for Health Care Providers and Public Health Programs

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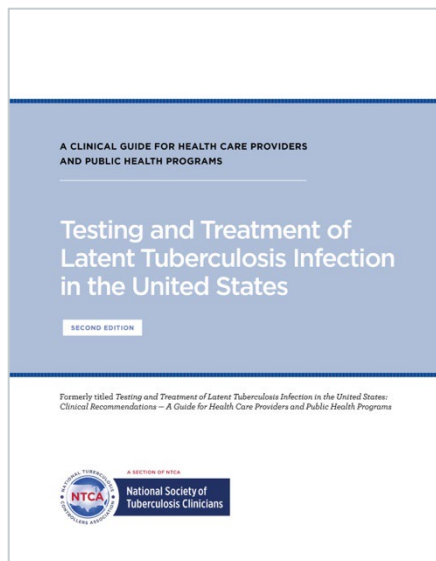


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Preface

The incidence rate of active tuberculosis (TB) disease in the United States is decreasing gradually, recently by 1.3% per year. However, an estimated 13 million persons in the United States have latent TB infection (LTBI) and face a lifelong threat of active TB disease, which treatment would prevent.

For the United States to speed its progress toward eliminating TB requires prevention: interrupting exposures to contagious cases, investigating contacts, and treating those persons who are at risk of developing TB disease. LTBI testing and treatment is an essential component of prevention and elimination of TB in our communities that reduces the lifetime risk of TB for these patients and the future transmission of TB in the community.

Historically, several barriers have blocked the effective, widespread use of LTBI testing and treatment to prevent active TB disease. TB programs in state and local health departments have been unable to reach and treat many of the persons who are infected with TB. When testing for TB infection is possible, testing algorithms require treating many persons in order to prevent one case of active TB disease. Isoniazid regimens tend to be longer and have poor completion rates and potentially serious isoniazid-associated adverse effects. Further complicating these challenges, there have been misconceptions about TB testing and prevention in the general medical and patient communities.

There are techniques and tools to overcome several of these barriers. Risk-based testing is used to prioritize those who might benefit from treatment. Newer, shorter rifamycin-based treatment regimens have dramatically increased rates of treatment completion and decreased rates of serious adverse effects. However, reaching a greater proportion of persons who are infected has proven difficult for state and local health departments. Improving TB prevention will depend on integrating it into primary health care and specialty medical care for persons with specific risk factors for TB, such as diabetes or human immunodeficiency virus (HIV) infection.

To promote these advances in TB prevention and broaden the foundations of knowledge about LTBI testing and treatment among health care providers throughout the United States, the National Society of Tuberculosis Clinicians has drawn upon published evidence and a network of national experts to prepare practical guidance on diagnosing and treating LTBI.

The *Testing and Treatment of Latent Tuberculosis Infection in the United States: A Clinical Guide for Health Care Providers and Public Health Programs* was developed for community health care providers and managers in diverse settings where TB prevention is not a primary focus, as well as for practitioners in state and local TB programs. Recommendations include the latest information on assessing for TB risks, testing for infection, evaluating the patient, selecting a regimen, and monitoring treatment. This document serves as a companion to the national guidance on treatment regimens, "Guidelines for the Treatment of Latent Tuberculosis Infection:

PREFACE

Recommendations from the National Tuberculosis Controllers Association and CDC, 2020." Also described are some of the advantages of nurse case management and provide resources for practitioners who want to learn more about it. Nurse case management is an effective strategy for integrating the multiple aspects of patient care and improving outcomes. It has been adopted in many state and local TB control programs and in other settings, such as health maintenance organizations, community health centers, and correctional facilities.

It is hoped that *Testing and Treatment of Latent Tuberculosis Infection in the United States: A Clinical Guide for Health Care Providers and Public Health Programs* will inform and empower more health care providers to test more patients at risk for TB and to treat those with LTBI. With each patient who completes a course of LTBI therapy, we not only reduce the future risk of TB for that patient, but we also bring the United States closer to eliminating TB in our communities.

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Abbreviations

1HP	1-month isoniazid-rifapentine treatment regimen
3HP	12-week isoniazid-rifapentine treatment regimen
3HR	3-month isoniazid-rifampin treatment regimen
4R	4-month rifampin treatment regimen
6H	6-month isoniazid treatment regimen
9H	9-month isoniazid treatment regimen
AFB	acid-fast bacilli
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATS	American Thoracic Society
BCG	bacille Calmette-Guérin
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CD4	cluster of differentiation 4
CKD	chronic kidney disease
CXR	chest radiograph
DOT	directly observed therapy
ELISA	enzyme-linked immunosorbent assay
ESRD	end-stage renal disease
FDA	Food and Drug Administration
H, INH	isoniazid
HCP	health care personnel
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assay
IL-6	interleukin-6
IL-17	interleukin-17

ABBREVIATIONS

IL-23	interleukin-23
INR	international normalized ratio
JAK	Janus kinase
LTBI	latent tuberculosis infection
MDR	multidrug-resistant
NAAT	nucleic acid amplification test
NTCA	National Tuberculosis Coalition of America
P or RPT	rifapentine
PPD	purified protein derivative
PT	prothrombin time
PTT	partial thromboplastin time
QFT-Plus	QuantiFERON®-TB Gold Plus
R, RIF, or RMP	rifampin
RB, RBT, or RBU	rifabutin
SAT	self-administered therapy
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SLE	systemic lupus erythematosus
TB	tuberculosis
TNF-alpha	tumor necrosis factor-alpha
T-Spot	T-SPOT®.TB
TST	tuberculin skin test
ULN	upper limit of normal
USPSTF	United States Preventive Services Task Force
vDOT	video directly observed therapy
WBC	white blood cell count

SECTION 1:

Immunologic Tests for Tuberculosis Infection

OVERVIEW

Latent tuberculosis infection (LTBI) is a symptom-free clinical state diagnosed by a positive test result for *Mycobacterium tuberculosis*-complex infection and an absence of clinical and radiographic findings of active tuberculosis (TB) disease. LTBI is presumed to be either a quiescent infection with *M. tuberculosis* or an indolent infection that is in equilibrium with the immune response to it. Treating the infection has a high likelihood of preventing active TB disease.

Immune-competent persons with LTBI have a risk of developing active TB that is about 5% in the first two years after initial infection and about 10% over a lifetime. In persons with untreated HIV infection, the **annual risk** is about 10%.

Testing for *M. tuberculosis* infection is indirect and based on immune recall responses following prior sensitization to *M. tuberculosis* antigens. The US Food and Drug Administration (FDA) has approved two methods of immunologic testing for *M. tuberculosis* infection: interferon-gamma release assays (IGRAs) and the tuberculin skin test (TST).

GENERAL PRINCIPLES

Follow these general principles when testing and interpreting tests for *M. tuberculosis* infection:

- ◆ Test only people at increased risk for TB to minimize the number and proportion of positive test results that are false-positives, which can be expected from testing low-risk persons. (However, in some jurisdictions and institutions these tests may be required by law, health code, or policy.)
 - ◆ Select the optimal test for each patient.
 - ◆ When interpreting test results for a diagnosis, consider patient-related and test-related variability factors.
 - ◆ None of these tests definitively predicts which persons with a positive result will develop active TB disease.
 - ◆ During or after treatment, IGRA and TST results are not informative for monitoring response to treatment of LTBI or active TB disease and should not be used for this purpose.
 - ◆ TST results can be expected to remain positive during and after treatment. Positive IGRA test results may be less durable than positive TST results.
- ◆ None of these tests is 100% sensitive or 100% specific:
 - ▶ People with LTBI can have negative test results. This is more common among people whose immunity is modified or impaired, but false negative results are possible without altered immunity.
 - ▶ People with active TB disease can have negative test results for infection. These tests should not be used to exclude active TB disease in someone with signs or symptoms consistent with active disease.
 - ▶ A positive result is not diagnostic of active TB disease in someone with signs or symptoms that are suggestive of active TB disease. A full clinical evaluation must be completed.

SECTION 1: IMMUNOLOGIC TESTS FOR TUBERCULOSIS INFECTION

<h3>CLINICAL BACKGROUND</h3> <p>Review the information below to guide test selection and interpretation of results:</p> <ol style="list-style-type: none">1. Test Descriptions2. Test Selection3. Test Procedures and Interpretation4. Next: Section 2: When to Test for LTBI <h3>RELATED TOPICS</h3> <ul style="list-style-type: none">◆ Section 2: When to Test for LTBI◆ Section 5: Considerations for Specific Populations	<h3>WARNINGS</h3> <ul style="list-style-type: none">◆ Patients who have signs, symptoms, or findings suggestive of active TB disease should be evaluated with bacteriologic studies and other methods specific to the site of disease.◆ Screen and test persons with an increased risk of TB, especially when there is also an increased risk of progression to active TB disease because of comorbidities.
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TEST DESCRIPTIONS

Interferon-Gamma Release Assays

The two IGRAs currently available for use in the United States are **T-SPOT®.TB (T-Spot)** and **QuantiFERON®-TB Gold Plus (QFT-Plus)**, the fourth generation of this test. Both tests require heparin-anticoagulated whole blood. For each, the specimens must be collected and handled in strict accordance with the test's instructions.

The IGRA antigens are designed to optimize test specificity. In these tests, synthetic polypeptide mixtures simulate proteins (antigens) that trigger sensitized T cells to release interferon-gamma. Each IGRA test runs two antigen mixtures simultaneously and includes a mitogen (positive) control and a nil (negative) control. In the positive control, the mitogen triggers the release of interferon-gamma to confirm that the sample contains enough responsive T cells and that interferon-gamma can be released and detected during the test. The nil (negative) control adjusts for nonspecific background release of interferon-gamma and other factors. When interpreting the results, the nil (negative) control is subtracted from the unadjusted antigen response values for both tests. The nil (negative) control is also subtracted from the unadjusted mitogen response value for QFT-Plus but not for T-Spot.

For test specificity, the IGRA antigens were selected because they are not found in bacille Calmette-Guérin (BCG), a live vaccine against TB that is administered at birth or during childhood in many countries but not in the United States. The IGRA antigens also do not match antigens from the majority of non-tuberculous mycobacteria. However, the IGRA antigen mixtures do match antigens from *Mycobacterium marinum*, *M. kansasii*, *M. goodii*, and *M. szulgai*, so infection with one of these organisms can cause positive IGRA results. Additionally, a positive T-Spot result was reported for one patient with *M. xenopi* infection. The IGRA antigens match antigens from *M. leprae*, but depending on the form of leprosy, the altered immunity from that disease can confound the results.

Tuberculin Skin Test

Two tuberculin-purified protein derivative (PPD) solutions are FDA approved for use in skin testing: **Aplisol®** and **Tubersol®**. In a TST, 0.10 ml of antigen solution is injected intradermally on the palmar surface of the forearm. The indurated reaction at the injection site is measured by palpation at the transverse axis of the arm after 48 to 72 hours and interpreted using cut-points established for different populations.

The tuberculin PPD solution contains antigenic compounds, mostly proteins secreted by *M. tuberculosis*-complex organisms. They also match or resemble antigens from BCG and non-tuberculous mycobacteria, which contributes to cross-sensitivity.

SECTION 1: IMMUNOLOGIC TESTS FOR TUBERCULOSIS INFECTION

BCG vaccination and infection cause false-positive TST results in some recipients because of the shared antigens. The likelihood of a false-positive TST result increases with the number of BCG doses given and decreases with time after the BCG vaccination. Persons who were vaccinated at birth are unlikely to have a false-positive TST result from BCG after 2 years of age. However, repeating TSTs can cause sustained BCG-associated false-positive TST results. IGRA results are not affected by BCG vaccination.

Infections with common non-tuberculous mycobacteria, such as *M. avium*, also can cause false-positive TST results. Asymptomatic infections with these mycobacteria are common, especially in persons from rural areas or tropical countries. IGRAs are not affected by this cross-reactivity except with *M. kansasii*, *M. szulgai*, *M. marinum*, and *M. goodii*, which may be pathogenic and can cause positive IGRA and TST results.

TEST SELECTION

In current diagnostic guidelines, IGRAs are generally preferred, but the TST is acceptable. Refer to **Table 1** for a comparison of the IGRA and TST. In choosing which test to use, consider the patient's history of BCG, age, and ability to return for a second appointment. IGRAs offer greater specificity than a TST in persons who were BCG vaccinated or who have non-tuberculous mycobacterial infections. For this reason, IGRAs are preferred for most non-US-born patients who received, or may have received, BCG vaccination. For other persons, either a TST or IGRA can be used depending on test availability and cost.



BCG VACCINATION POLICIES BY COUNTRY

Most people born outside of the United States have received BCG vaccination. To review the current and past national vaccination policy of a specific country, the *BCG World Atlas* offers a convenient way to find the information online at <http://bcgatlas.org/index.php>

IGRAs and TST have similar sensitivity for diagnosing infection in clinical studies among patients who have culture-confirmed active TB disease, and this similarity is assumed to extend to patients with LTBI, that is, with TB infection that has not progressed to active TB disease. In studies directly comparing the IGRA tests and TST, discordance of results is common. The most common pattern of discordance is a positive TST result with a negative IGRA result. This discordance is partially attributable to the known effects of BCG vaccination on test results, but it has not been fully explained by studies to date.

SECTION 1: IMMUNOLOGIC TESTS FOR TUBERCULOSIS INFECTION

For the pediatric use of IGRAs, relatively few infants and toddlers were included in the early studies of these tests. The rates of indeterminate or invalid results were greater in younger age groups in some studies, and the reliability of negative results was unconfirmed, leading to initial hesitation in adopting IGRAs in pediatrics. That opinion may be changing as findings from recent studies and general experience with IGRAs have been favorable. Some experts now prefer IGRAs over TST for testing all BCG-vaccinated children, regardless of age. However, 2016 Centers for Disease Control and Prevention (CDC) guidance lists TST as the preferred test for healthy children aged <5 years, and 2021 American Academy of Pediatrics guidance lists TST as the preferred test for children aged <2 years, and in some circumstances IGRAs are acceptable. In FDA-approved labeling, QFT-Plus has not been extensively evaluated in persons aged <17 years, and T-Spot has not been adequately evaluated in persons aged <2 years.

Pregnant persons have not been included in large enough numbers in studies of IGRAs for QFT-Plus or T-Spot labeling to advise on the use of these tests during pregnancy. No evidence has accumulated for a preference between TST and IGRAs during pregnancy, and either test can be used when testing is indicated by risk for infection or progression. IGRAs may be preferred for testing persons who were born in countries with systematic BCG vaccination or who might not return for the reading of a skin test.

Skin testing requires two health care appointments: the first to administer the test and the second to measure the reaction. IGRAs are preferred for persons who would have difficulty returning for a second appointment.

Table 1. Comparison of the Interferon-Gamma Release Assay and Tuberculin Skin Test

IGRA	TST
<i>In vitro</i> test, indirect	<i>In vivo</i> test, indirect
More specific antigens	Less specific antigens
Requires a blood test	Requires an intradermal test
Detects interferon-gamma release	Interpreted by induration, not erythema
A prior IGRA does not boost a subsequent IGRA; a prior TST can boost the IGRA after 72 hours and up to 6 months	A prior TST can boost a subsequent TST or IGRA
1 to 2 patient visits	2 to 4 patient visits
Fixed interpretation criteria	Risk-stratified interpretation
Results in 1 to 2 days (although batching extends the turnaround time)	Results in 2 to 3 days (10 days for two-step testing)
Not affected by BCG or most non-tuberculous mycobacteria	Cross-reacts with BCG and non-tuberculous mycobacteria
Standard laboratory reporting in medical records	Variability in where results are recorded

Interferon-Gamma Release Assay Selection

T-Spot and QFT-Plus perform similarly at the population level, and neither test has clear diagnostic advantages in sensitivity or specificity for any patient group that has been studied with direct comparison of the tests. In direct patient-by-patient comparisons of T-Spot and previous generations of QuantiFERON, concordance of results was moderate, without clear patterns that would explain discordant results.

The IGRA selection can be made based on convenience, cost, turn-around-time, customer service, dependability, and familiarity. An excess of unexplained indeterminate (QFT-Plus) or invalid (T-Spot) results or test wastage because of specimen handling errors may indicate a need to switch between products for operational reasons or to investigate and correct the causes of these issues.

Immunocompromised Patients

Both of the general test methods, TST and IGRAs, depend on intact immunity for positive results. Altered immunity, for example, immunosuppression, can cause false-negative results from either test method. Neither method used alone is superior for testing immunosuppressed patients. However, dual testing with TST and an IGRA simultaneously increases the overall sensitivity for infection. With human immunodeficiency virus (HIV) infection, the likelihood of false-negative results from TST and IGRAs increases progressively with decreasing CD4 <math><600/\text{mm}^3</math>. The rates of false-negative results with other immunosuppressive conditions are less well known.

Dual Testing

Simultaneous testing with a TST and an IGRA can increase overall sensitivity for *M. tuberculosis* infection, with a probable loss of specificity. When seeking increased sensitivity, this strategy can be useful, and a positive result from either test is taken as evidence of *M. tuberculosis* infection.

Dual testing should not be routine, but it may be considered for patients when there is concern about their ability to mount a strong immune response to a test, for persons who are at risk of severe forms of TB disease, or for persons in whom TB infection is strongly suspected because of exposure risks or symptomatology.

Children aged <math><2</math> years old can be included in a dual testing strategy if one of the above circumstances is present.

Serial Testing

When serial or periodic testing is required, as with some health care personnel at ongoing risk for TB exposure, either an IGRA or the TST may be used. For TST testing, the initial test should be a two-step TST. Because

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IGRAs do not cause boosting, serial testing with IGRAs does not require two-step testing to establish a baseline.

Positive TST results persist indefinitely on retesting for the majority of persons. However, in some persons who were infected with *M. tuberculosis* in the remote past and had no further exposure to TB, waning sensitivity can lead to a false-negative TST result. In such instances, an initial TST with a negative result can invoke an immune memory response so that a repeat TST, as soon as 1 to 2 weeks or as late as a year afterwards, would have a positive result, which is referred to as *boosting*. For persons who will be tested repeatedly (for example, in serial testing), who have an initial negative test, and who have not been tested in more than 1 year, two-step testing is used to distinguish between boosting and a positive TST result from recent *M. tuberculosis* infection.

Low-Risk Persons

When persons at low risk for TB infection or active TB disease are required to be tested by law or for other reasons, use either an IGRA or TST. If the result is positive, perform a second test with the same or a different method to confirm the test result. Using an IGRA first avoids the potential complication of skin test boosting from testing first with a TST.

Timing with Live Virus Vaccination

Because of the concern that live virus vaccines may impair immune responses, when both the MMR vaccine and a TB test are indicated, the Advisory Committee on Immunization Practices recommends the following:

- ◆ Administer the TST or IGRA simultaneously with the live vaccine (preferred scenario).
- ◆ If a TST or IGRA has already been administered, a live vaccine can be administered at any time >1 day after the administration of the TB test.
- ◆ If a live vaccine has already been administered, wait at least 28 days before administering a TST or IGRA.

In two-step testing, wait at least 28 days after the live vaccine is administered before administering the first TST. Continue from there to complete the two-step testing. Wait to administer any additional doses of live vaccine until after the second TST is measured. For more information on live virus vaccines, refer to the *General Best Practice Guidelines for Immunization*.

Timing with COVID-19 Vaccination

The CDC has issued national guidance on the timing of IGRAs, TSTs, and COVID-19 vaccinations. As this guidance may change when new vaccines and data are available, please refer to the NTCA COVID-19 Web page for current guidance: <http://www.tbcontrollers.org/resources/tb-and-covid-19/>

TEST PROCEDURES AND INTERPRETATION

T-SPOT®.TB

The FDA-approved labeling of T-Spot provides this advisory on using the T-Spot: “Diagnosing or excluding tuberculosis disease, and assessing the probability of LTBI, requires a combination of epidemiological, historical, medical and diagnostic findings that should be taken into account...” Currently this test is run at two main laboratories in the United States, with a uniform laboratory report.

During the test, white blood cells are separated from the whole blood sample, washed, and resuspended to a defined range of cell counts. The white cell suspension is transferred to test wells for incubating with the nil (negative) control, two antigen mixtures labeled Panel A and Panel B, and the mitogen (positive) control. During incubation, each cell that releases interferon-gamma is bound to a matrix, where a reaction creates a dye spot. The spots in each well are machine counted, and then a technician inspects all tests with positive results and tests meeting other criteria. The spot counts for the Panel A and the Panel B antigen wells are adjusted by subtracting the count for the nil well, and the results are derived from the test kit algorithm. For more information on how to interpret T-Spot results, see **Appendix 1: T-SPOT®.TB Test**.

Positive Result

If the spot count in the Panel A or the Panel B antigen well or both is ≥ 8 after subtracting the spots in the nil (negative) control well, the result is positive, regardless of the response to mitogen. This is evidence of TB infection, and it should be followed by further examination to exclude the possibility of active TB disease.

