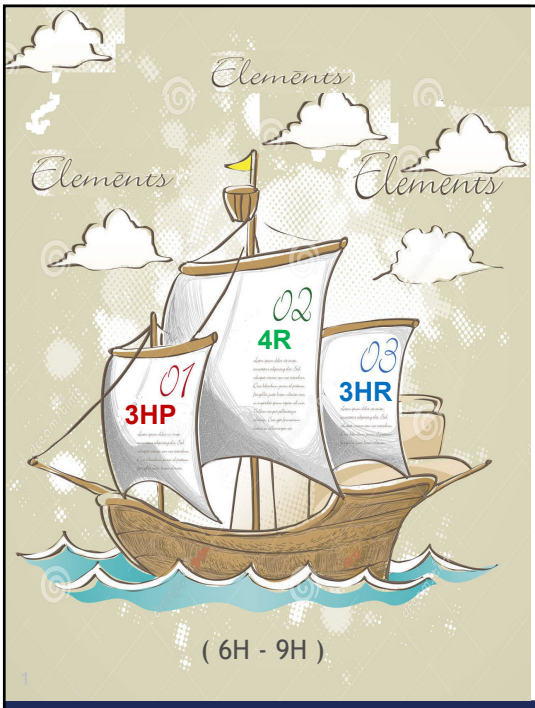


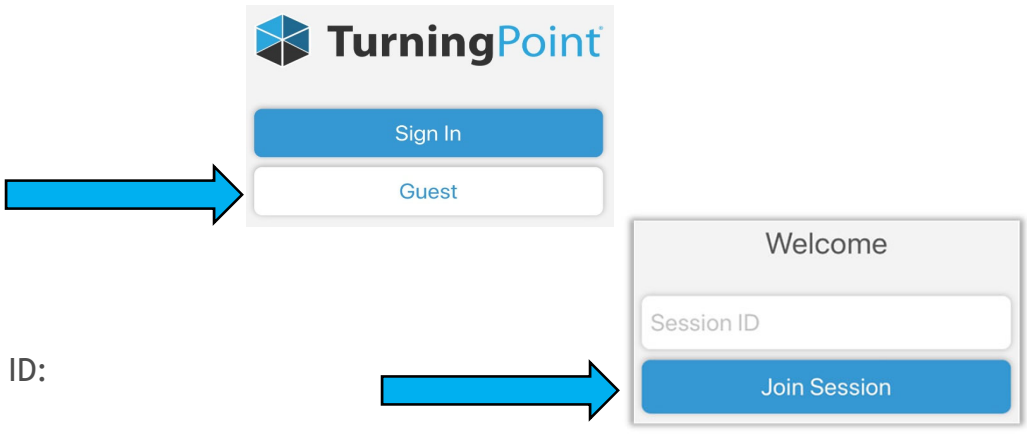
Guidelines for the Treatment of Latent Tuberculosis Infection (LTBI): Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

Thursday, February 11th, 2021

Adwoa Sam, RN
VDH TB Program

Polling Questions

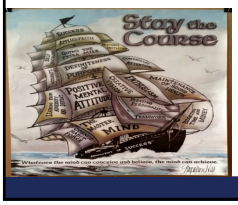
Visit: www.ttpoll.com



Session ID:

WEBINAR GOALS

- Discuss why LTBI is an important issue in TB elimination
- Discuss the LTBI screening/testing/treatment process
- Describe currently recommended LTBI treatment regimens
- Identify what is new/different about recommendations
- Discuss benefits of implementation of recommendations
- Provide resources to help operationalize recommendations



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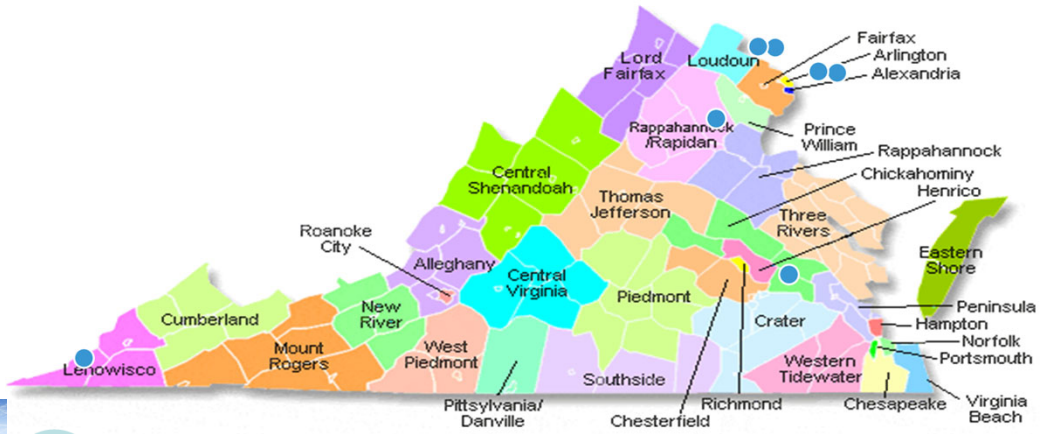
VIRGINIA! Where in our lovely state are you located? *



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* Please type in your location by state if not viewing from Virginia

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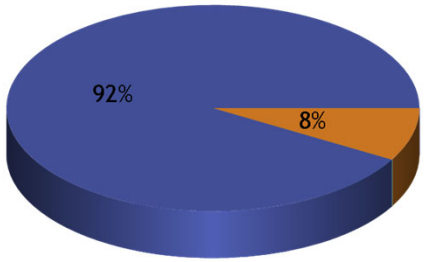
What type of work organization are you linked to?

