

Improving the Quality of Care: Treatment of Latent Tuberculosis Infection

January 27, 2023



Learning Objectives

- Describe populations at high risk for infection with *Mycobacterium tuberculosis* (*M. tuberculosis*) and for developing tuberculosis (TB) disease once infected.
- Explain the different testing options for diagnosing latent tuberculosis infection (LTBI), as well as their advantages and limitations.
- Summarize the 2020 guidelines for the treatment of LTBI recommended by the National Tuberculosis Controllers Association and the Centers for Disease Control and Prevention (CDC).

Key Points

- People with LTBI have been infected with *M. tuberculosis*, but do not have signs and symptoms of TB disease and cannot spread *M. tuberculosis* to others because the infection is contained. Without treatment, about 5 – 10% of people with LTBI will progress to active TB disease.
- More than two million Californians (6% of the population) have LTBI. Severe disparities in TB incidence rates exist, with incidence rates up to 52 times higher among non-U.S.-born racial and ethnic groups than among white people born in the U.S.
- During routine patient evaluations, healthcare providers can use the [California TB Risk Assessment Tools](#) to identify people at high risk for LTBI and recommend them for testing.
- Screening and treatment for LTBI decreased dramatically during 2020 within the Medi-Cal population. While rates have been steadily increasing, they are not yet at the levels seen prior to the coronavirus disease 2019 (COVID-19) pandemic.

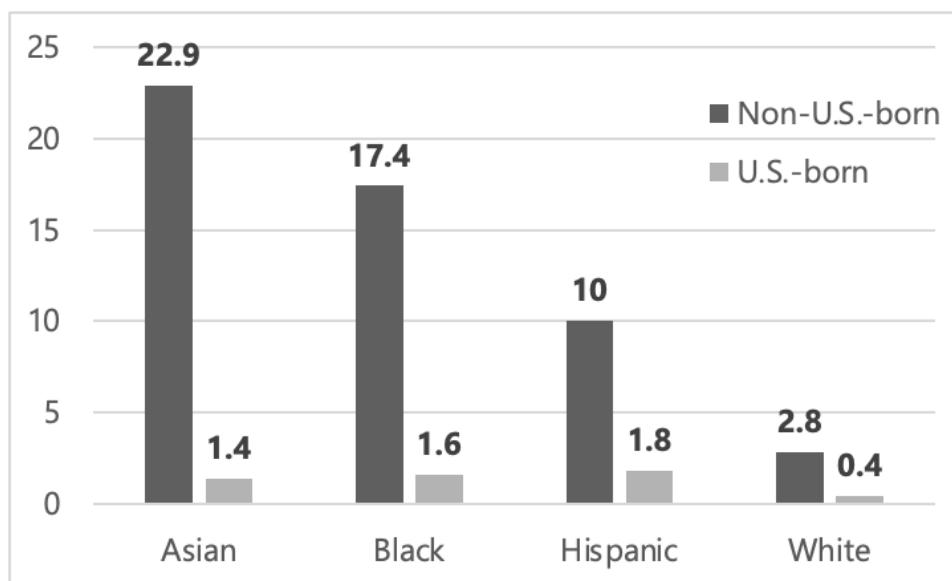
Background

TB is an infectious and potentially fatal disease that typically affects the lungs and is spread through airborne droplets when a person sick with TB coughs.¹⁻³ TB is caused by *M. tuberculosis* bacteria, although not everyone who is infected becomes sick with TB.¹⁻³ As a result, two TB-related conditions exist: LTBI and TB disease.¹⁻³

People with LTBI have been infected with *M. tuberculosis*, but do not have signs and symptoms of TB disease and cannot spread *M. tuberculosis* to others because their immune system keeps *M. tuberculosis* suppressed.¹⁻³ Without treatment, about 5-10% of people who have LTBI will develop TB disease.¹⁻³ An estimated 13 million people in the U.S. and more than two million Californians (6% of the population) have LTBI.^{4,5}

The medical and societal costs of TB in California reached \$203 million in 2021, with an overall annual TB incidence of 4.4 cases per 100,000 residents.^{5,6} Severe disparities in TB incidence rates exist, with incidence rates up to 52 times higher among non-U.S.-born racial and ethnic groups than among white people born in the U.S. (**Figure 1**).⁵