Negative Result

If the spot count in the Panel A and the Panel B antigen well is < 5 each after adjusting for the spots in the nil (negative) control well, and the response to the mitogen (positive) control is ≥ 20 spots, the result is negative. This is evidence of no TB infection; however, see warnings that negative results cannot exclude LTBI or active TB disease.

SECTION 1: IMMUNOLOGIC TESTS FOR TUBERCULOSIS INFECTION

Borderline (Equivocal) Result

T-Spot is the only test for infection with a results category of borderline (equivocal). If the spot count in either the Panel A or the Panel B antigen well is 5, 6, or 7 after subtracting the spot count in the nil (negative) control well, and the adjusted spot count for both antigen wells is <8 , the result is borderline (equivocal), regardless of the response to mitogen.

After a borderline (equivocal) result, another T-Spot or a different test can be done. Alternatively, if the likelihood of infection is low, the clinician can decide that the initial result is evidence of no infection, or, if the likelihood of infection is high or the hazards of a missed TB diagnosis are substantial, the initial result can be regarded as evidence of infection.

Invalid Result

The T-Spot result is designated as invalid primarily for one of two conditions: a mitogen (positive) control response <20 spots when the response in each antigen well is <5 spots after correcting for the count in the nil (negative) well; or a nil (negative) control count >10 spots, regardless of the responses to antigens and mitogen. Rarely, the result can be declared invalid for background staining that hinders counting the spots.

After an invalid result, another T-Spot or a different test is recommended.

Note: Immunosuppression, especially involving cellular immunity, can lead to a spot count <20 in the mitogen well and thus an invalid result. However, a response >20 spots is not assurance that a negative result is reliable for excluding TB infection in a patient who is immunosuppressed. With immunosuppression, the possibility of false-negative results should be considered, regardless of the response to mitogen.

Cancelled Test

The specimen can be rejected or the test can be cancelled because of administrative errors, specimen storage or transportation outside the recommended temperature ranges, arrival at the laboratory beyond the approved time limits, and insufficient quantity of blood or other blood problems such as clotting. Rarely, a second specimen of greater volume could be needed because of insufficient white blood cells in the initial specimen.

Refer to the **Test Variability** topic at the end of this section.

QuantiFERON®-TB Gold Plus

The FDA-approved labeling provides this advisory on using QFT-Plus: “QFT-Plus is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations...” QFT-Plus can be run in any laboratory with capacity for an enzyme-linked immunosorbent assay (ELISA). Numerous hospitals, free-standing clinical laboratories, and contract laboratories offer QFT-Plus.

Clinicians need to be familiar with the submission requirements of the laboratory where their QFT-Plus is run. Blood can be collected into a single heparinized tube and transferred to the four QFT-Plus blood collection tubes, or it can be collected directly into the QFT-Plus tubes. The QFT-Plus tubes are part of the test kit.

During the test, whole blood is incubated in the QFT-Plus tubes: a nil (negative) control, an antigen (TB1) tube containing peptide mixtures simulating two specific *M. tuberculosis* antigens, an antigen (TB2) tube containing the same mixtures plus peptides intended to stimulate CD8+ cells, and a mitogen (positive) control. After centrifuging, the plasma from each tube is collected for measuring the concentration of interferon-gamma by colorimetric ELISA. The interferon-gamma concentration of the TB1, the TB2, and the mitogen (positive control) tubes are adjusted by subtracting the concentration in the nil (negative control) tube, and the results are derived from the test kit algorithm. For more information how to interpret QFT-Plus results, see **Appendix 1: QuantiFERON®-TB Gold Plus Test**. The calculations and readout are automated in many laboratories.

The format of QFT-Plus laboratory reports is not standardized between laboratories. Clinicians need to be familiar with the reporting formats of the laboratory where their QFT-Plus is run. QFT-Plus results are reported as “Negative,” “Positive,” or “Indeterminate,” but clinicians should become familiar with the quantitative/numerical ranges of the test and insist on these values in the laboratory reports.

Positive Result

If the interferon-gamma concentration from TB1, TB2, or both, minus the interferon-gamma concentration from the nil (negative) control, is ≥ 0.35 IU/ml and $\geq 25\%$ of the interferon-gamma concentration from the nil control, the result is positive, regardless of the response in the mitogen (positive) control. A positive QFT-Plus result is evidence of infection with *M. tuberculosis* and should be followed by further examination for active TB disease.

Note: The comparison between the responses from the two tubes cannot be used to distinguish LTBI from active TB disease.

SECTION 1: IMMUNOLOGIC TESTS FOR TUBERCULOSIS INFECTION

Negative Result

If the interferon-gamma concentrations from TB1 and TB2, after subtracting the concentration from the nil (negative) control, both meet the criteria of <0.35 IU/ml or ≥ 0.35 IU/ml but $<25\%$ of the interferon-gamma concentration from the nil control, and the interferon-gamma concentration from the mitogen (positive) control, after subtracting the concentration from the nil control, is ≥ 0.50 , the result is negative. This is evidence of no TB infection. However, per the FDA-approved labeling: “A negative QFT-Plus result does not preclude the possibility of *M. tuberculosis* infection or TB disease: false-negative results can be due to stage of infection (for example, when a specimen is obtained prior to the development of cellular immune response), co-morbid conditions that affect immune function, incorrect handling of the blood collection tubes following venipuncture, incorrect performance of the assay, or other individual immunological variables.”

Indeterminate Result

The QFT-Plus result is designated as indeterminate for either of two sets of criteria: (1) the interferon-gamma concentration from the mitogen tube minus the concentration from the nil tube is <0.5 IU/ml in the absence of responses for a positive result from TB1 or TB2; or (2) an interferon-gamma concentration from the nil tube >8.0 IU/ml, regardless of concentrations from any other tubes.

An indeterminate result could be caused by patient factors or problems at any stage of the testing. It does not have a clinical interpretation. The test should be repeated with a new specimen, or a different test should be done.

Note 1: For healthy persons, a typical interferon-gamma concentration from the nil tube is 0.00 to 0.05 IU/ml. Although the manufacturer-defined upper limit is 8.0 IU/ml before the result is declared indeterminate, concentrations >0.10 IU/ml should raise concerns about problems with blood collection, storage, or shipment.

Note 2: Immunosuppression, especially involving cellular immunity, can lead to an interferon-gamma concentration from the mitogen tube, minus the concentration from the nil tube, <0.50 IU/ml, which is defined as an indeterminate QFT-Plus result, unless criteria are met for a positive result. However, a mitogen response (corrected for nil) >0.50 IU/ml is not assurance that a negative result is reliable for excluding TB infection in this scenario. With immunosuppression, the possibility of false-negative results should be considered, regardless of the response to mitogen.

SECTION 1: IMMUNOLOGIC TESTS FOR TUBERCULOSIS INFECTION

Cancelled Test

The routine causes of cancelled tests are administrative errors in labeling or specimen storage and delivery times later than the limits set by the manufacturer or the laboratory. Tests also can be cancelled for insufficient volume or clotted blood.

Refer to the ***Test Variability*** topic at the end of this section.

Tuberculin Skin Test

Persons who administer and read TSTs should have specific training to be qualified to do so. In the second appointment 48 to 72 hours after the injection, the indurated reaction at the injection site (not the redness) is palpated then measured across its transverse diameter. Test readings outside of the defined time interval are not supported by clinical studies and do not have standard interpretations. The measurements are interpreted using cut-points established for different populations. For more information on interpreting TST results, see **Appendix 1: Tuberculin Skin Test**.

Positive Result

The indurated reaction (induration instead of redness) at the TST site is measured in the transverse axis of (across) the arm 48 to 72 hours after administration, and the reading is risk stratified by patient group. (See **Appendix 1**.) The risk stratification is a method of adjusting the test sensitivity and specificity based on differences in risk for infection and progression among individuals. A positive TST result is evidence of infection, either LTBI or active TB disease. It should be followed by further examination for active TB disease.

Note: Some experts recommend performing a confirmatory IGRA when a patient has a positive TST result and no known risk for TB exposure or history of BCG vaccination. The role of IGRA in confirming a positive TST result in persons with known TB exposure has not been established by studies.

Negative Result

An indurated reaction smaller than a cut-point on the risk stratification is read as a negative result. This is evidence of absence of infection. However, a negative TST result cannot fully exclude *M. tuberculosis* infection. A negative result should be disregarded in persons who have signs, symptoms, or diagnostic findings suggestive of active TB disease. False-negative results are more likely when testing persons who have compromised or suppressed immunity.

Note: TST results are false-negative in up to 20% of patients with active pulmonary TB disease at the time of diagnosis and 40% of patients with TB meningitis. False-negative results are common in patients with compromised or suppressed immunity. The use of skin test controls (diluted tetanus toxoid, for example) is not recommended because it does not improve the reliability of a negative tuberculin PPD skin test result.

Tuberculin Skin Test Boosting, Two-Step Testing, and Serial Testing

For an explanation of *boosting* and the use of two-step testing to distinguish between boosting and a positive TST result from new *M. tuberculosis* infection, see the **Test Selection: Serial Testing** topic above. Although boosting may be attributed to *M. tuberculosis* infection from the remote past, it is also epidemiologically associated with BCG vaccination and non-tuberculous mycobacteria. Therefore, the interpretation of boosting for the diagnosis of LTBI requires assessing the likelihood of *M. tuberculosis* infection from a history of exposure risks.

Two-step testing is not recommended for routine diagnosis of LTBI.

Test Variability

When interpreting test results, consider the sources of variability for the test chosen.

For IGRAs, factors related to the patient and test can cause variability with results, especially when the response to an antigen is near a defining cut-point. Specimen collection and handling and laboratory steps of the IGRA test pose other potential sources of variability.

For the TST, factors related to the patient and test, such as cross-reactivity with BCG, can cause variability with results. Other sources of TST variability involve errors in technique. Incorrect injection of the antigen solution can cause false-negative results. Incorrect interpretation of the reaction can cause either false-positive or false-negative results. The tuberculin PPD solutions can be inactivated by incorrect storage of the reagent vial or by keeping the solution drawn up in a syringe for too long. Confusion between reagent vials has led to the inadvertent administration of the wrong antigen, such as tetanus toxoid, causing clusters of false-positive results.



THE ONLINE TST/IGRA INTERPRETER

This tool from McGill University may be useful for evaluating a specific person. You can access this guide at <http://www.tstin3d.com/en/calc.html>. However, take into consideration the following limitations of this assessment tool (version 3.0). It tends to overestimate risks of treatment because it considers the rate of side effects only for 9 months of isoniazid; it does not consider a negative IGRA result if a TST is also done in determining probability of a true positive TST; and it does not calculate lifetime risk of disease beyond age 80.

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SECTION 2:

When to Test for Latent Tuberculosis Infection

OVERVIEW

Approximately 80% of active TB disease in the United States is a result of the reactivation of LTBI, making greater implementation of testing and treatment for LTBI crucial to progress toward eliminating TB in the United States. To find persons with LTBI, screening for risk factors for TB infection and progression to active TB disease should be incorporated into primary health care for all persons. Patients with risk factors should be tested for TB and treated if they have LTBI.

GENERAL PRINCIPLES

Follow these principles when assessing risk for TB disease and testing for LTBI:

- ◆ Assess TB risk at least once. All adults and children should receive an assessment of TB risk factors at least once as part of routine primary care. At subsequent preventive health visits, screen persons for new risk factors that might have arisen since the previous screening.
- ◆ Do not conduct routine testing of low-risk populations, defined as persons with no known risks for exposure or progression to TB disease. Testing low-risk persons can result in unnecessary evaluations and treatment because of false-positive test results.
- ◆ Testing only persons at risk can simplify decisions regarding treatment because most persons with a risk factor and a positive TB test result should be treated for LTBI.
- ◆ When a person who previously had a negative TB test result has new risk factors since the last test, repeat the TB test. In general, retest with the same method as used for the first test.

Examples of new risk factors include the following events and conditions:

- ◆ Close contact to a patient with contagious TB disease since their last test
- ◆ Residence or travel in a high-incidence country for an extended time (>1 month)
- ◆ New or anticipated immunosuppressive therapy

CLINICAL BACKGROUND

Review the information below to guide risk assessment and testing for LTBI:

1. [Persons and Populations to Test](#)
2. [Tuberculosis Risk Assessment](#)
3. [Recent Tuberculosis Infection](#)
4. [Considerations for Specific Populations](#)
5. [Next: Section 3: Pretreatment Clinical Evaluation](#)

RELATED TOPICS

- ◆ [Section 1 Immunologic Tests for TB Infection](#)
- ◆ [California TB Risk Assessment Tool](#)

WARNINGS

- ◆ Avoid testing persons at low risk.

PERSONS AND POPULATIONS TO TEST

LTBI testing should be considered for persons with the following risk factors:

- ◆ **Birth or residence in a country with a high or medium incidence rate of TB, regardless of year of arrival in the United States**
These countries include most countries in Asia, Africa, Latin America, the Pacific Islands, and Eastern Europe. Refer to **Table 2: Countries with High or Medium Tuberculosis Incidence Rate**.
- ◆ **Travel for at least one month** in a country with a high or medium incidence rate of TB
- ◆ **Close contact to someone with infectious TB disease**
- ◆ **Immunosuppression, current or planned**
This includes HIV infection; organ transplantation; or treatment with tumor necrosis factor-alpha (TNF-alpha) antagonist (e.g., infliximab, etanercept, others), corticosteroids (equivalent of prednisone ≥ 2 mg/kg/day, or ≥ 15 mg/day for ≥ 1 month), or other immunosuppressive medication.
- ◆ **Other conditions or social circumstances** that meet criteria in state or local recommendations, such as homelessness, incarceration, or occupational risk of TB

When setting TB testing policies, check with state or local TB control programs for recommendations and consider information about local epidemiology, regulations, legal mandates, and patient populations.

TUBERCULOSIS RISK ASSESSMENT

Designed to be used among all patients and consistent with guidelines, a simplified assessment of TB risk can help to incorporate TB prevention into routine primary care.

The **California Tuberculosis Risk Assessment** was developed jointly by the Tuberculosis Control Branch at the California Department of Public Health, the California Tuberculosis Controllers Association, and the Curry International Tuberculosis Center to help clinicians select adults for LTBI testing who are at high risk for TB exposure or progression to TB disease.

To access the tool and more information about its use, see the Curry International Tuberculosis Center product Web page:

<http://www.currytbcenter.ucsf.edu/products/view/california-tuberculosis-risk-assessment>.

SECTION 2: WHEN TO TEST FOR LATENT TUBERCULOSIS INFECTION

Table 2. Countries with High or Medium Tuberculosis Incidence Rate

TB Incidence Rate Comparison	
	TB incidence rate per 100,000 person years
High incidence countries (estimated)	>100/100,000
Medium incidence countries (estimated)	10-100/100,000
United States (2019, reported)	2.7/100,000

Most Common Countries of Origin for Non-US-born Persons Diagnosed with Active TB Disease in the United States	
<p>Among persons in the United States with active TB disease who were non-US born, the most common countries of birth were Mexico, the Philippines, India, Vietnam, and China. The TB incidence rates in 2019 in those countries were estimated by the World Health Organization to be</p> <ul style="list-style-type: none">▶ Mexico: 23/100,000 (Medium)▶ The Philippines: 554/100,000 (High)▶ India: 193/100,000 (High)▶ Vietnam: 176/100,000 (High)▶ China: 58/100,000 (Medium) <p>Persons who were born in, or resided in, these countries should be tested at least once regardless of how long they have resided in the United States.</p>	
<p>Sources: For more information, refer to the World Health Organization's TB country profiles: https://www.who.int/teams/global-tuberculosis-programme/data</p> <p>CDC surveillance report "Tuberculosis, United States – 2019:" https://www.cdc.gov/tb/</p>	

RECENT TUBERCULOSIS INFECTION

Recent TB infection is a significant risk factor for progression to active TB disease. Recent infection is defined as any of the following:

- ◆ Newly positive TST or IGRA result in a person who had close contact with a patient with active infectious TB disease within the prior 2 years or other circumstances suggesting recent exposure: For more information, see the **Contact with a Person with Infectious Tuberculosis Disease** topic below.
- ◆ Positive TST or IGRA result in a child aged <2 years: TST is recommended for testing children aged <2 years because of a lack of data on IGRAs in this age group, but in some situations both the TST and an IGRA are done to increase sensitivity. For more information on using both the TST and an IGRA, see **Section 1: Immunologic Tests for Tuberculosis Infection: Test Selection: Dual Testing**.
- ◆ TB test conversion within the past 2 years with a confirmatory test for people with no known risk for TB exposure: A TST conversion is an increase in TST reaction by >10 mm from negative to positive in 2 years or less. An IGRA conversion is a change from negative to positive IGRA result in 2 years or less.

CONSIDERATIONS FOR SPECIFIC POPULATIONS

Birth or Residence in a Country with a High or Medium Incidence Rate

Persons born in, or former residents of, countries with high TB rate (>100 cases/100,000 person-years) or medium TB rate (10-99 cases/100,000 person-years) have an increased risk of TB exposure. The majority of persons with active TB disease in the United States were born in countries where TB is more common than the United States. The National TB Controllers Association (NTCA) and the United States Preventive Services Task Force (USPSTF) recommend testing all persons who were born in, or resided in, a country with higher TB incidence. Baseline testing should be performed regardless of how long persons have resided in the United States. For more information on countries with elevated TB rates, see **Table 2: Countries with High or Medium Tuberculosis Incidence Rate**.

Contact with a Person with Infectious Tuberculosis Disease

Close contact to a person with infectious TB disease poses a risk of TB infection. If the contact was recent (within the last 2 years), there is an added risk of progression to active TB disease.

Public health departments or infection control practitioners typically evaluate persons with recent contact as part of contact investigations. However, these investigations may miss some contacts, or the exposure may have occurred long ago when contact investigation was not commonly practiced (for example, when a household member was sick with or died from TB during a person's childhood).

If possible, clarify that your patient's contact was close contact and that it was contact with a person with active infectious TB disease, not LTBI. Ask for the name and age of the person with infectious TB disease. Especially if contact was recent, attempt to verify the exposure with the state or local TB program and obtain the drug susceptibility test results of the index patient. For more information on the testing and treatment of contacts, see **Section 5: Considerations for Specific Populations: Recent Contacts to Persons with Infectious Tuberculosis Disease**.

Immunosuppression

Even in the absence of a specific known risk factor for exposure to TB, test patients with current or planned immunosuppression that is likely to substantially elevate the risk of progression from latent infection to active TB disease. The following immunosuppressive conditions typically elevate the risk of progression:

- ◆ HIV infection, especially in patients with CD4 T lymphocyte (CD4) count <200 cells/mm³ or patients not receiving antiretroviral therapy (ART)
- ◆ Treatment with anti-inflammatory immunosuppressive drugs such as anti-TNF-alpha agents and other biologic agents targeting specific elements of the immune system
- ◆ Treatment with long-term high-dose steroids (equivalent of prednisone ≥ 2 mg/kg/day, or ≥ 15 mg/day for ≥ 1 month)
- ◆ Cancer chemotherapy
- ◆ Solid organ or bone marrow transplantation

For more information on persons with immunosuppression, see the **Section 5: Considerations for Specific Populations** topics titled **Persons with Comorbidities: Human Immunodeficiency Virus Infection** and **Iatrogenic Immunosuppression**.

Other Medical Conditions or Social Circumstances

Medical Conditions

All persons should be assessed for their TB risks. Furthermore, the following medical conditions elevate the need for TB screening and LTBI diagnosis in persons with a history suggestive of TB exposure because they increase the rate of progression from LTBI to active TB disease:

- ◆ Diabetes mellitus
- ◆ End-stage renal disease (ESRD)/chronic kidney disease (CKD)
- ◆ Leukemia or lymphoma
- ◆ Silicosis
- ◆ Cancer of the head or neck
- ◆ Intestinal bypass or gastrectomy
- ◆ Chronic malabsorption
- ◆ Body mass index ≤ 20
- ◆ Current or former cigarette smoking

Having one or more of these conditions without a history suggestive of TB exposure is not an independent reason for being tested for LTBI. However, testing for LTBI may be indicated for other reasons—for example, infection control at a hemodialysis center or local epidemiology showing an association between a condition and LTBI or TB disease. TB prevention should be a part of routine care at specialty medical clinics where patients receive care for these conditions, such as occupational health clinics treating patients for silicosis.

Age

Younger persons have more years of expected life during which progression from latent infection to active TB disease could occur. In addition, children aged <5 years are especially vulnerable to rapid progression to active TB disease if infected and are more likely to develop life-threatening central nervous system or disseminated TB disease, while they tend to have fewer adverse drug effects with treatment for LTBI. As in adults, assess all children for TB risk factors.

The American Academy of Pediatrics has published **four validated risk assessment questions for children** in the 2021 edition of the *Red Book*® in Table 3.76:

<https://publications.aap.org/redbook/book/347/chapter/5757587/Tuberculosis?searchresult=1> (A subscription is required for access.)