A-Public Health Departments and TB Programs
B-Community Health Clinics- includes Free/Charity, Rural Health
C-Hospital
D-Private Medical Practice
E-Long-Term Care
F-Correctional Facility-
G-Homeless Shelter
H-Other (enter in chat box)



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A B C D E F G H

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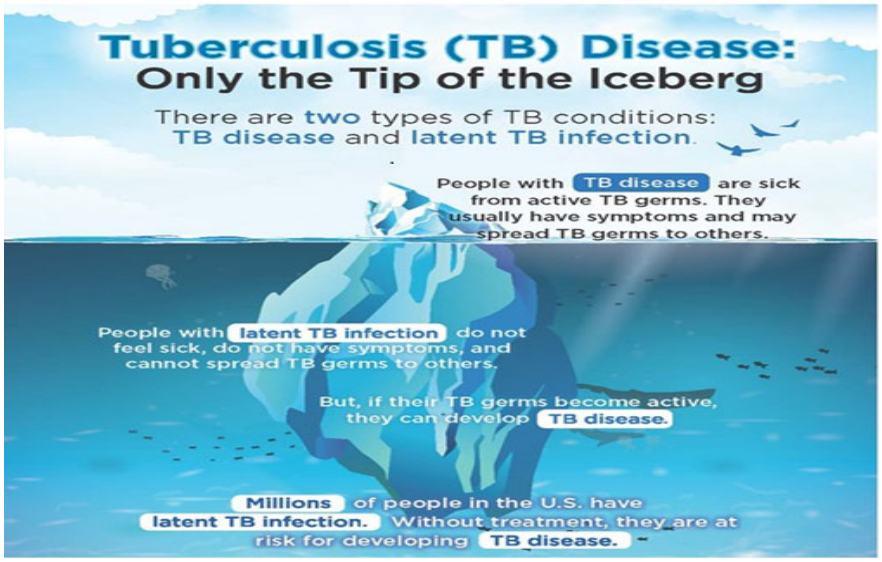
ROLE OF LTBI TREATMENT IN TB ELIMINATION



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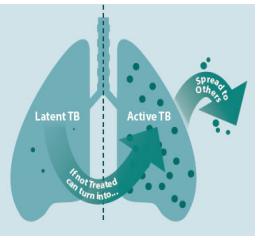
BREAKING THE CYCLE OF LTBI PROGRESSION TO TB



- Ultimate goal is to interrupt transmission of active TB.
- Adherence to treatment of active TB interrupts direct transmission.
- Treating LTBI prevents TB by indirectly interrupting transmission
- TB is thus not only treatable and curable, but also preventable

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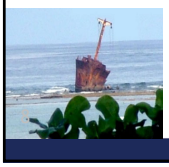
PREVENTION OF ACTIVE TB VIA LTBI TREATMENT MAKES SENSE

Individual	Organization	Society
Wellness	Investigations	Secondary transmission
Morale	Resources	Loss of work years
Productivity	Liability	Chronic morbidity
Lung health		



Treating latent TB infection is less costly than treating disease.