Figure 1. TB Rates in California by Place of Birth and Race/Ethnicity, 2021 (rate shown is per 100,000 residents).⁵



In August 2021, the California Tuberculosis Elimination Advisory Committee (CTEAC) published their [California Tuberculosis Elimination Plan](#), a five-year action plan with targets that include a 30% reduction in the annual number of TB cases in California by 2025.⁷ With approximately

87% of TB cases due to the progression from LTBI to active TB disease, any reduction in TB cases will require expanded testing and treatment of LTBI.^{5,7}

Testing for TB Disease^{1-3,8}

While anyone can become infected with *M. tuberculosis*, healthcare providers should be familiar with the [California TB Risk Assessment Tools](#) in order to identify individuals at high risk for LTBI and recommend testing them for LTBI during routine evaluations, including the following:

- Contacts of people known or presumed to have infectious TB disease
- People who were born in or who frequently travel to countries where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
- People who inject drugs
- Mycobacteriology lab personnel
- People who live or work in high-risk congregate settings such as homeless shelters, prisons, jails, or nursing homes
- Health care workers who care for patients at increased risk for TB disease

People who are at low risk generally should not be tested. Targeted testing is a strategy that should also be considered for those at high-risk for developing TB disease once infected with *M. tuberculosis* (see **Table 1**).^{1-3,8}

Table 1. Risk factors for TB Disease Development^{1-3,8}

Category	Risk Factors
Comorbid Conditions	<ul style="list-style-type: none"> • HIV infection (strongest known risk factor) • Silicosis, chronic renal failure, leukemia, diabetes mellitus, or cancer of the head, neck, or lung • Substance use (including injection drugs) • Current use of immunosuppressive therapy • Preparing for organ or hematological transplantation
Medical History	<ul style="list-style-type: none"> • Infection with <i>M. tuberculosis</i> within the last 2 years • Gastrectomy or jejunioileal bypass

Category	Risk Factors
	<ul style="list-style-type: none"> • Untreated or inadequately treated TB disease
Other	<ul style="list-style-type: none"> • Infants and children younger than 5 years of age or the elderly • Low body weight • High local incidence of TB disease, including medically underserved and low-income populations

Current diagnostic testing options for TB infection include two blood tests (interferon-gamma release assays [IGRAs]) and a skin test (Mantoux tuberculin skin test [TST]).^{1,3,8} The TST requires two visits with a provider for test administration and reading and interpretation within 48 – 72 hours after administration.^{1,3,8} In general, testing should not be performed if there is documentation of a prior positive TB test result.^{1,3,8} Detailed testing guidelines can be found on the [TB Testing & Diagnosis](#) page on the CDC website.¹

When choosing which test to recommend, health care providers often factor in test availability, cost, and the reason for testing.^{1,3,8} Using either the IGRA or TST test is acceptable. In general, the IGRA blood test is preferred for the following groups:

- People who might be less likely to return for TB skin test reading and interpretation.^{1,3,8}
- People who have received the Bacille Calmette-Guérin (BCG) vaccine, which is not commonly used in the United States, but it is often given to infants and small children in other countries where TB is common. BCG does not always protect people from getting infected with *M. tuberculosis*.^{1,3,8}
- People who are likely to be infected with *M. tuberculosis* and are at a low to intermediate risk of progression to TB disease.^{1,3,8}
- People who are unlikely to be infected with *M. tuberculosis*.^{1,3,8}

The TST is often recommended for children younger than 5 years of age, although some experts use IGRA in younger children.^{1,8} For updated guidance in this population, reference the [Tuberculosis Infection in Children and Adolescents: Testing and Treatment](#) guidelines published by the American Academy of Pediatrics (AAP) in 2021.⁹

Of note, a positive IGRA or TST cannot distinguish between LTBI or TB disease.^{1,3,8} Other tests, such as a chest x-ray and a sample of sputum, are needed to see whether the person has TB

disease.^{1,3,8} All patients being considered for treatment of LTBI should receive a medical evaluation to rule out TB disease, to identify details of any previous treatment for LTBI or TB disease, to identify any medical problems or other issues that may complicate treatment or require increased monitoring, and to determine if the patient is taking a medication that may interact with the medications needed to treat LTBI or TB disease.^{1,3,8} As HIV is the strongest known risk factor for progressing to TB disease, collecting a history of HIV status or HIV testing should be offered to all individuals evaluated for LTBI.^{1,3,8}