SECTION 2: WHEN TO TEST FOR LATENT TUBERCULOSIS INFECTION

The ***California Pediatric Tuberculosis Risk Assessment***, a simple risk assessment tool, is available at no cost on the California Department of Public Health TB Control Branch's website: <https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-CA-Pediatric-TB-Risk-Assessment.pdf>

For more information on the testing and treatment of children, see ***Section 5: Considerations for Specific Populations: Children***.

An upper age limit for testing has not been established. Test sensitivity with TST but not with IGRAs appears to decrease with age greater than 60 years. Some experts consider testing (or not testing) elderly persons with TB risk to be appropriate depending on the individual patient's risk for progression to active TB disease (for example, immunosuppression) and life expectancy.

Social Circumstances

Persons who have a history of being homeless or incarcerated or of being employed in a facility where these persons reside may have an increased risk of exposure to infectious TB. The USPSTF recommends testing and treating persons with these risk factors.

Risk of exposure varies by specific facility and setting. Screening and testing programs may exist in specific facilities and settings such as screening in certain homeless shelters or correctional facilities. Local TB programs can confirm whether populations in congregate settings (homeless shelters, for example) require testing. In addition, legal or regulatory requirements may mandate screening or testing among employees of these facilities.

Substance use disorders also may be markers of exposure risk. TB transmission has been traced back to communal drug use (methamphetamines and crack cocaine, for example), and substance use is part of a group of social risks for TB transmission for some persons.

HEALTH CARE PERSONNEL

"Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019" recommends the following TB prevention measures for health care personnel (HCP):

- ◆ TB screening with an individual risk assessment and symptom evaluation upon hire
- ◆ TB testing with an IGRA or TST for persons without documented prior TB or LTBI
- ◆ Confirmatory testing for a positive result: When there is a positive IGRA or TST result in an HCP without known exposure, do a repeat test with the same or another test. If the second test result is positive, it is accepted as evidence of TB infection.
- ◆ No routine serial TB testing at any interval after baseline in the absence of a known exposure or ongoing transmission
Exception: In settings where local epidemiology and experience indicate that patients with undiagnosed active TB disease enter an institution, periodic testing may be practiced for HCP who take care of these patients during aerosol-generating procedures.
- ◆ Annual symptom screening for HCP with untreated LTBI
- ◆ Annual TB education for all HCP
- ◆ *Strongly encouraged:* Treatment for all HCP with untreated LTBI, unless treatment is contraindicated

With overall decreasing incidence rates of TB in the United States and more effective infection control programs, HCP are not currently at increased risk for TB. However, some jurisdictions may have legal or regulatory requirements to test HCP, and the local TB epidemiology might indicate the need for testing HCP. For more information on screening HCP, see these guidelines:

- ◆ "Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019:"
https://www.cdc.gov/mmwr/volumes/68/wr/mm6819a3.htm?s_cid=mm6819a3_w
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SECTION 3:

Pretreatment Clinical Evaluation

OVERVIEW

A patient with a positive test result for TB infection should be evaluated for active TB disease before starting treatment for LTBI. To exclude active TB disease, the clinical evaluation should include a medical history, symptom review, focused physical examination, and chest radiography. Bacteriologic studies or other additional evaluation may be needed if indicated based on the initial evaluation. Report persons with suspected active TB disease to the state or local TB program.

GENERAL PRINCIPLES

During the pretreatment clinical evaluation, the health care provider should take the following steps to decide whether to treat the patient for LTBI:

- ◆ Exclude active TB disease
- ◆ Confirm the diagnosis of untreated or incompletely treated LTBI
- ◆ Assess the risk of progression to active TB disease

Patients at increased risk of developing active TB disease generally should be treated for LTBI and followed until treatment is completed.

CLINICAL EVALUATION COMPONENTS

Review the following information concerning the essential components of clinical evaluation:

1. Medical History
2. Symptom Review
3. Focused Physical Examination
4. Chest Radiography
5. Bacteriologic Studies
6. Baseline Laboratory Tests
7. Diagnosis of Latent Tuberculosis Infection
8. Next: Section 4: Deciding Whether to Treat and Choosing a Regimen

RELATED TOPICS

- ◆ Section 1: Immunologic Tests for TB Infection
- ◆ Section 2: When to Test for LTBI
- ◆ As needed, review Section 5: Children, Pregnancy, Breastfeeding, Postpartum, HIV Infection, Iatrogenic Immunosuppression, Liver Disease, Kidney Disease, Contacts, and Substance Use Disorder

WARNINGS

- ◆ Do not treat for LTBI until active TB disease is excluded.
- ◆ Contact your state or local health department if you suspect that the patient has active TB disease. A list of state TB offices is posted on the CDC website at www.cdc.gov/tb/links/default.htm.

MEDICAL HISTORY

Pretreatment clinical evaluation includes a history with a focus on the following information:

- ◆ **Positive test results for TB infection**
Review documentation of quantitative test results. For information on how to interpret test results, see **Section 1: Immunologic Tests for Tuberculosis Infection**.
- ◆ **Medical history**, including immunosuppressive conditions and medications
- ◆ **History of TB exposure, including risk factors**
- ◆ **Risk of developing active TB disease**
Patients may be at increased risk of progression to active TB disease because of recent infection. In addition, some medical conditions can increase the risk of progression and place patients at high priority for treatment of LTBI. Patients who were born in, or resided or travelled for >1 month in, countries with high or medium rates of TB should also be treated regardless of time in the United States.

For more information on recent infection and medical conditions associated with increased risk of progression to TB disease, see **Section 2: When to Test for Latent Tuberculosis Infection**. Review **Section 5: Considerations for Specific Populations** if your patient belongs to one of these groups:

- ▶ Children
 - ▶ Pregnant, breastfeeding, or postpartum persons
 - ▶ Recent contacts to infectious TB disease
 - ▶ Contacts to infectious, drug-resistant TB disease
 - ▶ Persons with the following comorbidities: HIV infection, iatrogenic immunosuppression, liver disease, kidney disease, diabetes, or substance use disorders
- ◆ **History of prior treatment for TB or LTBI**
In general, a patient should be treated for LTBI only once. The health care provider should collect the following information on the patient's history of prior treatment for active TB disease or LTBI, obtaining documentation if possible:
 - ▶ Dates and duration of treatment
 - ▶ Mode of treatment administration: self-administered or directly observed
 - ▶ History of adverse effects
 - ▶ Reasons for discontinuing treatment

SECTION 3: PRETREATMENT CLINICAL EVALUATION

- ▶ For a patient who was in contact with an index patient with active TB disease, obtain when possible the drug susceptibility test results for the index patient

Obtain documentation of prior treatment for LTBI. Do not assume that it was completed. If the history of prior treatment for LTBI is vague or unreliable and if the patient remains at risk of progression to active TB disease, consider recommending another course of LTBI treatment after excluding active TB disease.

SYMPTOM REVIEW

Assess for the following TB symptoms:

- ◆ Prolonged cough (>2-3 weeks)
- ◆ Hemoptysis
- ◆ Fever or chills
- ◆ Night sweats
- ◆ Unintended weight loss
- ◆ Loss of appetite
- ◆ Fatigue
- ◆ Chest pain
- ◆ Other symptoms or signs of extrapulmonary TB, depending upon the site affected

FOCUSED PHYSICAL EXAMINATION

Examine the oropharynx, neck, lungs, abdomen, and other organ systems depending upon the TB symptoms. Check especially for enlarged lymph nodes.

CHEST RADIOGRAPHY

All patients with TB infection should undergo a chest radiograph (CXR) as part of the evaluation. In the request for the study, alert the radiologist that the purpose is to check for TB disease. The CXR should be interpreted with a high index of suspicion for TB, especially in patients who have TB symptoms or who were recently exposed. In persons with TB symptoms, a normal CXR does not rule out TB disease, especially in patients who are immunocompromised.

Most experts recommend the following:

- ◆ **For all patients:** order a posterior-anterior CXR to screen for active TB disease.
- ◆ **For patients aged <5 years:** order a lateral CXR in addition to the posterior-anterior CXR to screen for active TB disease.
- ◆ **For patients with TB symptoms or patients who are immunocompromised:** consider ordering a lateral CXR in addition to the posterior-anterior CXR to screen for active TB disease.
- ◆ **For patients needing further evaluation for active TB disease:** order additional views (apical lordotic or lateral decubitus, for example) or additional radiographic studies (such as a computed tomography scan) as needed.

In general, most experts recommend that if a CXR was done in the 3 months prior to the medical evaluation, its findings were documented as normal, and the person is asymptomatic, then a repeat CXR is not necessary. If the previous study was not done as part of an examination for TB, then the study should be reviewed or repeated for the potential of a TB diagnosis.

If an asymptomatic, pregnant person has a positive TB test result, either IGRA or TST, the patient should receive a medical evaluation, including a CXR with a lead shield covering the abdomen and pelvis. The CXR may be deferred until after the first trimester **unless** the patient has one or more of the following:

- ◆ HIV or other immunosuppression
- ◆ History of recent contact with a person with infectious TB disease
- ◆ Documented TB infection test conversion in the past 2 years

For all other asymptomatic patients with a positive TB test result, the CXR may be deferred to the second trimester. The CXR should not be deferred until peri- or post-partum.

BACTERIOLOGIC STUDIES

Most patients evaluated for LTBI will not need these studies. If additional evaluation is needed, seek consultation from your state or local TB program or regional TB Center of Excellence and determine where to access the testing services described below in your community.

For information on management of patients with an abnormal CXR while awaiting culture results, see **Section 5: Considerations for Specific Populations: Persons with Radiographic Findings of Previous or Inactive Tuberculosis**.

If the patient has pulmonary TB symptoms or physical or radiographic findings suspicious for active TB disease, obtain 2 to 3 sputa specimens for acid-fast bacilli (AFB) smear and culture, including at least 1 early morning specimen and 1 specimen tested by nucleic acid amplification test (NAAT). If the patient has CXR abnormalities or pulmonary symptoms and is unable to expectorate sputum, collect specimens by sputum induction, ensuring that airborne infection isolation precautions are observed during sputum collection. Order other bacteriologic studies as needed for extrapulmonary TB.

If specimens are collected, do not start treatment for LTBI while culture results are pending. Seek consultation from your state or local TB program or regional TB Center of Excellence. Some patients may benefit from empiric treatment for active TB disease while AFB cultures are pending. The decision is based on the risk to the patient of disease progression and the risk to their contacts of TB transmission while waiting for cultures. The decision about empiric TB treatment should be made in consultation with the state or local TB program. For additional information about bacteriologic testing for TB, refer to links to references 2 and 5 below.

BASELINE LABORATORY TESTS

Baseline laboratory tests may be indicated in patients with certain medical conditions or who are being started on certain treatment regimens.

Patients who do not know their HIV status should be offered testing for HIV infection.

For more information on baseline laboratory studies, see **Section 4: Deciding Whether to Treat and Choosing a Regimen: Baseline Laboratory Tests**.

DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

At the completion of pretreatment clinical evaluation, if a patient with a positive test result for TB infection does not have any symptoms of TB, and the CXRs and other diagnostic tests results are normal, then active TB disease is excluded and LTBI is diagnosed.

With this diagnosis, the patient should be considered for treatment for LTBI, and the next step is to decide whether to recommend LTBI treatment and to provide appropriate patient education based on the recommendations.

For more information on treatment decisions and patient education, see **Section 4: Deciding Whether to Treat and Choosing a Regimen.**

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SECTION 4:

Deciding Whether to Treat and Choosing a Regimen

OVERVIEW

After excluding active TB disease and diagnosing LTBI, the decision can be made on whether to proceed with treatment for LTBI and, if so, which regimen to use. The clinician should decide in consultation with the patient whether to recommend LTBI treatment based on several factors, the most important of which is the patient's risk of developing active TB disease, from either risk of TB exposure or risk of progression to active TB disease.

Patients at increased risk of developing active TB disease generally should be treated for LTBI and followed until treatment is completed. Other factors to consider include the risk for drug toxicity, the patient's willingness to accept treatment, and the patient's likely adherence. Based on the recommendations, patient education should be provided. For patients at lower risk for active TB disease, who may have been tested for other reasons, treatment for LTBI may be recommended based on an individualized assessment of the risk of TB, the benefits and risks of treatment, and the patient's preference.

GENERAL PRINCIPLES

To ensure a patient-centered approach, these principles should be followed during the process of decision-making and preparing the patient to start a treatment regimen:

- ◆ Consult with the patient on the decisions whether to proceed with treatment and which regimen to use.
- ◆ Base decisions on the advantages and disadvantages of treatment for the patient, considering the patient's cultural beliefs, understanding of TB infection, behaviors, socio-economic factors, and health care access related to the safety and completion of LTBI treatment.
- ◆ Address barriers to adherence.
- ◆ Educate the patient about LTBI and its treatment.

STEPS IN TREATMENT INITIATION

Review the following information concerning the essential components of treatment initiation:

1. [Decision Whether to Treat](#)
2. [Selection of Treatment Regimen](#)
3. [Baseline Laboratory Tests](#)

4. [Interventions for Treatment Completion Challenges](#)
5. [Patient Education](#)
6. [Next: Section 6: Monitoring and Managing Treatment](#)

RELATED TOPICS

- ◆ [Appendix 2: Drugs for Treatment of LTBI](#)
- ◆ [Appendix 3: Dosages for Recommended Treatment Regimens](#)
- ◆ [Appendix 5: Directly Observed Therapy and Video Directly Observed Therapy](#)

WARNINGS

- ◆ Do not treat for LTBI until active TB disease is excluded.
- ◆ For patients with these conditions or characteristics, review Section 5: Children, Pregnancy, Breastfeeding, Postpartum, HIV Infection, Iatrogenic Immunosuppression, Liver Disease, Kidney Disease, Contacts, and Substance Use Disorders.
- ◆ Educate the patient to stop medications immediately and call the health care provider if any symptoms develop that are concerning for an adverse effect.

DECISION WHETHER TO TREAT

The decision to recommend LTBI treatment is made based on the patient's risk of developing active TB versus the risk of an adverse event from treatment. Review the patient's current medical conditions and medications against the list of known contraindications and drug-drug interactions of LTBI medications and regimens.

Counseling the patient in his or her preferred language, using a medical interpreter when needed, is important. Education and counseling should support a patient-centered approach that emphasizes shared decision making. Unless a regimen is contraindicated, the patient should be educated about the advantages and disadvantages of different treatments and offered a choice. The rationale for taking a medication with potential toxicity to prevent a possible future event when a patient currently feels well can be difficult. For some patients, the risks of adverse effects or drug-drug interactions may outweigh the risk of progression to active TB disease if untreated.

For more information on adverse effects, refer to the treatment regimen descriptions in this section and **Appendix 2: Drugs for the Treatment of Latent Tuberculosis Infection**.



THE ONLINE TST/IGRA INTERPRETER

This tool from McGill University may be useful for evaluating a specific person. You can access this guide at <http://www.tstin3d.com/en/calc.html>. However, take into consideration the following limitations of this assessment tool (version 3.0). It tends to overestimate risks of treatment because it considers the rate of side effects only for 9 months of isoniazid; it does not consider a negative IGRA result if a TST is also done in determining probability of a true positive TST; and it does not calculate lifetime risk of disease beyond age 80.

For information on facilitating treatment completion, DOT, and on patient education, see the **Interventions for Treatment Completion Challenges** topic in this section. Public health TB programs may provide nurse case management services and DOT for patients with LTBI. Contact the local health department to determine its policy for LTBI treatment services. For more information, see **Section 7: Nurse Case Management**.

SELECTION OF TREATMENT REGIMEN

This section is consistent with the "Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020." These guidelines focus on treating latent tuberculosis in areas with a low TB burden. It is important to recognize that these recommendations might differ from other clinical guidelines.

Regimens are ranked based on tolerability and effectiveness from randomized controlled trials, assumed equivalent effectiveness in broad populations with LTBI who were not studied, and the likelihood of treatment completion. These guidelines emphasize the use of shorter regimens for the treatment of LTBI based on randomized control treatment trials that have demonstrated efficacy and safety. As such, the short-course regimens that include rifampin or rifapentine are listed as preferred while isoniazid-only regimens are listed as alternatives.

- ◆ **Preferred regimens:** excellent tolerability and efficacy, shorter treatment duration, and higher completion rates
- ◆ **Alternative regimens:** excellent efficacy but longer treatment duration and lower completion rates

Table 3 summarizes the recommendations from the 2020 guidelines.

Table 3. Recommendations for Regimens to Treat Latent Tuberculosis Infection

Regimen	Priority Rank	Recommendation	Quality of Evidence
3HP: 3 months of isoniazid and rifapentine once weekly	Preferred	Strong	Moderate
4R: 4 months of rifampin daily	Preferred	Strong	Moderate (HIV-negative)*
3HR: 3 months of isoniazid and rifampin daily	Preferred	Conditional	Very low (HIV-negative) Low (HIV-positive)
6H: 6 months of isoniazid daily or twice weekly	Alternative	Strong [^] Conditional	Moderate (HIV-negative) Moderate (HIV-positive)
9H: 9 months of isoniazid daily or twice weekly	Alternative	Conditional	Moderate

* No evidence reported in persons with HIV infection.

[^] Strong recommendation for persons unable to take a preferred regimen (e.g., because of drug intolerability or drug-drug interactions)

Source: Adapted from Sterling TR, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep.* 2020 Feb 14;69(1):1-11.

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Two short-course regimens are now recommended: 3 months of isoniazid and rifapentine once weekly (3HP) and 4 months of rifampin daily (4R). Many jurisdictions in the United States use these regimens because of their higher completion rates and lower rates of associated hepatotoxicity.

Three months of isoniazid and rifampin given daily (3HR) is another short-course regimen more often used outside of the United States. Because there is less evidence from randomized control trials on 3HR than other regimens, there is concern about its hepatotoxicity. Based on this concern, 3HR has only a conditional recommendation.

Because of lower completion rates and higher risk of hepatotoxicity compared to 3HP and 4R, two other regimens now have conditional recommendations: 6 and 9 months of isoniazid (6H and 9H) given daily or twice weekly. While 9H was estimated to be more efficacious than 6H at reducing the risk of TB in one analysis, 6H has been studied more extensively, may be more cost-effective than 9H, and may have lower risk of hepatotoxicity. Nonetheless, 9H is probably more efficacious and is commonly recommended for patients who are immunosuppressed, tolerating treatment at 6 months, and willing to continue.

Note that twice-weekly isoniazid should be administered by directly observed therapy (DOT) for patients who may not be able to adhere to daily self-administered therapy (SAT) and cannot take 3HP by DOT. Be sure to use the correct dosing: daily and twice-weekly regimens have different dosages.

The US Department of Health and Human Services (DHHS) *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* (available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines>) recommend treatment of latent *M. tuberculosis* infection in HIV-positive individuals, in both the United States and other countries, including high-TB -burden regions. In their recent updated recommendations, the guidelines emphasize 3HP and 3HR as preferred regimens and 6-9H, 4R, and rifapentine and isoniazid (1HP) as alternative options.

The NTCA/CDC guidelines have not incorporated 1HP as a preferred or alternative choice mainly because the BRIEF-TB study centered on individuals with HIV in high-TB-prevalence areas, a majority of whom did not have a positive TB screening test result. For more information on 1HP, see its entry in the individual LTBI regimens below.

No single regimen is the best choice for all patients. Each patient must be evaluated based on individual characteristics, some of which may influence the choice of regimens. For patients where rifamycins are contraindicated, especially those with medications that significantly interact with rifamycins, shorter regimens are not recommended. For example, patients taking oral contraceptives have an increased risk of pregnancy if given a rifamycin, due to the drug-drug interaction between estrogen and rifamycins which increase estrogen metabolism and reduce its effectiveness as a contraceptive.

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Alternatives include 6H or 9H, or the use of a barrier method of contraception with or without continuing the oral contraceptive.

For a summary table of current treatment regimens, with dosing information, see **Appendix 3: Dosages for Recommended Treatment Regimens**.



ALERT

Concerns about nitrosamine contamination in rifapentine and rifampin are under investigation. For a summary of what is currently known and recommended, see the NTCA website at <http://www.tbcontrollers.org/resources/nitrosamines/>.

Rifapentine and Isoniazid Once Weekly for 3 Months (3HP)

Currently, 3HP is one of the preferred regimens for the treatment of patients with LTBI.

In a multi-center, randomized clinical trial, 3HP given by DOT was shown to be as effective as 9H for the treatment of LTBI, with a greater likelihood of completion and a lower incidence of hepatotoxicity. In a separate study, completion of 3HP given by SAT was noninferior to direct observation among participants enrolled in the United States. For 3HP, the decision to give it by DOT or SAT should be based on local practice, individual patient attributes, preferences, and risk for progression to severe forms of TB disease. See the **Methods of Treatment Administration** topic below and **Appendix 5: Directly Observed Therapy and Video Directly Observed Therapy**.