Treatment for LTBI

Treatment for LTBI should be offered to patients of all ages upon confirmation of a diagnosis of LTBI.¹⁰ The following short-course rifamycin-based options are preferred (**Table 2**):

- Three months of once-weekly isoniazid plus rifapentine (3HP) is strongly recommended for adults and children older than 2 years^{1,3,9,10}
- Four months of daily rifampin (4R) is strongly recommended for HIV-negative adults and children of all ages^{1,3,9,10}
- Three months of daily isoniazid plus rifampin (3HR) is conditionally recommended for adults and children of all ages^{1,3,9-11}

If short-course regimens are not feasible or available, six or nine months of daily isoniazid (6H/9H) are recommended as alternative regimens.³ As with all medications, potential drug-drug interactions should be reviewed before initiating treatment for LTBI. The [Rifamycin Drug-Drug Interactions: A Guide for Primary Care Providers Treating Latent Tuberculosis Infection](#) is a guide created to clarify drug interactions between rifamycins and drugs commonly used in primary care. For example, in people living with HIV, rifamycins can be used only in conjunction with selected antiretroviral therapy (ART), but isoniazid can be administered concurrently with any ART.^{10,11} Providers should consult the CDC recommendations for [Treatment of LTBI and TB for Persons with HIV](#) and the [Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV](#) for additional guidance.

For pregnant people with no risk factors for developing TB disease, LTBI treatment should be delayed until after delivery to avoid taking anti-TB medications during pregnancy.^{1,3} If LTBI is treated during the post-partum period, baseline liver function tests should be conducted.^{1,3} If treatment is given during pregnancy, 4R, 3HR, or the 6H/9H are appropriate regimens. 3HP is not recommended for people who are pregnant or expecting to become pregnant during

treatment.^{1,3} If isoniazid is prescribed to people who are pregnant or breastfeeding, a vitamin B6 supplement should be prescribed as well.^{1,3}

Once treatment has been initiated, it is important to schedule monthly clinical assessments to review for: signs and symptoms of active TB, adverse reactions to TB medications, adherence to treatment, and new medications with potential drug interactions.^{1,3} When possible, providers are encouraged to write prescriptions for treatment of LTBI as a one-month supply with monthly refills.³

Table 2. LTBI Treatments Available on the Medi-Cal Rx Contract Drugs List*

	Drug (Regimen)	Duration/Frequency	Total Doses	Dose and Age Group
Preferred	Isoniazid and Rifapentine (3HP)	3 months/ 1 x weekly	12	Adults and children aged \geq 12 yrs INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg max RPT: 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 \geq 50.0 kg; 900 mg max
				Children aged 2-11 yrs INH: 25 mg/kg; 900 mg max RPT: See above
	Rifampin (4R)	4 months/ 1 x day	120	Adults: 10 mg/kg; 600 mg max Children: 15-20 mg/kg; 600 mg max
Alternative	Isoniazid and Rifampin (3HR)	3 months/ 1 x day	90	Adults INH: 5 mg/kg; 300 mg max RIF: 10 mg/kg; 600 mg max
				Children INH: 10-20 mg/kg; 300 mg max RIF: 15-20 mg/kg; 600 mg max
	Isoniazid (6H)	6 months/ 1 x day	180	Adults Daily: 5 mg/kg; 300 mg max Twice weekly: 15 mg/kg; 900 mg max
6 months/ 2 x week		52		
Isoniazid (9H)	9 months/ 1 x day	270	Children Daily: 10-20 mg/kg; 300 mg max Twice weekly: 20-40 mg/kg; 900 mg max	
	9 months/ 2 x week	76		

* For current information on covered products, check the [Medi-Cal Rx Contract Drugs List](#) page on the Department of Health Care Services (DHCS) website.