CAUTION

Prescribing providers and pharmacists who are unfamiliar with the rifamycins might confuse the three drugs: **rifampin, rifapentine, and rifabutin are different drugs**, and caution should be taken to ensure that patients receive the correct medication and the correct dose for the intended regimen.

Advantages

- ▶ Lower hepatotoxicity than with daily isoniazid monotherapy
- ▶ Better treatment completion than with isoniazid regimens
- ▶ Fewest number of doses and total pills (12 doses; 120 pills for most)

Disadvantages

- ▶ Higher drug cost
- ▶ Drug-drug interactions
- ▶ Large pill burden for single dose
- ▶ Rare hypotension and syncope

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Contraindications

- ▶ Aged <2 years (studies have not been completed)
- ▶ Pregnancy
- ▶ Exposure to a patient with an isolate resistant to isoniazid or rifampin

Relative Contraindication

- ▶ HIV-positive status and taking an ART regimen with serious drug-drug interactions (possibility of inducing a virologic relapse)

Completion of Treatment

- ▶ Completion of treatment for 3HP is 12 doses within 16 weeks. (For patients who are unable to complete 12 doses, treatment can be considered complete if 11 doses are taken within 16 weeks.) Doses should be separated by >72 hours to be counted.

For LTBI treatment of persons on ART, see **Section 5: Considerations for Specific Populations: Persons with Comorbidities: Human Immunodeficiency Virus Infection.**



SPECIAL NOTE ON MONITORING AND PATIENT EDUCATION FOR 3HP

Patients must be educated about potential adverse effects, especially those that may be unique or more common with this regimen such as flu-like symptoms and near-syncope or syncope. Treatment-related side effects are most commonly reported after the third or fourth dose.

Treatment should be withheld if severe adverse effects occur, including uncontrolled nausea, vomiting, headache, light-headedness, dizziness, palpitations, or loss of consciousness. Anyone experiencing severe symptoms should be evaluated by a clinician who can determine if laboratory testing is needed and whether it is safe to continue versus switching to a different regimen.

Minor symptoms often resolve with continued treatment and may be mitigated by taking treatment before going to bed.

Rifampin (or Rifabutin) Daily for 4 Months (4R)

In two randomized clinical trials, 4 months of daily rifampin in adults and children was found to be at least as effective in preventing TB disease compared to 9 months of daily isoniazid, as well as to have a lower rate of treatment discontinuation because of adverse effects and hepatotoxicity. Therefore, 4 months of rifampin daily is a preferred regimen for HIV-negative adults and children of all ages. It also is recommended for patients who may have isoniazid-resistant TB. Some experts recommend treatment with rifampin for only 3 months, but only one older randomized control trial supports this treatment duration.

Some experts use rifabutin in situations where there would be drug-drug interactions with rifampin, such as when a patient has a substance use disorder involving opioids or benzodiazepines. Some experts also substitute rifabutin when rifampin has elevated bilirubin and serum transaminase concentrations; however, there are no studies or evidence related to this substitution of rifabutin. See **Appendix 2: Drugs for the Treatment of Latent Tuberculosis Infection** for more information on situations in which you may want to consider substituting rifabutin for rifampin.



CAUTION

Prescribing providers and pharmacists who are unfamiliar with the rifamycins might confuse the three drugs: **rifampin, rifapentine, and rifabutin are different drugs**, and caution should be taken to ensure that patients receive the correct medication and the correct dose for the intended regimen.

Advantages

- ▶ Lower hepatotoxicity than isoniazid
- ▶ Better adherence to treatment than with isoniazid regimens
- ▶ Treatment option after exposure to isoniazid-resistant but rifampin-susceptible TB
- ▶ Treatment option for persons unable to use isoniazid because of prior reaction to isoniazid or risk of intolerance (baseline liver disease, for example)

Disadvantage

- ▶ Many drug-drug interactions

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Contraindications

- ▶ HIV-positive status and presence of significant drug-drug interactions with ART
- ▶ History of allergic or other significant adverse effect to rifamycins
- ▶ It should be noted that rifabutin monotherapy is not recommended in patients with HIV by the [US Department of Health and Human Services \(DHHS\) HIV guidelines](#).

Completion of Treatment

- ▶ Completion of treatment is 120 doses within 6 months.

Isoniazid and Rifampin Daily for 3 Months (3HR)

Combination therapy for LTBI with isoniazid and rifampin is given daily for 3 months. It is listed as a preferred regimen that is conditionally recommended in the 2020 LTBI treatment guidelines. However, because of concerns about its tolerability and toxicity and the lack of evidence from randomized controlled trials, the 3HR regimen is infrequently used in the United States.



CAUTION

Prescribing providers and pharmacists who are unfamiliar with the rifamycins might confuse the three drugs: **rifampin, rifapentine, and rifabutin are different drugs**, and caution should be taken to ensure that patients receive the correct medication and the correct dose for the intended regimen.

Advantages

- ▶ Potentially effective treatment of infection with an unsuspected isoniazid-resistant organism
- ▶ Shorter duration of therapy compared to 4R and isoniazid regimens

Disadvantages

- ▶ Less experience with this regimen for the treatment of LTBI in the United States than with the other regimens
- ▶ Potential additive hepatotoxicity

Contraindications

- ▶ See the contraindications noted in information on isoniazid and rifampin.

Completion of Treatment

- ▶ Completion of treatment for 3HR is a total of 90 doses taken within 4 months.

Isoniazid for 6 Months (6H) or 9 Months (9H)

Numerous large, placebo-controlled clinical trials have demonstrated the efficacy of treatment of LTBI with isoniazid given daily. A risk-benefit analysis of these trials indicated that a treatment duration of 9 months would be more efficacious than 6 months. The most widely used regimen for LTBI treatment in the past 20 years was 9 months of daily isoniazid (9H). However, its acceptance and completion are reduced by its long duration and risk for hepatotoxicity.

In the 2020 guidelines for the treatment of LTBI, 6 months of isoniazid given daily is strongly recommended for HIV-negative patients and conditionally recommended for persons with HIV infection. Nine months of isoniazid given daily has a conditional recommendation.

For patients who are at increased risk of not completing treatment and for whom 3HP or 4R is unfeasible or contraindicated, some experts recommend treatment with isoniazid twice weekly for 6 to 9 months by DOT.

Advantages

- ▶ Low cost
- ▶ Few drug-drug interactions

Disadvantages

- ▶ Hepatotoxicity, more commonly in adults than in children, which can be serious and lead to liver failure and death
- ▶ Long duration of treatment leading to poor completion rates

Contraindications

- ▶ Acute active hepatitis
- ▶ Chronic hepatitis with liver-associated enzyme levels >3 to 5 times the upper limit of normal (ULN)
- ▶ Prior significant adverse effect related to isoniazid
- ▶ Heavy or daily alcohol use

Relative Contraindication

- ▶ Chronic hepatitis with liver enzyme levels that are abnormal, but <3 to 5 times the ULN
- ▶ For monitoring persons with chronic hepatitis, see **Section 6: Monitoring and Managing Treatment.**

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Completion of Treatment

DOT is required for intermittent dosing.

9H Regimen

- ▶ Daily: Completion of treatment is 270 doses within 12 months. For patients who are unable or unlikely to complete 270 doses, treatment may be considered to be completed if they have taken the number of doses in the time frame needed to complete the daily 6H regimen below.
- ▶ Twice weekly by DOT: Completion of treatment is 76 doses within 12 months.

6H Regimen

- ▶ Daily: Completion of treatment is 180 doses within 9 months.
- ▶ Twice weekly by DOT: Completion of treatment is 52 doses within 9 months.

See **Appendix 2: Drugs for the Treatment of Latent Tuberculosis Infection** for information on each drug's preparations, dosages, administration, contraindications, adverse effects, and drug-drug interactions.

For information on treatment of drug-resistant TB, see **Contacts to Persons with Infectious Drug-Resistant Tuberculosis Disease** in **Section 5: Considerations for Specific Populations**.

Rifapentine and Isoniazid Daily for 1 month (1HP)

The BRIEF-TB study showed that a 1-month duration daily combination of rifapentine and isoniazid (1HP) matches the effectiveness of the 9-month isoniazid (9H) regimen for HIV-positive individuals with better completion rates. Based on this study, the World Health Organization recommends 1HP as an option in all settings for TB preventive treatment for both HIV-positive and HIV-negative individuals.

The US DHHS *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* (available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines>) in their recent updated LTBI recommendations, included 1HP as alternative regimen for persons with HIV.

The NTCA/CDC guidelines have not incorporated 1HP as a preferred or alternative choice mainly because the BRIEF-TB study centered on individuals with HIV in high-TB-prevalence areas, a majority of whom did not have a positive TB screening test result. Ongoing studies on ultra-short course treatments like 1HP could potentially influence future updates to the NTCA/CDC guidelines.

Based on the BRIEF-TB study's findings and the regimen's safety and convenience, some clinicians might explore 1HP as an option for LTBI treatment. When contemplating 1HP for LTBI treatment in HIV-positive individuals, clinicians should be aware that rifapentine is recommended in conjunction with efavirenz-based ART. However, in the United States, this combination is less common due to the availability of safer and more effective alternatives.

Given the limited experience with 1HP regimen, readers should consult the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* (available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines>). This source provides further information on 1HP dosing and its indications as an LTBI treatment option for people with HIV.

BASELINE LABORATORY TESTS

Obtaining baseline blood studies should be considered, including liver function tests and complete blood count (CBC), for the following patients:

- ◆ Patients with HIV infection
- ◆ Patients with daily or heavy alcohol use, liver disease, or chronic hepatitis
- ◆ Pregnant and postpartum patients (up to 2 to 3 months after delivery)
- ◆ Patients currently injecting drugs
- ◆ Patients on other potentially hepatotoxic medications
- ◆ Patients with prior elevated serum transaminase concentrations
- ◆ Patients with hematologic conditions
- ◆ Other patients based on clinical discretion

Test for hepatitis A, B, and C antibodies and obtain other tests as indicated. Offer HIV testing for all patients who do not know their HIV status. Some patients will require periodic follow-up laboratory studies based on the results of the baseline tests, the prescribed regimen, individual patient characteristics, and local programmatic preferences.

Routine laboratory testing may not be necessary in patients without any underlying medical conditions.

For recommendations on follow-up laboratory studies **Section 6: *Monitoring and Managing Treatment***.

INTERVENTIONS FOR TREATMENT COMPLETION CHALLENGES

None of the treatment regimens is effective unless it is completed. The health care provider should ask the patient about practical challenges to treatment—for example, clinic access, work schedule, lack of transportation, homelessness, or substance use—and should learn about the patient's perspective on LTBI and its treatment.

To address adherence barriers, consider one or more of the following interventions: prescribing a shorter treatment regimen, using directly observed or video directly observed therapy, providing incentives, ensuring enablers, and educating the patient.

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Although studies have shown that adherence to treatment is unpredictable, it may be reasonable to decide not to start treatment when a patient has one or more of the following barriers to adherence:

- ◆ History of medical nonadherence
- ◆ Life challenges affecting the ability to take scheduled medications regularly
- ◆ Current substance use disorder
- ◆ Poorly controlled mental illness or cognitive dysfunction
- ◆ Homelessness

For information on monitoring adherence and addressing treatment interruptions, see **Section 6: Monitoring and Managing Treatment**.

Methods of Treatment Administration

The three types of treatment administration are in-person directly observed therapy (DOT), video directly observed therapy (vDOT, live or recorded), and self-administered therapy (SAT).

With DOT, a trained health care worker is physically present when the patient ingests the medications and uses a symptom checklist for adverse effects. DOT is the best method to ensure medication adherence and monitor for side effects.

vDOT has emerged using secure platforms for live or recorded videos that facilitate observing medication ingestions remotely. vDOT provides greater patient flexibility while still ensuring the safe and effective completion of treatment.

SAT allows the greatest flexibility but places most of the responsibility for treatment adherence and monitoring of side effects on the patient.

Daily LTBI treatment regimens are typically administered by SAT. Depending on the individual patient and available resources, 3HP may be administered by SAT, DOT, or vDOT. Twice-weekly 6H and 9H should be administered by DOT or vDOT. In special circumstances, such as when patients are at high risk for adverse reactions, providers may want to administer other regimens by DOT. In certain settings, such as correctional facilities, all treatment is administered by DOT.

For more information on DOT and vDOT, see **Appendix 5: Directly Observed Therapy and Video Directly Observed Therapy**.

Incentives and Enablers

Incentives and enablers can sometimes be provided by the state or local TB program for patients treated in their programs. Incentives motivate the patient to complete treatment and can include gift cards or small cash payments. Enablers, which facilitate treatment completion, include a range of measures such as convenient office hours, transportation vouchers, using pharmacists and other health care providers to provide DOT, and providing cell phones or additional cell phone minutes for patients on vDOT. Reminder calls for patient clinic visits, minimizing clinic wait times, and performing pill counts can help promote adherence.



NURSE CASE MANAGEMENT

Public health TB programs may provide nurse case management services, DOT, incentives and enablers, and educational materials for patients with LTBI. Contact your state or local health department to determine its policy for LTBI treatment services. For more information on nurse case management, see **Section 7: Nurse Case Management**.

PATIENT EDUCATION

The health care provider should educate the patient about TB. Education can promote adherence by addressing any confusion and questions about transmission, exposure, infection, testing, and disease progression and by explaining the advantages of treatment.

All encounters with the patient should be conducted in the patient's preferred language and at the patient's educational level. A certified medical interpreter (by phone, video, or in person) and other assistance should be used as needed. During patient encounters, allow ample opportunity for the patient to ask questions.



CAUTION

For patients taking 3HP, see the **Special Note on Monitoring and Patient Education for 3HP** in the treatment description **Rifapentine and Isoniazid Once Weekly for 3 Months (3HP)** above in this section.

Educate the patient to “STOP all LTBI medications immediately and CALL” the clinical care team if any symptoms of adverse effects are suspected.

SECTION 4: DECIDING WHETHER TO TREAT AND CHOOSING A REGIMEN

Education is an ongoing process that should occur at every patient encounter. Before starting treatment, provide the patient an oral explanation and, whenever possible, written educational materials on the following topics:

- ◆ Advantages of completing LTBI treatment in the absence of symptoms or radiographic abnormalities
- ◆ Treatment plan
- ◆ Symptoms of adverse effects
- ◆ What to do about a suspected adverse effect
- ◆ Disease process
- ◆ Differences between injections, vaccines, and a TST or an IGRA
- ◆ The meaning of test results and of the words “positive” and “negative” as they relate to test results
- ◆ The meaning of a normal CXR in the context of infection
- ◆ Modes of TB transmission and prevention
- ◆ Difference between exposure and becoming infected
- ◆ Safety of family and friends around someone with LTBI

Patient education should be provided at each regular appointment as a tool to support the patient through treatment completion. Education is also important for early patient recognition of potential side effects and of signs and symptoms of adverse effects. If the patient declines treatment, provide education on the symptoms of active TB disease and the importance of seeking care promptly if TB symptoms should occur.



NURSE CASE MANAGEMENT

A state or local TB nurse consultant or liaison may provide expertise on the use of nurse case management services and patient education.

Check the NTCA online directory for a state or local TB nurse consultant in your area:

<http://www.tbcontrollers.org/community/statecityterritory/>

For information on nurse case management, see **Section 7: Nurse Case Management**.

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For patient education materials, consult these resources:

- ◆ Centers for Disease Control and Prevention: Patient and General Public Materials:
https://www.cdc.gov/tb/education/patient_edmaterials.htm and Patient Education Materials Series:
<https://www.cdc.gov/tb/publications/culturalmaterials.htm>
- ◆ Rutgers Global Tuberculosis Institute: Patient Education:
http://globaltb.njms.rutgers.edu/educationalmaterials/productlist_patient.php
- ◆ Southeastern National Tuberculosis Center: Patient Fact Sheets on Anti-TB Drugs and *You Can Prevent Tuberculosis: A Patient Education Handout* (various languages):
<https://sntc.medicine.ufl.edu/>

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SECTION 5:

Considerations for Specific Populations

OVERVIEW

When testing for and treating LTBI, some groups of patients have greater risk for progression to active TB disease or have medical conditions or social circumstances that require different approaches to test interpretation, clinical evaluation, treatment regimens, clinical and laboratory monitoring, and interventions to support completion of treatment.

SPECIFIC POPULATIONS

Review the following information on testing and treatment approaches when working with the following populations:

1. [Children](#)
2. [Pregnant, Breastfeeding, and Postpartum Persons](#)
3. [Persons with Comorbidities](#)
4. [Recent Contacts to Persons with Infectious TB Disease](#)
5. [Contacts to Persons with Drug-Resistant Tuberculosis Disease](#)
6. [Persons with Radiographic Findings of Previous or Inactive TB](#)
7. [Persons with Culture-Negative TB Disease](#)

RELATED TOPICS

- ◆ [Section 1: Immunologic Tests](#)
- ◆ [Section 3: Pretreatment Clinical Evaluation](#)
- ◆ [Section 4: Deciding Whether to Treat and Choosing a Regimen](#)
- ◆ [Section 6: Monitoring Treatment](#)
- ◆ [Appendix 2: Drugs for Treatment of LTBI](#)
- ◆ [Appendix 3: Dosages for Recommended Treatment Regimens](#)

WARNINGS

- ◆ Do not treat for LTBI until active TB disease is excluded.
- ◆ Educate the patient to stop medications immediately and call the health care provider if any symptoms develop that are concerning for an adverse effect.
- ◆ Consult with your state or local TB program or regional TB Center of Excellence.

CHILDREN

Whom to Treat

Treatment is recommended for all children and adolescents diagnosed with LTBI because of the following biological, medical, and social factors:

- ◆ Infants and young children are at higher risk for progression to TB disease.
- ◆ The medications used are generally well tolerated by children.
- ◆ Infection with *M. tuberculosis* is more likely to have been recent.
- ◆ Children have more potential time in which to develop TB disease during their entire life.

Window Period Treatment after Close Contact

Window period treatment refers to LTBI treatment given to someone with a negative test result but who had recent close contact to a person with pulmonary TB disease. The window period is the 8 or 10 weeks after the period of last potential exposure and represents the time it takes to develop an immunologic response that is detectable by a TST or IGRA. Window period treatment is most often given to young children but may also be considered for adults who are severely immunosuppressed.

All contacts aged <5 years, regardless of the initial test result, should be evaluated immediately with a symptom review, physical examination, and chest radiography. If there are no findings suggestive of TB disease, treatment for LTBI should be initiated promptly after evaluation. A second test should be administered 8 to 10 weeks after the last exposure to infectious TB.

If the result of the second test is negative, and the child is at least 6 months of age, window period treatment can be discontinued, and the child can be considered not infected. However, in some circumstances where TST and IGRA results may be unreliable (such as children < 6 months of age or severely immune compromised children or adults), the individual may receive a full course of LTBI treatment at the discretion of the treating physician.

If the result of the second test is positive, a full course of treatment for LTBI should be completed.

For information on contact investigations, see the topic *Contacts to Persons with Infectious Tuberculosis Disease* below in this section.

SECTION 5: CONSIDERATIONS FOR SPECIFIC POPULATIONS

Window period treatment can be discontinued if **all** of the following conditions are met:

- ◆ The infant is at least 6 months of age.
- ◆ The second test result is also negative.
- ◆ The second test was performed at least 8 weeks after the child was last exposed to an adult with infectious TB disease.

If the second test is positive or, if the treating physician deems it necessary, a full course of LTBI treatment should be administered.

Treatment Options

For regimens for LTBI treatment in children, see **Section 4: Deciding Whether to Treat and Choosing a Regimen** and **Appendix 2: Drugs for the Treatment of Latent Tuberculosis Infection**.

Do not treat children aged <2 years with the 3HP regimen, as the studies in children in this age range have not been completed.



TREATMENT OF TB IN CHILDREN FACT SHEET

For concise guidance on treating LTBI in children, see the *Treatment of Tuberculosis in Children – 2019* fact sheet from the Heartland National TB Center. It is available at https://www.heartlandntbc.org/wp-content/uploads/2022/03/TB_CHILDREN_TX_tbl_12.pdf.

Medications for LTBI may be crushed or the capsules opened, mixed with food, and immediately administered with minimal effect on bioavailability. Review the following tips on administering TB medications to children:

- ◆ Liquid formulations of medications may need to be compounded by a pharmacy. Sorbitol-based isoniazid formulation may cause diarrhea.
- ◆ Medications can be mixed with semi-solid food, such as yogurt, or with sugar preparations, such as grape jelly.
- ◆ Administer medications that are crushed and mixed with a food substance within 30 minutes of mixing. As the bioavailability of medications mixed with food can decrease rapidly over time, administer them as quickly as possible after mixing. They should not be stored overnight as glucose will chemically combine with isoniazid, producing an inactive substance.
- ◆ Older children can be encouraged to practice swallowing tablets using similarly sized candies.

Routine laboratory testing is generally not necessary in healthy children.

PREGNANCY, BREASTFEEDING, AND THE POSTPARTUM PERIOD

Whom to Treat

Pregnancy may not in itself be a risk factor for progression from LTBI to active TB disease. Screen pregnant persons for risk factors and test them only if they have a risk factor for infection or for progression to active TB disease.

For information on risk factors for infection or for progression from LTBI to active TB disease, see *Section 2: When to Test for Latent Tuberculosis Infection*.

An asymptomatic, pregnant person with a positive TB test result, either IGRA or TST, should receive a medical evaluation, including a CXR with a lead shield. The CXR may be deferred until after the first trimester **unless** the patient has one or more of the following:

- ◆ HIV or other immunosuppression
- ◆ History of recent contact with a person with infectious TB disease
- ◆ Documented TB infection test conversion in the past 2 years

In general, if a CXR was done in the 3 months prior to the medical evaluation, its findings were documented as normal, and the person is asymptomatic, then a repeat CXR is not necessary.

For all other asymptomatic patients with a positive TB test result, the CXR may be deferred to the second trimester. The CXR should not be deferred until the peri- or post-partum period.

For persons who access medical care only when they are pregnant, prenatal visits represent a unique opportunity for targeted testing and treatment of LTBI. Bear in mind that maternal health care benefits may be lost after one postpartum visit. If treatment is deferred, a referral should be made to a provider who offers treatment of LTBI.

Treatment Options

The decision of whether to treat LTBI during pregnancy should be made on a case-by-case basis.

Recommendations to delay LTBI treatment during pregnancy have largely been based on increased risk of hepatotoxicity with isoniazid. This increase in risk has not been documented with rifampin-based regimens. When making the decision whether to treat for LTBI in pregnant women, one should consider:

- ◆ Factors that would increase the risk of progression to active TB disease in non-pregnant persons (Section 2) are likely to increase the risk in pregnant individuals.
- ◆ The risk of poor outcomes to a pregnant individual and their child if active TB disease develops is significant. These risks can include
 - ▶ Potential for infectiousness at delivery which would expose providers as well as the infant to TB
 - ▶ Need for multiple medications in the post-partum period when hepatotoxicity is more prevalent
 - ▶ Most concerning, the potential for congenital TB, which has very high mortality

With better tolerated LTBI treatment available with rifampin, the benefits of treatment may outweigh the risk posed by treating during pregnancy.

First-line TB drugs are considered safe in pregnancy, and all LTBI regimens (with the exception of 3HP) can be used to treat LTBI in this population. 3HP has not been studied in pregnant women and should not be offered.

All first-line TB drugs are found in breast milk at low levels. Women can safely breastfeed while on any of the approved regimens for LTBI treatment. Rifampin monotherapy offers the shortest and most tolerable treatment option and should be considered. If a pregnant patient is unable to take rifampin, rifabutin is another drug that can be used safely in pregnancy.

Isoniazid monotherapy should be used with caution in pregnant persons, especially those with HIV.

Rifampin and isoniazid are found in breast milk at low levels. Breastfeeding is safe during any of the approved regimens for LTBI treatment.

Prescribe supplemental pyridoxine when a pregnant or breastfeeding patient is receiving isoniazid for the treatment of LTBI. The infant does not need supplemental pyridoxine unless the infant is receiving isoniazid treatment in addition to the mother.

Monitoring during Treatment

Some studies have shown an increase in hepatotoxicity in the first 3 months postpartum in patients taking isoniazid for LTBI; however, no studies have been done on the tolerance of other regimens given in the postpartum period. Consider laboratory monitoring throughout LTBI treatment if the patient is pregnant or in the postpartum period and taking isoniazid.

PERSONS WITH COMORBIDITIES

The treatment of patients with comorbid conditions may be challenging because of increased complications from drug-drug interactions and adverse effects. The treatment of LTBI in patients with some comorbidities has not been specifically studied. TB prevention for patients with HIV co-infection has been specifically studied, with proven efficacy for 6H and 3HP.

Human Immunodeficiency Virus Infection

TB remains the leading cause of death among people with human immunodeficiency virus (HIV). The diagnosis and treatment of LTBI in this population significantly reduces morbidity and mortality. Therefore, all persons with HIV infection should be screened for LTBI, which should include a test for TB infection, as soon as HIV infection is diagnosed regardless of their epidemiologic risk of TB exposure. Patients with a negative TB test result with advanced HIV infection (defined as a CD4 cell count <200 cells/mm³) who may have a false-negative test result should be retested once they attain a CD4 count ≥ 200 cells/mm³ or if they have ongoing risk for TB exposure.

The sensitivity of immunologic tests for TB infection is reduced in persons with HIV infection and further declines as the CD4 count is depleted. For this reason, if the HIV-infected person with a CD4 count <200 cells/mm³ has a negative test result for TB infection and has a significant risk factor for having acquired TB infection (close contact with a person with infectious TB disease, for example), many experts recommend performing a second test for TB infection. Annual testing for LTBI is not recommended for people with HIV in low incidence settings, unless they are at high risk of repeated infection or have a recent exposure to active TB disease. (See Section 2: When to Test for Latent Tuberculosis Infection.)

Because of the high rate of progression to TB, window period treatment for possible LTBI is recommended for persons with HIV infection after exposure to TB, regardless of TB test results or prior history of treatment for TB infection or disease. Window period treatment refers to LTBI treatment given to someone with a negative test result but who had recent close contact to a person with pulmonary TB disease. The window period is the 8 or 10 weeks after the period of last potential exposure and represents the time it takes to develop an immunologic response that is detectable by a TST or IGRA. A pretreatment clinical evaluation should exclude TB disease before treatment for LTBI is started. Treatment for LTBI in these patients generally should be completed even if LTBI testing is negative. Persons who receive a full course of treatment should still have a second test 8-10 weeks after the last exposure to infectious TB to document conversions to positive and for contact investigation purposes.

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Detailed recommendations for coadministration of rifamycins and antiretroviral drugs have been published in multiple HIV guidelines. For patients taking ART with interactions with rifamycins, many experts recommend isoniazid daily for 6 to 9 months. For patients not taking ART or taking an ART regimen that does not have interactions with rifamycins, a shorter, rifamycin-based regimen such as 3HP or 4R can be prescribed.

The recent *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* recommend 1HP as an LTBI treatment alternative. However, 1HP is not included by the current CDC/NTCA guidelines as an alternative. (See Section 4: Deciding Whether to Treat and Choosing a Regimen.)

Rifabutin, with dose adjustments, may be able to be substituted for rifampin for use with certain ART regimens. Consider consulting an expert in managing HIV and TB for treatment of LTBI.

Iatrogenic Immunosuppression

Adults and children with iatrogenic immunosuppression because of anti-inflammatory immune-modulating drugs, cancer chemotherapy, or solid organ or bone marrow transplants are at increased risk of LTBI progressing to active TB disease. The risk of progression depends upon the underlying disease state and the immunosuppressive treatments used.

A test for TB infection should be performed prior to initiation of any immunosuppressive treatment, and patients with LTBI should begin treatment prior to the start of immunosuppressive treatment. Most experts recommend starting an immunosuppressive agent after at least 1 month of LTBI treatment has been completed to ensure adherence to and tolerance of the selected LTBI regimen. This recommendation is particularly applicable when initiating biologic agents (see below). However, sometimes 1 month of LTBI treatment cannot be completed prior to immunosuppression, and the medical necessity of an immunosuppressive treatment or transplant may outweigh the risks of not having 1 or more months of LTBI treatment completed.

In a contact investigation, window period treatment for possible LTBI is recommended for contacts with iatrogenic immunosuppression regardless of their immunologic test results because of this population's high rate of progression to TB. Window period treatment refers to LTBI treatment given to someone with a negative test result but who had recent close contact to a person with pulmonary TB disease. The window period is the 8 or 10 weeks after the period of last potential exposure and represents the time it takes to develop an immunologic response that is detectable by a TST or IGRA. A pretreatment clinical evaluation should exclude TB disease before treatment for presumed LTBI is started. Treatment for LTBI in these patients should be completed if the subsequent TST or IGRA is positive at repeat testing in 8 to 10 weeks from last exposure. For immunosuppressed patients who are close contacts to an active TB case (for example, a household member), LTBI treatment should be completed regardless of the repeat TST or IGRA. These persons should still have a second test 8-10 weeks after the last exposure to infectious TB to document conversions to positive and for contact investigation purposes.

Transplantation

Solid organ transplant recipients and persons receiving bone marrow transplants are at higher risk of having LTBI progress to active TB disease. Bone marrow transplantation is associated with a risk of progression to active TB disease at approximately 10 times the background rate.

Cancer and Chemotherapy

Both cancer and cancer chemotherapy could be associated with an increased risk of progression to active TB disease, and these patients should be screened for TB risk factors.

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Anti-Inflammatory Immunosuppressive Drugs

Anti-inflammatory immunosuppressive drugs can increase the risk of progression to active TB disease by downregulating the immunologic functions that contain TB organisms. This risk varies by drug class and mechanism of action.

Corticosteroid-induced immunosuppression increases the risk in a dose-dependent fashion, with higher rates of disease seen with prolonged administration (prednisone equivalent of ≥ 2 mg/kg/day, or ≥ 15 mg/day for ≥ 1 month).

Treatment with biologic agents, particularly inhibitors of TNF-alpha, leads to markedly higher rates of progression to active TB disease. The risk from biologic agents varies by the drug and its mechanism of action. Infliximab and adalimumab (monoclonal anti-TNF-alpha antibodies) are associated with a higher risk than etanercept (soluble TNF-alpha receptor). Population-based studies with other non-TNF biologics such as tocilizumab have reported higher risk of TB, but generally lesser risk with abatacept or rituximab. Synthetic targeted small molecules such as Janus kinase (JAK) inhibitors also appear to increase TB risk. Patients should be screened for LTBI with a TST or IGRA prior to starting these immunomodulatory treatments. If a patient tests positive by TST or IGRA, active TB disease must be excluded. Emerging evidence demonstrates that the use of PD1/PDL1 checkpoint inhibitors has been associated with progression to active TB disease, and assessment for LTBI may be indicated. Current PD1/PDL1 checkpoint inhibitors include pembrolizumab (Keytruda), nivolumab (Opdivo), cemiplimab (Libtayo), atezolizumab (Tecentriq), avelumab (Bavencio), and durvalumab (Imfinzi).

The list of available biologic agents continues to increase, and our understanding of the risk for developing active TB with these agents is evolving. Before initiating any biologic agent, refer to the manufacturer's package insert to see if testing for LTBI is indicated. Patients diagnosed with LTBI should be started on treatment prior to initiating the immunosuppressive treatment. Patients taking immunosuppressive medications and at increased risk of exposure should be screened annually for new TB infection, or sooner if exposed to a case of active TB disease.

Table 4 summarizes the risk of TB for a select list of biologic and small molecule therapies as of June 2022. The highest risk is with biologic agents that block JAKs, interleukin-6 (IL-6), and TNF-alpha. There is lower risk with interleukin-17 (IL-17) and interleukin-23 (IL-23). Note that this list of immunosuppressive drugs does not include all immunosuppressive drugs. There are new biologic agents coming into the market. For patients who are receiving these agents, consult with a TB specialist.

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Table 4. Select Biologic Agents and Mechanisms of Action, June 2022

Drug	Mechanism of Action	Risk of TB
Higher Risk of TB		
adalimumab	Monoclonal anti-tumor necrosis factor-alpha (TNF-alpha) antibodies	Higher
baricitinib	Janus kinase (JAK) inhibitor	Higher
certolizumab	Anti-TNF-alpha antibody (Fab' fragment)	Higher
etanercept	Soluble TNF receptor fusion protein	Higher
filgotinib	JAK inhibitor	Higher
golimumab	Anti-TNF-alpha kappa IgG1	Higher
infliximab	Monoclonal anti-TNF-alpha antibodies	Higher
peficitinib	JAK inhibitor	Higher
sarilumab	Interleukin (IL)-6 blockade	Higher
tocilizumab	IL-6 receptor inhibitor	Higher
tofacitinib	JAK inhibitor	Higher
upadacitinib	JAK inhibitor	Higher
Potentially Increased Risk of TB		
abatacept	Selective T cell costimulation modulator	Potentially Increased
anakinra	IL-1 receptor antagonist	Potentially Increased
belimumab	B-cell inhibitor	Potentially Increased
brodalumab	IL-17 receptor antibody	Potentially Increased
canakinumab	Anti-IL-1 beta monoclonal antibody	Potentially Increased
guselkumab	IL-23 blockade	Potentially Increased
ixekinumab	IL-17 blockade	Potentially Increased
risankizumab	IL-23 blockade	Potentially Increased
rituximab	B-cell depletion	Potentially Increased
rilonacept	IL-1 inhibitor	Potentially Increased
secukinumab	IL-17 blockade	Potentially Increased
tildrakizumab	IL-23 blockade	Potentially Increased
ustekinumab	IL-12 and IL-23 monoclonal antibody	Potentially Increased

Liver Disease and Chronic Viral Hepatitis

If LTBI treatment is indicated, some experts recommend treatment with 4R. Isoniazid may cause drug-induced hepatotoxicity. The risk and severity of hepatotoxicity with isoniazid is increased when a patient has underlying liver disease. Less frequently, rifamycins also may cause hepatotoxicity.

Be aware of the following risk factors for underlying liver disease:

- ◆ History of regular alcohol ingestion
- ◆ Injection drug use
- ◆ HIV infection
- ◆ History of liver disease including non-alcoholic steatosis
- ◆ Known hepatitis B or C
- ◆ Birth in Asia or Africa where hepatitis B and C are common
- ◆ Malnutrition
- ◆ Use of other hepatotoxic drugs

For patients with risk factors for, symptoms of, or clinical signs of liver disease, check baseline laboratory tests including CBC, serum transaminase concentrations, and serologic testing for hepatitis A, B, and C.

For monitoring persons with risk factors for liver disease, see **Section 6: *Monitoring and Managing Treatment***.

Isoniazid is contraindicated for patients with advanced liver disease indicated by any of the following test results: transaminases >3 to 5 times the ULN, elevated total bilirubin >2.0, prolonged international normalized ratio (INR), prothrombin time (PT), or partial thromboplastin time (PTT). If LTBI treatment is indicated, some experts recommend treatment with 4R.

Patients treated with isoniazid should limit or avoid the concomitant use of alcohol, hepatotoxic drugs such as acetaminophen, and herbal supplements.

Chronic Kidney Disease and End-Stage Renal Disease

Persons with chronic kidney disease (CKD) and end-stage renal disease (ESRD) have an increased risk of TB compared to the general population. Some of these patients have other comorbidities, such as diabetes, that also increase the risk of progression to active TB disease. Prevention of TB in CKD patients is very important because of the possibility of TB transmission in health care facilities such as dialysis centers, the anticipation of renal transplantation, and the difficulty diagnosing and treating TB disease in CKD/ESRD patients.

CKD/ESRD patients have impaired cell-mediated immunity, and some have cutaneous anergy, making a negative TST result less reliable because of concerns about a false-negative result. In a small case series of IGRA testing in ESRD patients, the rate of indeterminate QuantiFERON results or invalid T-Spot results was greater than among healthy subjects.

Evaluate a patient for TB infection as soon as the diagnosis of CKD is made. Testing for TB infection during the earlier stages of CKD, when cell-mediated immunity may be less impaired, may maintain the sensitivity of the TST or IGRA. If the patient is diagnosed with LTBI, treatment is generally indicated.

Isoniazid and rifamycins are primarily metabolized by the liver and can be used for LTBI treatment in patients with CKD. Dose adjustment of these medications is not necessary. These medications should be given after hemodialysis on the day of dialysis.

There is limited data on the use of 3HP in CKD/dialysis patients, but small reported case series demonstrate mixed results. Completion rates range from 65.4% to 93% and the rate of adverse events from 7.0% to 69.2%. In these studies, with small numbers of patients, there was no hepatotoxicity or death seen with the 3HP regimen. The main adverse events were fatigue, fever, nausea, vomiting, and dizziness. Administer 3HP after hemodialysis and at the start of the longest interval between hemodialysis treatments to allow the drugs to stay in the system for as long as possible.

If the patient is on hemodialysis, consider providing DOT at the dialysis facility. To facilitate DOT, provide dialysis staff with medications, medication administration reporting forms, education on the possible adverse effects, and instructions to stop the treatment and contact the health care provider if the patient reports adverse effects.

For information on providing DOT at a dialysis facility, refer to **Appendix 4: Collaborations Between the Public Health Department and Community Service Providers**.

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Diabetes

Poorly controlled diabetes increases the risk of progression from LTBI to active TB disease two- to three-fold.

In some populations with high incidence of TB and diabetes (including, but not limited to, Pacific Islanders and Native Americans), TB testing should be routine. All patients with diabetes should be screened for TB risk factors. If risk factors are present, they should be tested for TB. In a low-TB-incidence country like the United States, testing for LTBI is not recommended solely on the basis of diabetes. However, persons with LTBI and diabetes should generally be treated for LTBI.

For a full discussion of TB risk factors, see **Section 2: When to Test for Latent Tuberculosis Infection.**

Rifamycins decrease the levels of many anti-diabetic agents including sulfonylureas, meglitinide analogues, thiazolidinediones, and dipeptidyl peptidase IV inhibitors. Although rifamycins are generally not contraindicated when patients are taking these anti-diabetic agents, monitor blood glucose more closely while the patient is on LTBI treatment.

Isoniazid may exacerbate diabetic peripheral neuropathy during the treatment of LTBI, and pyridoxine (vitamin B6) 25 to 50 mg daily should be routinely prescribed.

Substance Use Disorders

Persons with substance use disorders, including alcohol or other recreational drugs, tend to be overrepresented in patients with active TB disease in the United States. Transmission of TB has been documented to occur in this population, and substance use is known to be biologically and socially connected with progression to TB. For these reasons, testing and treatment of persons with substance use disorders is recommended.

To minimize drug toxicities when choosing an LTBI treatment, determine which prescription or non-prescription drugs, including herbal medications, the patient is taking. If a chosen TB medication decreases the effectiveness of another drug being taken, the patient may have decreased incentive to continue treatment. In general, patients with substance use disorder should be counseled and referred to drug treatment programs based on their motivation and available resources.

Alcohol

LTBI treatment in persons with alcohol use disorder requires careful monitoring, and the patient should be counseled to avoid other hepatotoxic agents. In some cases, the risk of liver toxicity with continued alcohol consumption may outweigh the benefits of treatment.

Persons consuming alcohol are at 4 times greater risk of isoniazid-induced hepatitis than persons who do not consume alcohol. In these patients, 3HP or 4R may be a better choice. If 3HP is used, you may decide to check transaminases 2 weeks into treatment. If a patient does not stop consuming alcohol and is unable to tolerate treatment with 3HP or rifampin, then isoniazid may be used with careful monitoring of transaminases.

For information on monitoring hepatotoxicity, see **Section 6: *Monitoring and Managing Treatment***.

Opioids

The rifamycins increase the metabolism of opioids such as heroin, codeine, morphine, and methadone. Rifabutin has less effect than other rifamycins on the metabolism of opioids and generally is preferred as a treatment option. If the rifamycins cannot be used, isoniazid is an acceptable alternative in patients using opioids.

In situations where rifampin or rifapentine may need to be used, be aware that starting these rifamycins can induce an opioid withdrawal. Conversely, when stopping the rifamycin, patients should be counseled about the increased risk of opioid overdose, particularly if use or dosages increased while on LTBI treatment. The provider should

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contact the methadone maintenance program, and many programs will adjust the dosage of methadone accordingly.

DOT is recommended for such patients if feasible. If the patient is enrolled in a methadone maintenance program, LTBI treatment can be observed at that facility.

Benzodiazepines

Rifampin also greatly increases the metabolism of benzodiazepines, which may negate many of the anxiolytic effects of these drugs.

RECENT CONTACTS TO PERSONS WITH INFECTIOUS TUBERCULOSIS DISEASE

A *TB contact* is someone who has been exposed to *M. tuberculosis* infection by sharing air space with a person with infectious TB disease. TB contacts are at high risk of both being infected with TB and, if infected, progressing to active TB disease, commonly within 2 years of infection.

For each person diagnosed with active infectious TB, the state or local TB program will perform a *contact investigation* to identify that person's contacts and ensure appropriate evaluation and treatment that may be conducted by providers outside of the TB program. If a contact presents for care before being identified by the TB program, the health care provider should contact the TB program to discuss the evaluation and treatment.

Contacts should be tested with an IGRA or TST and evaluated for active TB disease unless documented to have been previously positive.

If the initial test result is negative, the test is repeated 8 to 10 weeks after the period of last potential exposure, and window period treatment may be considered.