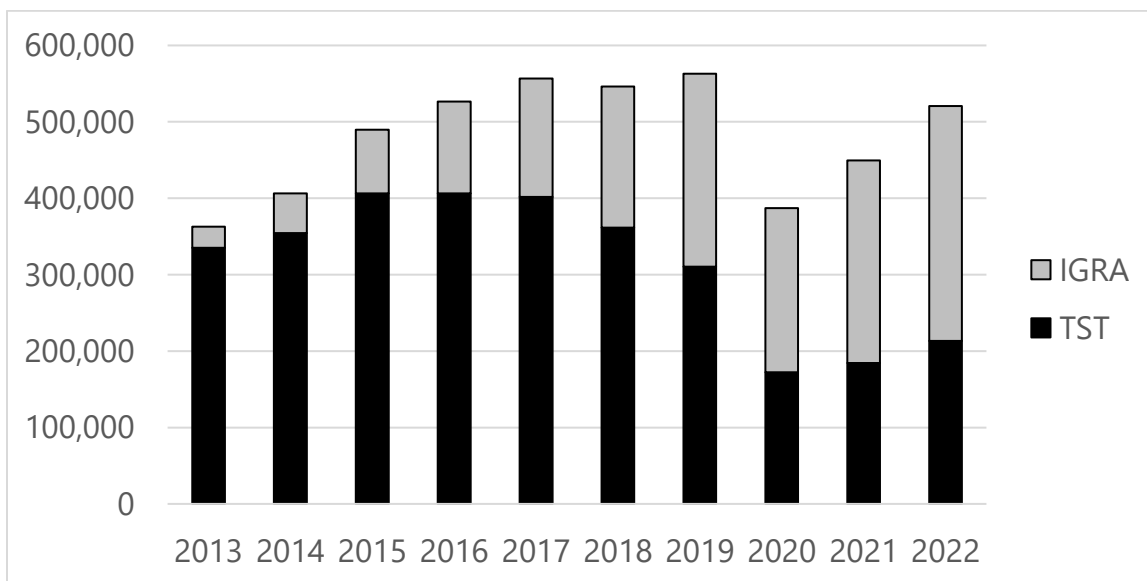
LTBI in the Medi-Cal Population

A retrospective administrative claims analysis was conducted to evaluate LTBI screening, diagnosis, and treatment over time within the Medi-Cal population. All paid medical and pharmacy claims were reviewed for eligible Medi-Cal beneficiaries with a date of service between January 1, 2013, and December 31, 2022. Beneficiaries that were dually eligible with Medicare were excluded from the study population. Current Procedure Terminology (CPT) codes were used to determine screening completed using either IGRA (CPT codes 86480 and 86481) or TST (CPT code 86580). Medi-Cal beneficiaries with a pharmacy or medical claim that included a primary or secondary ICD-10-CM code for LTBI (Z22.7) were included in the study population as being diagnosed with LTBI. Of note, diagnostic and treatment data are limited to dates of service after October 1, 2019, as diagnostic codes prior to this date did not clearly distinguish LTBI from active TB disease.

Results

Within the Medi-Cal population, TB screening decreased dramatically during 2020 (**Figure 2**).

Figure 2. Total Paid Claims for TB Screening Tests in the Medi-Cal Population between January 1, 2013, and December 31, 2022.



While TB screening rates have been steadily increasing over the last two years, they are not yet at levels seen prior to the onset of the COVID-19 pandemic. Between October 1, 2019, and December 31, 2022, a total of 41,195 Medi-Cal beneficiaries were diagnosed with LTBI and 34% (n=13,859) initiated treatment for LTBI.

Discussion/Conclusion

The COVID-19 pandemic disrupted healthcare services and led to a reallocation of resources to COVID-19 care.¹² The prioritization of COVID-19 among public health agencies and clinical laboratories have contributed to reduced access to TB screening and services in recent years.¹² This has resulted in projections for a 5-year setback in terms of mortality from TB and a 9-year setback in terms of TB detection.¹² Hopefully within the Medi-Cal population, focusing on efforts that can improve screening, diagnosis, and treatment for LTBI can counter these dire projections and instead meet statewide goals for a 30% reduction in the annual number of TB cases in California by 2025.

Clinical Recommendations

Recommendations for Screening and Testing for TB:

- During routine patient evaluations, healthcare providers should be familiar with the [California TB Risk Assessment Tools](#) in order to identify individuals at high risk for LTBI and test them for LTBI. People who are at low risk generally should not be tested. People at high risk include 1) those who are at high risk for exposure to or infection with *M. tuberculosis*, and 2) people who are at high risk for developing TB disease once infected with *M. tuberculosis*.
- Educate patients at high risk about the need for LTBI testing and treatment for LTBI. Clinicians can reference the talking points listed in [How to Talk to Patients about LTBI - Adult](#) and [Pediatric](#) developed by the CDPH Tuberculosis Control Branch.