Window period treatment refers to LTBI treatment given to someone with a negative test result but who had recent close contact to a person with pulmonary TB disease. The window period is the 8 or 10 weeks after the period of last potential exposure and represents the time it takes to develop an immunologic response that is detectable by a TST or IGRA. Window period treatment is most often given to young children but may also be considered for adults who are severely immunosuppressed. All contacts aged <5 years, regardless of the initial test result, should be evaluated immediately with a symptom review, physical examination, and chest radiography. If there are no findings suggestive of TB disease, treatment for LTBI should be initiated promptly after evaluation. A second test should be administered 8 to 10 weeks after the last exposure to infectious TB. If the result of the second test is negative, and the child is at least 6 months of age, window period treatment can be discontinued, and the child can be considered not infected. However, in some circumstances if the result of the second test is positive, a full course of treatment for LTBI should be completed.

For contacts aged between 5 and 17 years with a negative test result, treatment for LTBI may be started at the discretion of the physician in consultation with the state or local TB program. For more information on evaluation and treatment of contacts 17 years and younger, see the topic on *Children* in this section.

Immunosuppressed contacts of any age, who may have a false-negative TB test, should generally complete treatment for LTBI regardless of their test results. These contacts should still have a second test 8-10 weeks after the last exposure to infectious TB to document conversions to positive and for contact investigation purposes. Consult with your state or local TB program

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on treatment of these contacts. For more information on evaluation and treatment of immunosuppressed contacts, see the topics on *HIV Infection* and *Iatrogenic Immunosuppression* in this section.

Evaluation of a contact with a positive test result should include a symptom review, assessment for additional TB risk factors, physical examination, and a CXR. For information on evaluation, see **Section 3: Pretreatment Clinical Evaluation**.

If active TB is excluded, the patient should be treated for LTBI with a regimen to which the organism in the index case was susceptible. If the isolate showed isoniazid monoresistance, the patient should generally be treated with 4R.

In general, patients are treated for LTBI only once. Some circumstances, such as re-exposure to a highly infectious source case patient, may indicate re-treatment for presumptive reinfection, especially in immunocompromised patients. Seek consultation from your state or local TB program, regional TB Center of Excellence, or an expert clinician in these circumstances.

For more information on testing and treatment:

- ◆ Testing for TB infection, see **Section 1: Immunologic Tests for Tuberculosis Infection**.
- ◆ Additional risk factors see **Section 2: When to Test for Latent Tuberculosis Infection**.
- ◆ How to diagnose LTBI, see **Section 3: Pretreatment Clinical Evaluation**.
- ◆ Treatment regimens see **Section 4: Deciding Whether to Treat and Choosing a Regimen**.

For information on testing, evaluating, and treating high-risk groups:

- ◆ Pediatric contacts see **Section 5: Considerations for Specific Populations: Children**.
- ◆ Contacts with HIV see **Section 5: Considerations for Specific Populations: Persons with Comorbidities: Human Immunodeficiency Virus Infection**.
- ◆ Contacts with other immunosuppressive conditions, see **Section 5: Considerations for Specific Populations: Persons with Comorbidities: Iatrogenic Immunosuppression**.

CONTACTS TO PERSONS WITH INFECTIOUS DRUG-RESISTANT TUBERCULOSIS DISEASE

There is no direct test for drug susceptibility in a patient with LTBI. When the index patient is known, treatment decisions should be based on the drug susceptibility test results of the index patient.

Isoniazid Resistance

Isoniazid resistance with rifampin susceptibility is the most frequently encountered TB drug resistance pattern in the United States. Recent contacts to isoniazid-resistant TB disease generally should be treated with the 4R regimen.

Multidrug Resistance

Multidrug-resistant (MDR) TB is defined as resistance to both isoniazid and rifampin, with or without resistance to other drugs. Consider MDR-LTBI in a patient with LTBI who is known, or likely, to be a contact to a person with infectious MDR-TB disease.



Expert consultation should be obtained for these patients.

Prior to the decision to treat, evaluate the contact to determine the likelihood that LTBI resulted from exposure to MDR-TB based on the infectiousness of the source MDR-TB case patient, the closeness and intensity of exposure, and the likelihood of prior infection with a drug-susceptible strain.

Individualized treatment should be given to those for whom LTBI is likely to be due to MDR-TB based on the source case patient's drug susceptibility results. Optimal regimens and duration of treatment for MDR-LTBI are not known. Several clinical trials are in progress.

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Current LTBI treatment regimens most frequently use a third-generation fluoroquinolone:

- ◆ Regimens use levofloxacin or moxifloxacin for 6 months. The length of treatment can vary based on clinical and epidemiological factors.
- ◆ No fluoroquinolones have an FDA-approved indication for treating TB infection (LTBI or active TB disease). All fluoroquinolones are labeled for short-term administration, and the potential adverse effects of long-term administration should be reviewed with the patient.

If the source case patient's isolate is resistant to fluoroquinolones and the contact is at increased risk of progressing to active TB disease, LTBI treatment decisions should be made in consultation with an expert in treating drug-resistant TB.



DRUG-RESISTANT TUBERCULOSIS: A SURVIVAL GUIDE FOR CLINICIANS

For detailed information regarding drugs for treatment after exposure to drug-resistant TB, see the forthcoming updated edition of the *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians* available in December 2022 at <http://www.currytbcenter.ucsf.edu/> in the Products listings.

Whether or not a contact with LTBI is treated, the CDC recommends follow-up of contacts to persons with infectious MDR-TB disease with clinical and radiographic evaluation at 6 to 12-month intervals for a total of 2 years.

PERSONS WITH RADIOGRAPHIC FINDINGS OF PREVIOUS OR INACTIVE TUBERCULOSIS



Decisions on the evaluation and treatment of patients with this condition should be made in coordination with the state or local TB program. All patients started on empiric treatment for suspected active TB disease should be reported to the state or local TB program.

Persons with radiographic evidence (CXR or computed tomography) consistent with prior active TB disease and who were not adequately treated are at increased risk of recurrent active TB disease. Radiographic findings consistent with prior active TB disease include fibro-nodular lesions and fibrosis, frequently in the upper lobes. The radiographic findings alone cannot differentiate active TB disease from latent TB infection even in people who are asymptomatic. Active TB disease should be evaluated in people with an abnormal chest imaging by collecting sputum for AFB smear, culture, and NAAT testing. For more information on these tests, see **Section 3: Pretreatment Clinical Evaluation: Bacteriologic Studies**.

Patients with signs or symptoms of active TB disease or who have a high risk of transmitting TB if the diagnosis is delayed should be considered for empiric treatment of active TB disease with 4 drugs and reported to the public health department while awaiting culture results. Do not start treatment for LTBI until culture results have been finalized.

PERSONS WITH CULTURE-NEGATIVE TUBERCULOSIS DISEASE



Decisions on the evaluation and treatment of patients with this condition should be made in coordination with the state or local TB program. All patients started on empiric treatment for suspected active TB disease should be reported to the state or local TB program.

Lack of success in isolating *M. tuberculosis* from satisfactorily collected specimens in persons with radiographic evidence of previous or inactive TB does not exclude a diagnosis of active TB disease. Depending on the clinical presentation, alternative diagnoses must be considered, and other appropriate diagnostic studies should be performed before making a probable diagnosis of AFB smear- and culture-negative TB disease.

A short 4-month treatment regimen is recommended for AFB smear- and culture-negative pulmonary TB with an intensive phase of isoniazid, rifampin, ethambutol, and pyrazinamide and a continuation phase of 2 drugs (isoniazid and rifampin) for 2 months. Some experts may continue all 4 drugs for the 4 months if the patient is tolerating them, has a history of TB treatment, or comes from a country with high rates of drug resistance.

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SECTION 6:

Monitoring and Managing Treatment

OVERVIEW

Patients undergoing treatment for LTBI will have different risks for progression to active TB disease, medical conditions that may increase their risk for toxicity, and socio-economic barriers to adherence that require different approaches to clinical and laboratory monitoring and interventions to support treatment completion.

GENERAL PRINCIPLES

Treatment monitoring is recommended for all patients being treated for LTBI to detect potential adverse effects of the medication and to support treatment completion. To ensure a patient-centered approach, these principles should be followed in monitoring treatment:

- ◆ Always talk to patients in their preferred language using a medical interpreter unless a patient specifically indicates a preference to have a family member or friend translate.
- ◆ Ask if patients have any concerns about their treatment before asking targeted questions about specific potential side effects.
- ◆ Approach adherence difficulties with an openness to understanding what barriers the patient is experiencing and a willingness to make changes to address these barriers.

STEPS IN TREATMENT MONITORING

Review the following information concerning the essential components of monitoring treatment:

1. [Periodic Assessment](#)
2. [Clinical Monitoring](#)
3. [Laboratory Monitoring](#)
4. [Interventions for Treatment Completion Challenges](#)
5. [Management of Adverse Effects](#)
6. [Management of Treatment Interruption](#)
7. [Follow-up after Treatment Completion](#)

RELATED TOPICS

- ◆ [Appendix 2: Drugs for Treatment of LTBI](#)
- ◆ [Appendix 3: Dosages for Recommended Treatment Regimens](#)

WARNINGS

- ◆ Educate the patient to stop medications immediately and call the health care provider if any symptoms develop that are concerning for an adverse effect.
- ◆ Consult with your state or local TB program or regional TB Center of Excellence.

PERIODIC ASSESSMENT

The health care provider should conduct a clinical assessment at least monthly. Assess the patient for signs and symptoms of active TB disease, medication adherence, and adverse effects at least monthly during treatment. This assessment may be performed in person or by telephone or via other electronic technology, considering the risk of hepatotoxicity or other serious adverse effects. Most experts recommend a face-to-face evaluation when a patient has symptoms of an adverse effect.

During the periodic assessment, the health care provider should complete the following tasks:

- ◆ Assess the patient's adherence with treatment.
- ◆ Perform a symptom review for symptoms of an adverse effect and further assess a patient who reports any such symptoms.
- ◆ Conduct directed clinical examinations as needed.
- ◆ Obtain laboratory tests as clinically indicated.
- ◆ Provide medications sufficient to last until the next assessment, with a few extra doses to minimize disruptions in treatment.
- ◆ Continue to educate the patient about the symptoms of adverse effects, the advantages of completing treatment, and the length of treatment.

All encounters with the patient should be conducted in the patient's preferred language and at the patient's educational level. A certified medical interpreter (by phone, video, or in person) and other assistance should be used as needed. Continue to educate the patient about the symptoms of adverse effects and the need to immediately stop medication and call the health care provider if symptoms of adverse effects occur. Give ample opportunities for the patient to ask questions.

For patients taking 3HP by DOT, the health care worker who administers medications should ask specifically about any symptoms that may have followed the previous dose. Patients taking 3HP by SAT should be educated at baseline and asked specifically about any symptoms during monthly evaluations.

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Communicate carefully to ensure that the patient does not miss appointments or doses:

- ◆ Send reminder communications.
- ◆ Remind the patient to bring in medication bottle(s).
- ◆ Follow up promptly on missed appointments to prevent interruption or cessation of treatment.



CAUTION

Educate the patient to “STOP all LTBI medications immediately and CALL” the clinical care team if any symptoms of adverse effects are suspected.



PATIENT PERIODIC CLINICAL ASSESSMENT

State and local TB programs may have a state TB nurse consultant or liaison who can provide nurse case management services or information on clinical standardized assessments tools that may be utilized.

Check the NTCA online directory at <http://www.tbcontrollers.org/community/statecityterritory/>

See **Section 7: Nurse Case Management** for links to examples of nursing assessment tools and resources and more information on nurse case management.

CLINICAL MONITORING

At the periodic assessments, perform a symptom review for adverse effects, including unexplained symptoms such as the following:

- ◆ Flu-like symptoms (fever, chills, myalgias)
- ◆ Headaches
- ◆ Syncope or near-syncope
- ◆ Rash
- ◆ Easy bruising
- ◆ Anorexia, nausea, vomiting, weight loss
- ◆ Abdominal pain (especially in the right upper quadrant)
- ◆ Jaundice, dark urine
- ◆ Paresthesia of the hands or feet
- ◆ Persistent fatigue and weakness

For patients with symptoms of a possible adverse effect, perform directed physical examinations as needed to evaluate those symptoms.

LABORATORY MONITORING

Consider obtaining follow-up liver function tests monthly (or more frequently when clinically indicated) for patients with the following test results, symptoms, or medical history:

- ◆ Patients with daily or heavy alcohol use, liver disease, or chronic hepatitis
- ◆ Pregnant and postpartum patients (up to 2 to 3 months after delivery)
- ◆ Patients currently injecting drugs
- ◆ Patients on other potentially hepatotoxic medications
- ◆ Patients with prior elevated serum transaminase concentrations
- ◆ Other patients based on clinical discretion

Additional baseline labs and periodic laboratory testing should be performed as clinically indicated or based on programmatic preferences.

Offer HIV testing for all patients who do not know their HIV status.

Routine laboratory testing may not be necessary without any underlying medical conditions. For recommendations on baseline laboratory studies see *Section 4: Baseline Laboratory Tests*.

INTERVENTIONS FOR TREATMENT COMPLETION CHALLENGES

The health care provider should assess what motivates the patient and identify any barriers that may interfere with adherence to treatment. The state or local TB program may be able to offer nurse case management services to assist patients in completing treatment. For more information, see **Section 7: Nurse Case Management**.

Treatment with DOT or vDOT provides a direct assessment of the doses taken and missed and offers opportunities to enforce patient understanding and assess for adverse effects. For patients taking SAT, gather information for an accurate assessment of medication adherence. Check patient pill bottles to monitor pill counts. If pill bottles are not available, contact the patient's pharmacy to determine the dates and quantities of medication dispensed. Patients commonly over-estimate the number of doses actually ingested. Patients who experience minor adverse effects may skip doses to reduce these symptoms; this practice should be discouraged.

For patients who have missed doses of their medication, assess and address barriers to treatment adherence to the extent possible. For example, many patients simply forget to take their medication regularly. Advise the patient to take the medication at the same time each day, perhaps in association with a specific meal or an activity such as brushing teeth. Using a calendar or an electronic reminder may be helpful. Other patients may have psychosocial problems, such as homelessness or a substance use disorder, that make adherence difficult. For these patients, consider a referral to a social services support agency.

For information on identifying barriers to treatment completion, see **Section 4: Deciding Whether to Treat and Choosing a Regimen: Interventions for Treatment Completion Challenges**.

For information on managing regimens when treatment is interrupted, see the **Management of Treatment Interruption** topic below.

MANAGEMENT OF ADVERSE EFFECTS

Adverse effects vary in severity from minor reactions, during which LTBI treatment may be continued with symptomatic management of the adverse effect, to severe reactions, during which treatment must be discontinued. Adverse effects can result in hospitalization, serious complications such as liver transplantation, or death. Early detection of adverse effects, especially by the patient, can minimize the risk of such events. When the LTBI regimen needs to be stopped and the adverse effect has resolved, often an alternative regimen can be used.

The following recommended responses to adverse effects are based on expert opinion. For a list of adverse effects to each drug, see **Appendix 2: Drugs for the Treatment of Latent Tuberculosis Infection**.

Arthritis

- ◆ Arthralgias are fairly common with isoniazid, sometimes very challenging for the patient although they resolve when drug is stopped. These are not associated with positive markers for systemic lupus erythematosus (SLE).
- ◆ Isoniazid can also induce SLE or a lupus-like syndrome, with arthralgias and even alopecia. If markers for SLE are positive, discontinue isoniazid and refer the patient to a rheumatologist.
- ◆ Joint pain rarely is caused by the rifamycins.

Dermatologic Reactions

- ◆ Evaluate for other causes of a rash by obtaining a history for exposure.
- ◆ Discontinue treatment if fever, mucous membrane involvement, or systemic toxicity occurs with the rash.
- ◆ Maculopapular rash (a fine pink rash) usually resolves without discontinuing an LTBI regimen. It can be treated with over-the-counter hydrocortisone cream, other topical agents, or an antihistamine.
- ◆ Significant dermatologic reactions may involve other organ systems. Check laboratory test results for liver, renal, and hematologic toxicity. Consider a dermatology consultation.

Gastrointestinal Reactions

- ◆ Gastrointestinal discomfort can be seen early in treatment and may resolve.
- ◆ Nausea may be averted by consuming food with the medication.
- ◆ More severe nausea and sometimes vomiting can occur early in treatment, and LTBI treatment may need to be discontinued. Test serum transaminase concentrations.

Hematologic Reactions

- ◆ Rifampin and rifapentine can cause leukopenia or thrombocytopenia.
- ◆ If severe thrombocytopenia develops, do not re-start rifamycins.
- ◆ If the white blood cell count (WBC) is decreased, check the absolute neutrophil count (ANC). If the ANC remains >1000 , rifampin can generally be continued with frequent monitoring of the ANC count.
- ◆ Follow the WBC as needed if a rifamycin is continued. If leukopenia is marked, stop the rifamycin and refer the patient to a hematologist.
- ◆ Educate the patient to notify the health care provider if signs or symptoms of infection occur or, if the health care provider cannot be reached, to seek care at a local emergency department.
- ◆ Isoniazid can cause leukopenia, although this is unusual. If the WBC is only slightly decreased, it can be monitored. If leukopenia is marked, stop isoniazid and refer the patient to a hematologist.

Hepatotoxicity

Isoniazid can cause hepatotoxicity, which can be serious and may lead to hospitalization, liver transplantation, or death. Less frequently, rifamycins also may cause hepatotoxicity.

ALT (serum glutamic-pyruvic transaminase [SGPT]) is more specific for hepatocellular injury. AST (serum glutamic-oxaloacetic transaminase [SGOT]) also may indicate injury to heart, kidney, and skeletal muscle. Mild elevations in ALT less than 3 times the ULN occur commonly in the first month of treatment and are not a reason to stop LTBI treatment.

If the bilirubin, alkaline phosphatase, or both are increased, but the hepatocellular enzymes are minimally elevated, consider evaluation for hepatocellular obstruction and consider other causes of hepatitis, such as viral hepatitis, gallstones, or pancreatitis, in the differential diagnosis. Rifampin more commonly causes a cholestatic pattern.

If transaminase levels are >3 times the ULN and the patient is symptomatic, or if the transaminase levels are >5 times the ULN and the patient is not symptomatic, discontinue treatment.

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If the transaminase levels are greater than normal but <5 times the ULN and the patient has no symptoms, continue treatment, but advise the patient to stop medication immediately if symptoms occur. Monitor serum transaminase concentrations at least monthly, even if the patient remains asymptomatic.

If treatment with isoniazid is discontinued, continue laboratory monitoring until transaminases return to normal. Consider completion of treatment with the 4R regimen, depending on the patient's risk of TB and willingness to complete treatment. See the topic below on ***Management of Treatment Interruption***.



CAUTION

Counsel all patients **to immediately stop LTBI treatment and return to the clinic for clinical evaluation if they develop symptoms of drug-induced hepatotoxicity**. For symptoms of hepatotoxicity, see the symptoms listed above under ***Clinical Monitoring***.

Most patients with drug-induced hepatotoxicity will improve over time after the offending medication is discontinued. Consider a specialty consultation for patients with any of the following:

- ◆ Serum transaminase concentrations >8 times the ULN
- ◆ Serum transaminase concentrations >3 times the ULN, and elevated total bilirubin >2.0, and prolonged INR or PT/PTT
- ◆ Serum transaminase concentrations persistently greater than normal despite negative initial evaluation for hepatotoxicity, hepatitis, gallstones, and pancreatitis

Hypersensitivity (Flu-like Symptoms)

- ◆ Fever, chills, muscle pain, headache, and dizziness can occur with any LTBI regimen but are more common with intermittently administered rifampin and rifapentine.
- ◆ Patients with mild symptoms can usually complete the 3HP regimen.
- ◆ If symptoms are severe, discontinue 3HP and consider completion of treatment with isoniazid. Consultation with a TB expert is advised.

Optic Neuritis

- ◆ In rare instances, isoniazid can cause optic neuritis.
- ◆ If the patient experiences blurry vision or loss of color vision, perform testing for visual acuity with corrective lenses (Snellen) and red-green color discrimination (Ishihara).
- ◆ If optic neuritis is suspected, stop isoniazid, and refer the patient to an ophthalmologist. If no abnormalities are found, isoniazid can be resumed.

Peripheral Neuropathy

- ◆ Isoniazid can cause peripheral neuropathy because of induction of the metabolism of pyridoxine (vitamin B6), especially in patients with HIV infection, poorly controlled diabetes, substance use disorder, and malnutrition. Symptoms include paresthesias and numbness of the feet and hands (with or without peripheral motor weakness). If the patient is not receiving pyridoxine, it should be started. If symptoms persist, discontinue isoniazid and consider an alternative regimen.
- ◆ The neuropathy usually subsides over weeks to months, but, if not, consider other causes of neuropathy and consult with a neurologist.
- ◆ Note that daily doses of 100–200 mg or more can cause cumulative toxicity manifesting mainly as neuropathy when pyridoxine is taken chronically.

MANAGEMENT OF TREATMENT INTERRUPTION

Completion of treatment is based on the number of doses taken in a specified period. Many patients who miss doses can extend treatment until the correct number of doses has been taken.

For more information on the number of doses and duration for each regimen, see **Section 4: Deciding Whether to Treat and Choosing a Regimen** and **Appendix 3: Dosages for Recommended Treatment Regimens**.

Options for When Doses Are Missed

Most of the following recommendations for management of patients with treatment adherence challenges are based on expert opinion. For patients whose treatment has been interrupted, but who are still able to complete their regimen within the specified period, most experts recommend that their treatment be extended until the designated number of doses has been ingested to complete treatment.

For patients taking isoniazid, for whom 9 months of treatment is preferable to a shorter duration, consider those who miss doses to have completed treatment if 180 doses (6 months) have been ingested within 9 calendar months, as they are unlikely to complete 270 doses within 12 calendar months.

To help overcome identified barriers, consider providing DOT, enablers, and incentives. For more information on strategies to facilitate treatment completion, see **Section 4: Deciding Whether to Treat and Choosing a Regimen: Interventions for Treatment Completion Challenges**. Consult with your state or local TB program or your regional TB Center of Excellence.

For patients who are unable to complete treatment within the specified period of time, options include the following:

- ◆ Consider DOT: Change the mode of treatment administration to DOT or vDOT, if available, to complete the current, or an alternative, regimen. For more information on DOT, see **Appendix 5: Directly Observed Therapy and Video Directly Observed Therapy**.
- ◆ Switch to a different regimen: See the topic below on **Changing Treatment Regimens**.
- ◆ Discontinue all therapy for LTBI: Reinforce patient education on the symptoms of active TB disease and the importance of seeking care promptly if TB symptoms should occur.

Changing Treatment Regimens

Many experts recommend completing a full course of the new regimen when switching treatment, particularly if the person is at high risk for progression.

To minimize the overall duration of treatment, some experts consider switching from one regimen to another using the following method to calculate the number of doses needed to complete treatment with a different regimen.

1. **Completed Dose Count:** Count the doses taken during the first regimen.
2. **Proportion of 1st Regimen Completed:** Calculate the proportion of the first regimen that was completed.
3. **Proportion of 1st Regimen Not Completed:** Subtract the proportion of the regimen completed from 100%.
4. **Doses to Complete 2nd Regimen:** Multiply the percentage of the first regimen that was not completed by the number of doses for the full second regimen. The result will be the number of doses needed to complete treatment in the second regimen.

FOLLOW-UP AFTER TREATMENT COMPLETION

The following recommendations for patient management are based on expert opinion. When the health care provider determines that the patient has completed the prescribed regimen, documentation of the treatment completion should be entered prominently into the patient's medical record. The patient should be given written documentation of completion as well. Educate the patient about the symptoms of active TB disease, the importance of seeking care promptly, and where to call if symptoms occur. Patients who had normal findings on chest radiography do not need a follow-up study if they remain asymptomatic. No routine TB follow-up, including chest radiography in the absence of specific indications, is necessary following treatment completion.

The duration of positive IGRA results after *M. tuberculosis* infection, whether LTBI or active TB disease, has not been extensively studied. In some patients, the response to the antigens decreases over months or years, but in others, it is durable. Positive TST results are durable in the majority of patients, although the reaction size can decrease over an interval of years, even with intact immunity.

In general, patients should not be treated for LTBI more than once, and patients who have completed treatment should not be re-tested for LTBI, even if re-exposed. In certain circumstances, such as a patient who has completed treatment for LTBI who is re-exposed to a patient with active, infectious TB disease, it may be appropriate to re-treat a patient for possible recurrent LTBI due to possible re-infection. Other factors to consider are the infectiousness of the second index patient, whether the re-exposed patient is immunosuppressed, and whether the patient was previously treated by DOT or SAT. Such decisions should be based on the recommendation of the state or local TB program.

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SECTION 7:

Nurse Case Management

OVERVIEW

Nurse case management, the use of incentives and enablers, and treatment administration by a patient-centered approach have proven to be an effective triad to provide patient-centered care for safe and documented completion of LTBI treatment.

Nurse-guided treatment management has been a model successfully used in public health to promote safety during treatment and increase treatment completion rates for persons with LTBI. Health care providers treating patients with LTBI are encouraged to use existing nurse case management services in their community to which their patients may have access or to create new nurse case management programs in their own facilities.

GENERAL PRINCIPLES

- ◆ Nurse case management is a strategy for integrating the multiple aspects of patient care and improving outcomes.
- ◆ Nurses providing nurse case management should receive specialized training.

RELATED TOPICS

- ◆ [Section 3: Pretreatment Clinical Evaluation](#)
- ◆ [Section 4: Deciding Whether to Treat and Choosing a Regimen](#)
- ◆ [Section 6: Monitoring Treatment](#)
- ◆ [Appendix 2: Drugs for Treatment of LTBI](#)
- ◆ [Appendix 3: Dosages for Recommended Treatment Regimens](#)

ROLE

The nurse case manager is an integral part of the patient care team and, qualified by knowledge and experience, brings to the team an understanding of the clinical process of assessment, planning, implementation, and evaluation. The nurse case manager coordinates all aspects of patient care before and during treatment and often works with standardized protocols and procedures under the supervision of the health care provider. The nurse case manager works collaboratively with the health care provider, other staff and the patient, to assess and advocate for the most effective treatment regimen to meet the goal of completing treatment.

To help meet that goal, the nurse case manager works before and during treatment to assess adherence barriers, the need for incentives, enablers, and DOT or vDOT and to educate the patient about LTBI and its treatment.

Effective follow-up services, which may include nurse case management, with or without DOT, may be provided in a variety of settings:

- ◆ Public health departments
- ◆ Community health centers
- ◆ Employee health programs
- ◆ Correctional facilities
- ◆ Hemodialysis centers
- ◆ Residential and outpatient drug treatment centers
- ◆ Schools and universities
- ◆ Private medical offices
- ◆ Other settings (such as pharmacies, etc.)

RESOURCES

Nurses providing nurse case management should receive specialized training in the treatment of LTBI. Innovative approaches have been developed in many state and local TB programs to provide community health care providers with ongoing education to develop expertise in treating LTBI.

A state or local TB nurse consultant or liaison may provide expertise on utilization of nurse case management services and patient education.

Check the NTCA online directory for a state/local TB nurse consultant in your area at <http://www.tbcontrollers.org/community/statecityterritory/>.

To review and download an assessment tool for LTBI treatment, see the NTCA website at <http://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/>.

The regional TB Centers of Excellence are good sources for further information and assistance on training. A map of the regions and contact information is available at https://www.cdc.gov/tb/education/tb_coe/.

The National TB Nurse Coalition (NTNC) published in 2021, Tuberculosis Nurse Case Management: Core Competencies for nurse case managers who provide direct care for persons with TB infection and disease. The Core Competencies provide a framework to expand the knowledge of new nurses and assist in the mastery of skills required to practice TB nurse case management. The Core Competencies can be found at the NTCA website: <https://www.tbcontrollers.org/resources/core-competencies/tb-nurse-case-manager/>

A TB NCM certificate program is currently under development by the NTNC.

APPENDIX 1

Interpretation of Test Results

TUBERCULIN SKIN TEST

All tests should be interpreted based on patient risk and test characteristics.

Table 5. Classification of the Tuberculin Skin Test Reaction

≥5 mm Induration	≥10 mm Induration	≥15 mm Induration
<p>Considered positive in the following persons:</p> <ul style="list-style-type: none"> • Persons living with the human immunodeficiency virus (HIV) • Recent contacts of a person with tuberculosis (TB) disease • Persons with chest radiograph (CXR) findings suggestive of previous TB disease • Patients with organ transplants • Persons who are immunosuppressed for other reasons (e.g., prolonged therapy with corticosteroids equivalent of ≥15 mg per day of prednisone for 1 month or longer or those taking tumor necrosis factor-alpha [TNF-alpha] antagonists) 	<p>Considered positive in the following persons:</p> <ul style="list-style-type: none"> • Persons born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB • Persons with substance use disorders • Mycobacteriology laboratory personnel • Residents and employees of high-risk congregate settings such as nursing homes, homeless shelters, or correctional facilities • Persons with certain medical conditions that place them at high risk for TB, such as silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions • Persons <90% of ideal body weight • Children aged <5 years • Infants, children, and adolescents exposed to adults in high-risk categories 	<p>Considered positive in any person, including persons with no known risk factors for TB.</p>

Adapted from *Fact Sheets: Tuberculin Skin Testing*. Atlanta, GA: Centers for Disease Control and Prevention; 2020. Available at: <https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm>. Accessed November 10, 2020.

QUANTIFERON®-TB GOLD PLUS TEST

All tests should be interpreted based on patient risk and test characteristics.

Table 6. Interpretation of QuantiFERON®-TB Gold Plus Test Results

Nil (IU/ml)	TB1 minus Nil (IU/ml)	TB2 minus Nil (IU/ml)	Mitogen minus Nil (IU/ml)*	QFT-Plus Result	Report/ Interpretation
≤8.0	≥0.35 and ≥25% of Nil	Any	Any	Positive [†]	<i>M. tuberculosis</i> infection likely
	Any	≥0.35 and ≥25% of Nil			
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	≥0.50	Negative	<i>M. tuberculosis</i> infection NOT likely
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	<0.50	Indeterminate [‡]	Likelihood of <i>M. tuberculosis</i> infection cannot be determined
>8.0 [§]	Any				

* Responses to the mitogen positive control (and occasionally TB antigen) can be outside the range of the microplate reader. This has no impact on test results. Values >10 IU/ml are reported by the QFT-Plus software as >10 IU/ml.

† Where *M. tuberculosis* infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate in the QFT-Plus ELISA. If repeat testing of one or both replicates is positive, the test result is considered positive.

‡ For possible causes, refer to the “Troubleshooting” section in the package insert at <https://www.qiagen.com/us/resources/resourcedetail?id=ac068fc7-a994-4443-ac7c-dda43ce2bc5e&lang=en>.

§ In clinical studies, less than 0.25% of subjects had interferon-gamma levels of >8.0 IU/ml for the Nil value.

Source: QuantiFERON®-TB Gold Plus (QFT®-Plus) [ELISA package insert]. Germantown, MD: Qiagen; June 2022. Available at: https://www.quantiferon.com/wp-content/uploads/2017/04/English_QFTPlus_ELISA_R04_022016.pdf. Accessed May 31, 2023.

T-SPOT[®].TB TEST

All tests should be interpreted based on patient risk and test characteristics.

Results for the T-SPOT.TB test are interpreted by subtracting the spot count in the nil control well from the spot count in each of the panels, according to the following algorithm:

- ◆ The test result is positive if (Panel A-Nil) or (Panel B-Nil) is ≥ 8 spots and if the nil well has ≤ 10 spots.
- ◆ The test result is negative if both (Panel A-Nil) and (Panel B-Nil) are ≤ 4 spots and if the nil well has ≤ 10 spots and the mitogen well has ≥ 20 spots. This includes values less than zero for the corrected Panel A or Panel B.
- ◆ Results where the highest of the Panel A or Panel B spot count is such that the (panel minus nil) spot count is 5, 6, or 7 spots should be considered borderline (equivocal). Retesting is the routine option for a result of borderline.
- ◆ If the result is still borderline (equivocal) on retesting with another specimen, then other diagnostic tests or epidemiologic information should be used to help determine TB infection status of the patient.
- ◆ The test result is invalid for one of two conditions: (1) a mitogen (positive) control response is < 20 spots while both (Panel A-Nil) and (Panel B-Nil) are ≤ 4 spots; or (2) a nil (negative) control count is > 10 spots, regardless of the responses to antigens and mitogen.

Refer to the Quality Control section in the package insert before applying the criteria above.

Adapted from T-SPOT[®].TB [package insert]. Marlborough, MA: Oxford Immunotec; September 2020. Available at: <https://www.tspot.com/wp-content/uploads/2020/09/TB-PI-US-0001-V8.pdf>. Accessed May 31, 2023.

APPENDIX 2:

Drugs for the Treatment of Latent Tuberculosis Infection

INTRODUCTION

First-line medications recommended for the treatment of LTBI include rifamycins and isoniazid and are generally well-tolerated at the recommended doses. There are three antimycobacterial rifamycins used for the treatment of LTBI: rifapentine, rifampin, and rifabutin. These drugs are used in different dosages and for specific purposes, and they may not be interchangeable in the regimens.

Note that dosing of rifapentine and isoniazid for 3HP differs from that for 1HP. For detailed information on 1HP dosing and its application as an LTBI treatment for those patients with HIV infection, consult the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* (available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines>).



CAUTION

Prescribing providers and pharmacists who are unfamiliar with the rifamycins might confuse the three drugs: **rifampin, rifapentine, and rifabutin are different drugs**, and caution should be taken to ensure that patients receive the correct medication and the correct dose for the intended regimen.



ALERT

Concerns about nitrosamine contamination in rifapentine and rifampin are under investigation. For a summary of what is currently known and recommended, see the NTCA website at <http://www.tbcontrollers.org/resources/nitrosamines/>.



DRUG-DRUG INTERACTION CHECKERS

Known drug-drug interactions are listed under each drug. However, because information on drug-drug interactions changes frequently, research potential interactions online. Some suggested websites include the following:

- Drugs.com: <http://www.drugs.com/drug-interactions/>
- Medscape: <https://reference.medscape.com/drug-interactionchecker>
- HIV.gov: <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines>
- NAM AIDSMap: <https://www.aidsmap.com/about-hiv/hiv-treatment-and-drug-drug-interactions>

RIFAPENTINE

Rifapentine (P, RPT, or RFP) is a long-acting rifamycin that has been shown to be effective for LTBI when given in combination with isoniazid once weekly for 12 doses. It should not be used alone. It is used in combination with isoniazid for the treatment of LTBI.

Preparation

- ◆ Tablets: 150 mg

Dosage

Adults and Children, once weekly:

- ◆ 10–14.0 kg: 300 mg
- ◆ 14.1–25.0 kg: 450 mg
- ◆ 25.1–32.0 kg: 600 mg
- ◆ 32.1–49.9 kg: 750 mg
- ◆ ≥ 50.0 kg: 900 mg
- ◆ Maximum dose 900 mg

Administration

Administration of rifapentine with high-fat meals increases the area under the curve and the maximum serum concentration by 40 to 50%. However, the clinical significance of such an effect is unknown, as rifamycins generally have a wide therapeutic window (that is, that they are safe and effective at a wide range of serum concentrations). For persons who cannot swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food and consumed immediately. Oral bioavailability is 70%.

Adverse Effects

The following adverse reactions have been reported in $\geq 1\%$ of patients treated with rifapentine in combination with isoniazid (as rifapentine is generally used with isoniazid, and monotherapy data is scarce). When available, data from randomized control trials is reported (instead of from non-randomized studies).

- ◆ Cardiovascular: Chest pain (3–6%), edema (1%)
- ◆ Constitutional: Fatigue/weakness (2–9%)
- ◆ Dermatologic: Diaphoresis (2–5%), skin rash ($\leq 1\%$), pruritus ($\leq 3\%$)
- ◆ Endocrine/Metabolic: Hypoglycemia (5–10%), hyperglycemia (1–4%)

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Adverse Effects

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- ◆ Gastrointestinal: Anorexia (3–4%), nausea ($\leq 2\%$), vomiting ($\leq 2\%$), dyspepsia ($\leq 2\%$), constipation (1–2%), abdominal pain ($\leq 1\%$), diarrhea ($\leq 1\%$)
- ◆ Hematologic: Anemia ($\leq 11\%$), lymphocytopenia (3–11%), neutropenia ($\leq 9\%$), leukopenia (4–7%), thrombocytosis ($\leq 6\%$), leukocytosis (2%), neutrophilia (1–3%), thrombocytopenia (1–2%)
- ◆ Hepatic: Increased serum alanine aminotransferase (2–5%), increased serum aspartate aminotransferase (2–4%), hepatotoxicity ($\leq 2\%$)
- ◆ Immunologic/Lymphoid: Hypersensitivity reaction (adults $\leq 4\%$; children and adolescents 1%), fever (2–8%), lymphadenopathy ($\leq 1\%$)
- ◆ Musculoskeletal: Back pain ($\leq 4\%$), arthralgia/myalgia ($\leq 1\text{--}7\%$)
- ◆ Neurologic: Headache ($\leq 3\%$), dizziness (2–5%)
- ◆ Ophthalmic: Conjunctivitis ($\leq 2\%$)
- ◆ Urinary: Uremia (1–3%)
- ◆ Other:
 - ▶ Orange-red discoloration of body fluids (urine, tears, sputum, feces, and cerebrospinal fluid)
 - ▶ Flu-like syndrome (usually only with intermittent administration)

Major Drug-Drug Interactions

The drug-drug interactions of rifapentine are similar to the other rifamycins. Like all rifamycin drugs, rifapentine is an inducer of hepatic microsomal CP-450 enzymes. Both rifapentine and rifampin are inducers of cytochrome P450 isoenzymes.

Potential drug-drug interactions with rifapentine should be anticipated for all drugs that have been found to interact with rifampin. The magnitude of the interactions may be less when the drugs are used intermittently and at a lower dose.

Similar to rifampin, rifapentine has serious significant interactions with some drugs used for hepatitis C, some HIV antiretrovirals, warfarin derivatives and other anticoagulants, glucocorticoids, hormonal contraceptives, opioids,

APPENDIX 2: DRUGS FOR THE TREATMENT OF LTBI

glipizide, glyburide, oral contraceptives, trazadone, and sildenafil. See the rifampin section below for other potential drug-drug interactions.

After determining what medications and drugs the patient is taking, research potential interactions online using one of the suggested interactive online drug checkers in the introduction to this appendix.



ALERT

Concerns about nitrosamine contamination in rifapentine and rifampin are under investigation. For a summary of what is currently known and recommended, see the NTCA website at <http://www.tbcontrollers.org/resources/nitrosamines/>.

RIFAMPIN

Rifampin (R, RIF, or RMP) is a bactericidal drug.

Preparations

- ◆ Capsules: 150 and 300 mg
- ◆ Oral liquid: Powder from capsules can be suspended by a pharmacist for oral administration.
- ◆ IV: Lyophilized powder must be reconstituted by a pharmacist.

Dosage

- ◆ **Adults:** Daily: 10 mg/kg, maximum 600 mg/day
- ◆ **Children aged >2 years:** Daily: 15–20 mg/kg, maximum 600 mg/day
- ◆ **Infants and children aged ≤2 years:** Daily: 20–30 mg/kg, maximum 600 mg/day

Administration

Rifampin should be administered on an empty stomach (i.e., 1 hour prior to, or 2 hours after meals or antacids) for increased and rapid absorption; food (high-fat meals) delays absorption and decreases bioavailability (by ~16%). However, the clinical significance of such an effect is unknown, as rifamycins generally have a wide therapeutic window (that is, that they are safe and effective at a wide range of serum concentrations).

For persons who cannot swallow tablets, options include: (a) mixing the contents of capsule(s) with applesauce or jelly; and (b) extemporaneously compounded oral solutions that should be shaken well before ingesting and have any remaining solution discarded after 28 days. (Suspensions may need to be compounded by a pharmacist.)

Oral bioavailability of rifampin is initially 90 to 95% but decreases to 68 to 70% after 3 weeks due to autoinduction of its own metabolism.

Relative Contraindications

- ◆ Active viral hepatitis
- ◆ End-stage liver disease
- ◆ Severe thrombocytopenia

Adverse Effects

- ◆ Constitutional: Fatigue ($\leq 1\%$)
- ◆ Dermatologic: Skin rash ($\leq 1\%$), pruritis ($\leq 1\%$), flushing ($\leq 1\%$)
- ◆ Gastrointestinal: Gastrointestinal intolerance (nausea and/or vomiting and/or diarrhea and/or abdominal discomfort/pain or distension) ($\leq 1\%$)
- ◆ Hematologic: Hemolytic anemia ($\leq 1\%$), neutropenia ($\leq 1\%$), thrombocytopenia ($\leq 1\%$)
- ◆ Hepatic: Hepatotoxicity ($\leq 1\%$)
- ◆ Immunologic/Lymphoid: Hypersensitivity reaction ($\leq 1\%$), fever ($\leq 1\%$)
- ◆ Musculoskeletal: Myalgia ($\leq 1\%$)
- ◆ Neurologic: Fatigue ($\leq 1\%$), headache ($\leq 1\%$)
- ◆ Urinary: Interstitial nephritis ($\leq 1\%$)
- ◆ Other:
 - ▶ Orange-red discoloration of body fluids (urine, tears, sputum, feces, and cerebrospinal fluid)
 - ▶ Flu-like syndrome (usually only with intermittent administration)

Major Drug-Drug Interactions

Rifampin has numerous drug-drug interactions. Rifampin induces the activity of cytochrome P-450 enzymes, thereby increasing the metabolism and decreasing serum levels and effectiveness of many drugs, including opioids, warfarin derivatives and other anticoagulants, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, cyclosporine, theophylline, levothyroxine, and antiretrovirals such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) including rilpivirine, and NRTIs such as tenofovir alafenamide.