Recommendations for LTBI Treatment:

- Review the [Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020](#) or [Latent Tuberculosis Infection: A Guide for Primary Health Care Providers](#) developed by the CDC.

- All patients being considered for treatment of LTBI should receive a medical evaluation to rule out TB disease, identify the details of any previous treatment for LTBI or TB disease, identify any medical problems or other issues that may complicate treatment or require increased monitoring, and determine if the patient is taking a medication which may interact with the medications taken for LTBI.
- As HIV is the strongest known risk factor for progressing to TB disease, collecting a history of HIV status or HIV testing should be offered to all individuals evaluated for LTBI. For patients with HIV, providers should consult the CDC recommendations for [Treatment of LTBI and TB for Persons with HIV](#) and the [Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV](#) for additional guidance.
- To reduce toxicity and improve treatment adherence, the following short-course rifamycin-based options are preferred for LTBI treatment:
 - Three months of once-weekly isoniazid plus rifapentine (3HP) is strongly recommended for adults and children older than 2 years
 - Four months of daily rifampin (4R) is strongly recommended for HIV-negative adults and children of all ages
 - Three months of daily isoniazid plus rifampin (3HR) is conditionally recommended for adults and children of all ages
- If short-course regimens are not feasible or available, six or nine months of daily isoniazid (6H/9H) are recommended as alternative regimens.
- Clinicians should decide between directly observed therapy or self-administered therapy based on patient attributes and preferences, risk of progression to severe TB disease, and local practices.
- Patient education should be provided in the patient's primary language. [Educational materials](#) for patients can be found at the CDC's website.
- Individuals treated for LTBI should be informed of the potential adverse reactions to their medication and be instructed to seek medical attention immediately if these symptoms occur.
- Evaluate individuals treated for LTBI at least monthly for adherence, signs and symptoms of TB disease, and adverse reactions. When possible, clinicians are encouraged to write prescriptions for treatment of LTBI as a one-month supply with monthly refills.

- Encourage the use of pill boxes, [medication trackers](#), or other reminders to promote adherence.
- Patients should be given documentation of treatment completion for LTBI, such as the [LTBI Treatment Completion Card](#) available on the Tuberculosis Control Branch Website by the CDPH.
- Clinicians should consult the [California Tuberculosis Control Branch](#) and local TB control offices for additional information on diagnosing and treating LTBI.

Recommendations for LTBI Treatment while Pregnant or Breastfeeding:

- For pregnant people with no risk factors for developing TB disease, LTBI treatment should be delayed until after delivery to avoid taking anti-TB medications during pregnancy. If LTBI is treated during the post-partum period, baseline liver function tests should be conducted.
- If treatment is given during pregnancy, the 4-month daily regimen of RIF (4R), 3-month daily regimen of INH and RIF (3HR), or the 6- or 9-month daily regimen of INH (6H or 9H) are appropriate regimens. The 12-dose regimen of isoniazid and rifapentine is not recommended for people who are pregnant or expecting to become pregnant during treatment.
- People who are pregnant or breastfeeding should be given a vitamin B6 supplement if isoniazid is prescribed.

Pharmacist-Specific Recommendations for LTBI Treatment:

- Ensure that patients who are prescribed 3HP receive the correct medications for LTBI treatment (isoniazid and rifapentine), as rifampin can be confused with rifapentine.
- Pharmacists should check for potential drug interactions when LTBI treatments are prescribed. The [3HP Drug Interactions Guide](#) by the CDPH Tuberculosis Control Branch can be referenced for additional information on common drug interactions related to the 3HP regimen for LTBI.
- People who use hormonal birth control and are prescribed rifamycins should be advised to add, or switch to, a barrier method.
- Pharmacists should monitor and evaluate for LTBI treatment adherence. If non-adherence is identified, pharmacists should contact the patient to discuss and assess reason for late refill and non-adherence, counsel patient on any reported side effects, and reinforce the

importance of adhering to and completing the prescribed LTBI treatment. Pharmacists should also inform the prescriber of identified non-adherence and provide the dates for when the LTBI prescriptions were filled and any information regarding barriers to adherence such as side effects or difficulty adhering to the regimen. Prescribers and pharmacists can discuss approach and actions that will be helpful in supporting the patient to adhere and complete their LTBI treatment.

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