Patients on hormonal contraceptives should be encouraged to continue the hormonal contraceptive but also to use a barrier method for contraception. For more information on the CDC recommendations on the use of contraceptive methods during treatment with rifampin, see the *Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use* at <https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-english-bw-508-tagged.pdf>

APPENDIX 2: DRUGS FOR THE TREATMENT OF LTBI

Before prescribing any drug, health care providers should use an interactive online drug checker. Some suggested ones are in the introduction to this appendix.



ALERT

Concerns about nitrosamine contamination in rifapentine and rifampin are under investigation. For a summary of what is currently known and recommended, see the NTCA website at <http://www.tbcontrollers.org/resources/nitrosamines/>.

RIFABUTIN

Rifabutin (RB, RBT, or RBU) is a bactericidal drug. Although clinical studies have not directly assessed the efficacy of rifabutin for the treatment of LTBI, some experts consider that it may be substituted for rifampin in many cases. Like rifampin, rifabutin induces the activity of cytochrome P-450 enzymes, but to a lesser degree.

Rifabutin is not approved for treatment of LTBI, so this is an off-label use. It should be noted that rifabutin monotherapy is not recommended in patients with HIV by the [US Department of Health and Human Services \(DHHS\) HIV guidelines](#).

Preparation

- ◆ Tablets: 150 mg

Dosage

- ◆ **Adults:** 5–10 mg/kg, maximum 300 mg/day
- ◆ **Children:** 5 mg/kg, maximum 300 mg/day

Administration

Rifabutin can be administered with or without food. It can be administered with food in persons with gastrointestinal intolerance. A high-fat meal may decrease the rate, but not the extent, of absorption. For persons who cannot swallow tablets, options include mixing of tablet(s) with applesauce. The oral bioavailability is approximately 16 to 20%.

Adverse Effects

- ◆ Dermatologic: Skin rash (11%)
- ◆ Gastrointestinal: Nausea (6%), abdominal pain (4%), dysgeusia (3%), dyspepsia (3%), eructation (3%), vomiting (3%), flatulence (2%)
- ◆ Hematologic: Neutropenia (25%), leukopenia (10%–17%), thrombocytopenia (5%)
- ◆ Hepatic: Hepatotoxicity
- ◆ Immunologic/Lymphoid: Fever (2%), hypersensitivity reactions
- ◆ Musculoskeletal: Myalgia (2%)

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Adverse Effects

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- ◆ Ophthalmic: Uveitis (rare; dose-dependent; risk is significantly increased by concomitant administration of drugs that increase serum concentration)
- ◆ Other:
 - ▶ Orange-red discoloration of body fluids (urine, tears, sputum, feces, and cerebrospinal fluid)
 - ▶ Flu-like syndrome (usually only with intermittent administration)

Major Drug-Drug Interactions

Rifabutin induces the activity of cytochrome P-450 enzymes, but to a lesser degree than rifampin, thereby increasing the metabolism and decreasing serum levels and effectiveness of many drugs, including opioids, warfarin derivatives and other anticoagulants, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, cyclosporine, theophylline, and levothyroxine. Rifabutin also reduces the efficacy of the antiretroviral medication tenofovir alafenamide through another mechanism to a similar degree as rifampin.

Patients on hormonal contraceptives should be encouraged to continue the hormonal contraceptive but also to use a barrier method for contraception. For more information on the CDC recommendations on the use of contraceptive methods during treatment with rifabutin, see the *Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use* at <https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-english-bw-508-tagged.pdf>

Before prescribing any drug, health care providers should use an interactive online drug checker. Some suggested ones are in the introduction to this appendix.

ISONIAZID

Isoniazid (H or INH) is a bactericidal drug.

Preparations

- ◆ Tablets: 100 and 300 mg
- ◆ Syrup: 50 mg/5 mL (not recommended because of sorbitol-induced gastrointestinal side effects and the difficulties of accurate measurement of dose and assessment of adherence)

Dosage

Adults:

- ◆ Daily: 5 mg/kg/day, maximum 300 mg/day
- ◆ Intermittent (twice weekly): 15 mg/kg, maximum 900 mg/day
- ◆ Dosing for 3HP: 15 mg/kg, maximum 900 mg/day

Children:

- ◆ Daily: 10–20 mg/kg/day*, maximum 300 mg/day
- ◆ Intermittent (twice weekly): 20–40 mg/kg/day*, maximum 900 mg (DOT)
- ◆ Dosing for 3HP (rounded to the nearest 50 to 100 mg):
 - ▶ Aged 12–17 years: 15 mg/kg, maximum 900 mg
 - ▶ Aged 2–11 years: 25 mg/kg, maximum 900 mg



NOTE ON ISONIAZID PEDIATRIC DOSING

The isoniazid dose ranges for children are taken from Table 4 in Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep.* 2020;69(No. RR-1):1-11. doi: <http://dx.doi.org/10.15585/mmwr.rr6901a1>. However, some pediatric experts recommend lower dosages, and the American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.

Administration

Isoniazid should be taken with water on an empty stomach 1 hour before or 2 hours after meals because food significantly reduces bioavailability. If the patient is unable to swallow tablets, the tablet may be crushed and mixed in a portion of soft food or liquid, or starch-based pudding (chocolate pudding, for example) and administered as a slurry.

Oral bioavailability of isoniazid is nearly 100% on an empty stomach, but peak concentration may be reduced up to 50% with a fatty meal.

Contraindications

- ◆ History of a *severe* adverse reaction to isoniazid (such as drug-induced liver injury, fever, chills, or arthritis)
- ◆ Hypersensitivity to isoniazid or any component of the formulation
- ◆ Acute liver disease
- ◆ Close TB contact with a person with isoniazid-resistant TB

Relative Contraindications

- ◆ Active viral hepatitis
- ◆ End-stage liver disease

Adverse Effects

- ◆ Cardiovascular: Vasculitis
- ◆ Constitutional: Decreased appetite (>10%), weakness (>10%), fatigue, malaise
- ◆ Dermatologic:
 - ▶ *Skin*: Rash (<1%; may be morbilliform, maculopapular, or exfoliative), acne (exacerbation that does not respond to topical anti-acne medications and that resolves when isoniazid is discontinued)
 - ▶ *Hair*: Minor hair loss (uncommon, and recovers after completion of treatment), alopecia (rare; may be the first manifestation of SLE, so check for markers of SLE including anti-nuclear antibodies; if associated with mucous membrane involvement, exfoliation, or fever, then stop isoniazid immediately and consider consultation with a dermatologist)

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Adverse Effects

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- ◆ Endocrine/Metabolic: Gynecomastia, hyperglycemia, metabolic acidosis, pellagra (<1%), pyridoxine deficiency
- ◆ Gastrointestinal: Nausea (<0.1%), vomiting (<0.1%), abdominal discomfort or pain (<0.1%), hyperbilirubinemia, jaundice, pancreatitis (<0.1%)
- ◆ Hematologic: Agranulocytosis (<0.1%), anemia (sideroblastic, hemolytic, aplastic, or megaloblastic) (<0.1%), thrombocytopenia (<0.1%) eosinophilia
- ◆ Hepatic: Drug-induced liver injury or hepatitis from isoniazid is idiosyncratic (i.e., independent of dose), and the risk increases depending on risk factors (increasing age, pre-existing liver disease, heavy alcohol use, HIV infection, injection drug use, possibly the immediate postpartum period, and concomitant administration of medications with hepatotoxic potential.
 - ▶ Mild and transient elevation of transaminases (10–20%) that is asymptomatic and resolves despite continuation of therapy (See Section 5: Considerations for Specific Populations: Persons with Comorbidities: Liver Disease and Chronic Hepatitis and Section 6: Monitoring and Managing Treatment: Management of Adverse Effects.)
 - ▶ Hepatitis, with transaminase greater than 5 times the ULN (0.5% in persons <35 years of age without identifiable risk factors; 2% in patients ≥50 years; as high as 5.2% in persons with a renal failure) which, if not recognized early, can be fatal (1 to 7 per 100,000). The FDA has issued a black box warning. Severe hepatitis may be ameliorated by promptly discontinuing isoniazid.
- ◆ Immunologic/Lymphoid: Fever, urticaria, toxic epidermal necrolysis (<0.1%), drug reaction with eosinophilia syndrome (DRESS) (<0.1%)
- ◆ Musculoskeletal: Arthralgias (<1%); lupus-like syndrome (<1%)

(continued on next page)

Adverse Effects

(continued from previous page)

- ◆ Neurologic:
Peripheral neuropathy: dose-related in adults, 0.2% at the recommended dosage of 5 mg/kg/day but 10–20% in adults if dosed at 10 mg/kg/day; increased risk in persons with pre-existing neuropathy or the following conditions: age >50 years, pregnancy, breastfeeding, malnutrition, alcohol use disorder, chronic liver disease, HIV infection, renal failure, diabetes mellitus; paresthesia, generalized seizures (<0.1%), headache, somnolence, insomnia, toxic psychosis, memory impairment

Note that daily doses of pyridoxine of 100–200 mg or more can cause cumulative toxicity manifesting mainly as neuropathy when pyridoxine is taken chronically.

- ◆ Ophthalmic: Optic neuritis, optic atrophy
- ◆ Renal: Bilirubinuria

Major Drug-Drug Interactions

- ◆ Isoniazid may *increase* the serum concentrations of the following medications: carbamazepine, disulfiram (Antabuse), dofetilide, flibanserin, fosphenytoin, lemborexant, lomitapide, nimodipine, phenytoin, pimozone, tacrolimus, theophylline, triazolam, ubrogepant, valproic acid, and warfarin.
- ◆ Isoniazid may *decrease* the serum concentrations of the following medications: itraconazole, and ketoconazole.
- ◆ Isoniazid's serum concentration may be decreased by systemic corticosteroids.
- ◆ Isoniazid's absorption may be reduced if taken less than one hour before, or less than 2 hours after, taking aluminum-containing antacids (Mylanta or Gelusil, for example).

Drug-Food Interactions

When taking isoniazid, the consumption of foods and beverages with a high monoamine content—tyramine (aged cheeses, red wines, soy sauce, bananas, avocados, for example) or histamine (scombroid fish, including tuna, for example)—can cause monoamine poisoning (headache, skin flushing, sweating, palpitations, lightheadedness, nausea, vomiting, diarrhea, and pruritus).

Before prescribing any drug, health care providers should use an interactive online drug checker. Several are suggested in the introduction to this appendix.

Vitamin B6 (Pyridoxine)

Isoniazid can increase pyridoxine metabolism, which can lead to peripheral neuropathy. Give 25 mg/day of pyridoxine for patients with symptoms of, or at increased risk of, peripheral neuropathy (see *Isoniazid* above). Note that daily doses of pyridoxine of 100–200 mg or more can cause cumulative toxicity manifesting mainly as neuropathy when pyridoxine is taken chronically.

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APPENDIX 3:

Dosages for Recommended Treatment Regimens

APPENDIX 3: DOSAGES FOR RECOMMENDED TREATMENT REGIMENS

Table 7. Dosages for Recommended Treatment Regimens for Latent Tuberculosis Infection

Regimen	Duration	Dose and Age Group	Frequency	Total Doses
Isoniazid* and rifapentine† (3HP)	3 mos	<p>Adults and children aged ≥12 years Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum Rifapentine†: 10–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: 900 mg maximum</p> <p>Children aged 2–11 years Isoniazid*: 25 mg/kg; 900 mg maximum Rifapentine†: see above</p>	Once weekly	12
Rifampin [¶] ** (4R)	4 mos	<p>Adults: 10 mg/kg Children aged >2 years: Daily: 15–20 mg/kg Infants and children aged ≤2 years: Daily: 20–30 mg/kg^{† †} Maximum dose: 600 mg</p>	Daily	120
Isoniazid* and rifampin [¶] (3HR)	3 mos	<p>Adults Isoniazid*: 5 mg/kg; 300 mg maximum Rifampin[¶]: 10 mg/kg; 600 mg maximum</p> <p>Children aged >2 years Isoniazid*: 10–20 mg/kg^{§§}; 300 mg maximum Rifampin[¶]: 15–20 mg/kg; 600 mg maximum</p> <p>Infants and children aged ≤2 years Isoniazid*: 10–20 mg/kg^{§§}; 300 mg maximum Rifampin[¶]: 20–30 mg/kg; 600 mg maximum^{† †}</p>	Daily	90
Isoniazid* (6H, 9H)	6 mos	Adults: 5 mg/kg	Daily	180
		Children: 10–20 mg/kg ^{§§}		
		Maximum dose: 300 mg		
	9 mos	Adults: 15 mg/kg	Twice weekly [§]	52
		Children: 20–40 mg/kg ^{§§}		
		Maximum dose: 900 mg		
9 mos	Adults: 5 mg/kg	Daily	270	
	Children: 10–20 mg/kg ^{§§}			
	Maximum dose: 300 mg			
9 mos	Adults: 15 mg/kg	Twice weekly [§]	76	
	Children: 20–40 mg/kg ^{§§}			
	Maximum dose: 900 mg			

APPENDIX 3: DOSAGES FOR RECOMMENDED TREATMENT REGIMENS

Notes for Table 7

Adapted from Sterling TR, Njie G, Zenner D, et al. Table 4. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep.* 2020;69(No. RR-1):1-11. doi:

<http://dx.doi.org/10.15585/mmwr.rr6901a1>

* Isoniazid is formulated as 100 mg and 300 mg tablets.

† Rifapentine is formulated as 150 mg tablets in blister packs that should be kept sealed until use.

§ Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication).

¶ Rifampin (rifampicin) is formulated as 150 mg and 300 mg capsules.

** When rifampin cannot be used because of significant drug-drug interactions, rifabutin may be used. Note that rifabutin has a different dosing. See *Section 4* and *Appendix 2*.

†† The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (Source: American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Disease*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829-53).

§§ The American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.



CAUTION

Prescribing providers and pharmacists who are unfamiliar with the rifamycins might confuse the three drugs: **rifampin, rifapentine, and rifabutin are different drugs**, and caution should be taken to ensure that patients receive the correct medication and the correct dose for the intended regimen.

APPENDIX 4:

Collaborations Between the Public Health Department and Community Service Providers

PURPOSE

Collaborations between clinical care services outside the health department and those within the health department will increase the number of patients completing treatment for LTBI in the community by bringing together complementary resources:

- ◆ Stable connections to specific communities where the prevalence of LTBI or factors associated with the risk of progression to TB disease warrants a focused intervention
- ◆ Systems that are designed for continuity of health care and data collection
- ◆ Infrastructure, such as clinic space, vehicles, and communication networks
- ◆ Personnel, such as nurses, midlevel health care providers, pharmacists, community outreach workers, mental health social workers, community councils, and volunteers
- ◆ Funding, as part of programs for preventive or general integrated health care
- ◆ Integration of expertise and experience, in the areas of community relations, communications, health education, public health and surveillance, quality assurance, system operations, infectious diseases, chronic diseases, and TB diagnosis and treatment

SETTINGS

Settings where primary care services are delivered, such as health care maintenance organizations, community health centers, and private medical clinics, should add or improve TB prevention services selectively based on the TB epidemiology for their service population. Consultation with the state or local TB program is recommended for making this determination.

Some settings have service populations or circumstances that may be historically associated with TB. Examples of these settings are listed below.

- ◆ Health care systems that are dedicated to specific groups, such as the following:
 - ▶ Clinics providing services for historically underserved populations including minorities, low-income communities, migrant or seasonal farm workers, or persons experiencing homelessness
 - ▶ Health clinics at colleges and universities with substantial immigrant or international student enrollment
 - ▶ Centers for refugees and immigrants
 - ▶ Clinics with designated civil surgeons
 - ▶ Employee health clinics of selected institutions or facilities
- ◆ Specialty care for conditions that are associated with TB disease, especially if patients can be tested and treated at these clinics with continuity of care, for example:
 - ▶ Dialysis centers or nephrology clinics
 - ▶ Diabetes and endocrinology clinics
 - ▶ Oncology centers
 - ▶ Rheumatology, dermatology, or gastroenterology clinics, for patients who are immunosuppressed by biologic agents
 - ▶ Treatment centers for persons living with HIV/AIDS
 - ▶ Drug treatment programs including methadone treatment facilities
- ◆ Institutions such as correctional facilities, long-term care facilities, or shelters with onsite health care for persons experiencing homelessness
- ◆ Facilities of national agencies for health care or including health care services:
 - ▶ Indian Health Service
 - ▶ Tribally operated hospitals and clinics
 - ▶ US Department of Veterans Affairs and military installations
 - ▶ Bureau of Prisons

APPENDIX 5:

Directly Observed Therapy and Video Directly Observed Therapy

The three common types of treatment administration in the United States are in-person directly observed therapy (DOT), video directly observed therapy (vDOT) live or recorded, and self-administered therapy (SAT). With DOT, a trained health care worker is physically present when the patient ingests the medications and uses a symptom checklist for adverse effects. Studies have shown that DOT ensures that the number of doses ingested and treatment duration are as close as possible to the target and verifies that treatment is completed. DOT is generally recommended for persons who are not adherent with SAT or have one of the following barriers to adherence: use of drugs or alcohol, homelessness, or psychiatric or cognitive impairment. In practice, individual providers or programs may use additional or different criteria for selecting the mode of administration.

vDOT (sometimes referred to as electronic DOT or eDOT) has emerged using secure platforms for live or recorded videos that facilitate observing medication ingestions remotely. vDOT provides greater patient flexibility while still ensuring the safe and effective completion of treatment. Live vDOT usually requires the patients to take treatment during normal business hours when a trained health care worker is available to observe them. Recorded vDOT also allows patients to take medications at a time that is most convenient for them. vDOT can also facilitate more frequent dosing while still maintaining observation including weekends, holidays, and when a patient is travelling.

APPENDIX 5: DIRECTLY OBSERVED THERAPY AND VIDEO DIRECTLY OBSERVED THERAPY

Several resources provide more in-depth information on DOT and vDOT:

- ◆ ***Guidelines for Electronic Directly Observed Therapy (eDOT) Program Protocols in California*** The California Department of Public Health Tuberculosis Branch, California Tuberculosis Controllers Association, University of California, San Diego School of Medicine, and the Center for Connected Health Policy:
https://ctca.org/wp-content/uploads/2018/11/CDPH_CTCA-eDOT-Guidelines-Cleared-081116.pdf
- ◆ ***Directly Observed Therapy Training Curriculum for TB Control Programs***
Curry International Tuberculosis Center:
<https://www.currytbcenter.ucsf.edu/products/directly-observed-therapy-training-curriculum-tb-control-programs>
- ◆ ***Center for Connected Health Policy website:***
<https://www.cchpca.org/>
The Center provides information on telehealth-related laws, regulations, and Medicaid programs. On the website, providers can view either current state laws and policies or pending legislation and regulations. Interactive maps include a search tool to identify the policies in your state.

Table 8 summarizes the advantages and disadvantages of each mode of administration.

APPENDIX 5: DIRECTLY OBSERVED THERAPY AND VIDEO DIRECTLY OBSERVED THERAPY

Table 8. Comparison of Modes of Treatment Administration

Mode of Administration	Advantages	Disadvantages
Directly Observed Therapy (DOT)	<ul style="list-style-type: none"> Ensures the highest quality and safety of treatment Provides the regular opportunity to check for signs and symptoms of adverse reactions Confirms that treatment is completed May benefit persons at risk for progression to severe forms of active TB disease if adherence is poor, such as persons younger than 5 years of age and persons with immunosuppression Providers may be able to bill for this service 	<ul style="list-style-type: none"> Places greater burden and expense on patients and providers compared to SAT May impair the patient's sense of autonomy related to treatment Increases vulnerability to disclosure and stigma (violation of confidentiality) when a patient is having multiple health care encounters
Video Directly Observed Therapy (vDOT)	<ul style="list-style-type: none"> Provides most of the advantages of DOT Provides greater patient autonomy: patients can take medications on their own schedule Poses less risk of disclosure (violation of confidentiality) than DOT Facilitates more frequent dosing that has been shown to improve outcomes and can allow monitoring therapy when people travel including out of the country (previously not possible with in-person DOT) Has lower personnel time and transportation costs than traditional face-to-face DOT 	<ul style="list-style-type: none"> vDOT has higher equipment costs. Cellular data limitations and internet connectivity issues could be a barrier to successful observations. Has less provider experience with its methods than with DOT, but with COVID-19, that can be changing Physical, psychiatric, or cognitive challenges may make it difficult for the patient to use the communication devices
Self-Administered Therapy (SAT)	<ul style="list-style-type: none"> Places lower burden and expense on patients and providers compared to DOT Provides patient autonomy 	<ul style="list-style-type: none"> Provides the opportunity to skip doses, changes dosages, or to take only one drug in a two-drug regimen Lacks observed confirmation that treatment is completed

This table is a summary of expert opinion of the NTCA authors.

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