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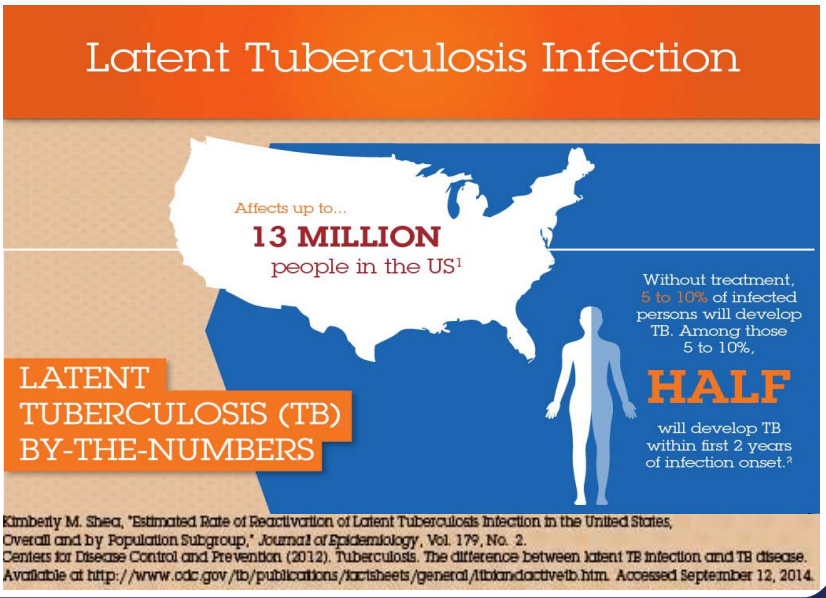
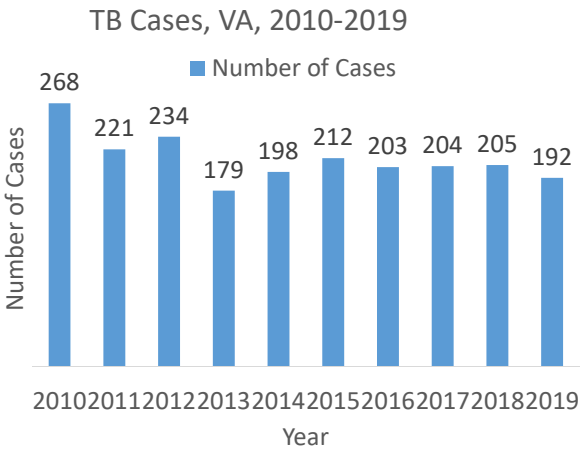
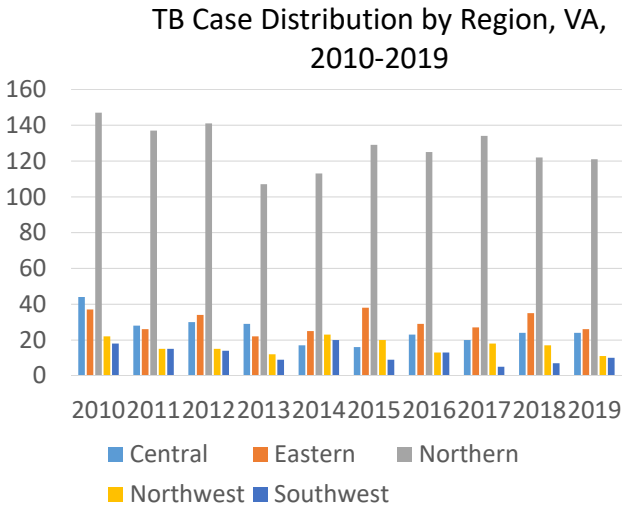
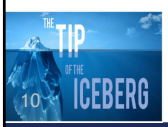
BURDEN OF LTBI IN THE UNITED STATES



TB IN VIRGINIA (VA), 2010-2019



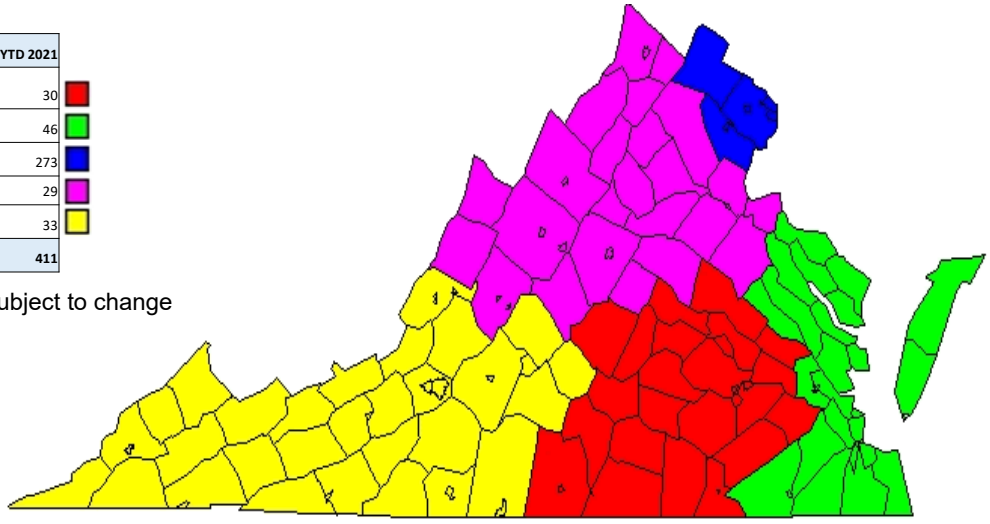




LTBI BURDEN IN VIRGINIA BY HEALTH PLANNING REGION

	2019	2020	YTD 2021
Central	612	526	30
Eastern	829	630	46
Northern	4190	3588	273
Northwest	503	459	29
Southwest	531	365	33
Grand Total	**6665**	**5568**	**411**

Data is preliminary and subject to change



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https://www.vdh.virginia.gov/content/uploads/sites/13/2016/03/Maps05-1.pdf

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REACHING THE US GOAL OF TB ELIMINATION

- Modeling studies suggest TB elimination goal possible with LTBI testing/treatment increase strategy
- Finding/treating those at high risk for LTBI a priority as rate of active TB disease decreases
- Persons at high risk for LTBI fall into 2 categories:
  - Those who have been recently infected
  - Those with clinical conditions that increase risk of progressing from LTBI to TB disease

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- Clinicians, health care agencies, & community organizations serving at-risk populations, critical to TB elimination goal

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LTBI: SCREENING…TESTING….TREATMENT

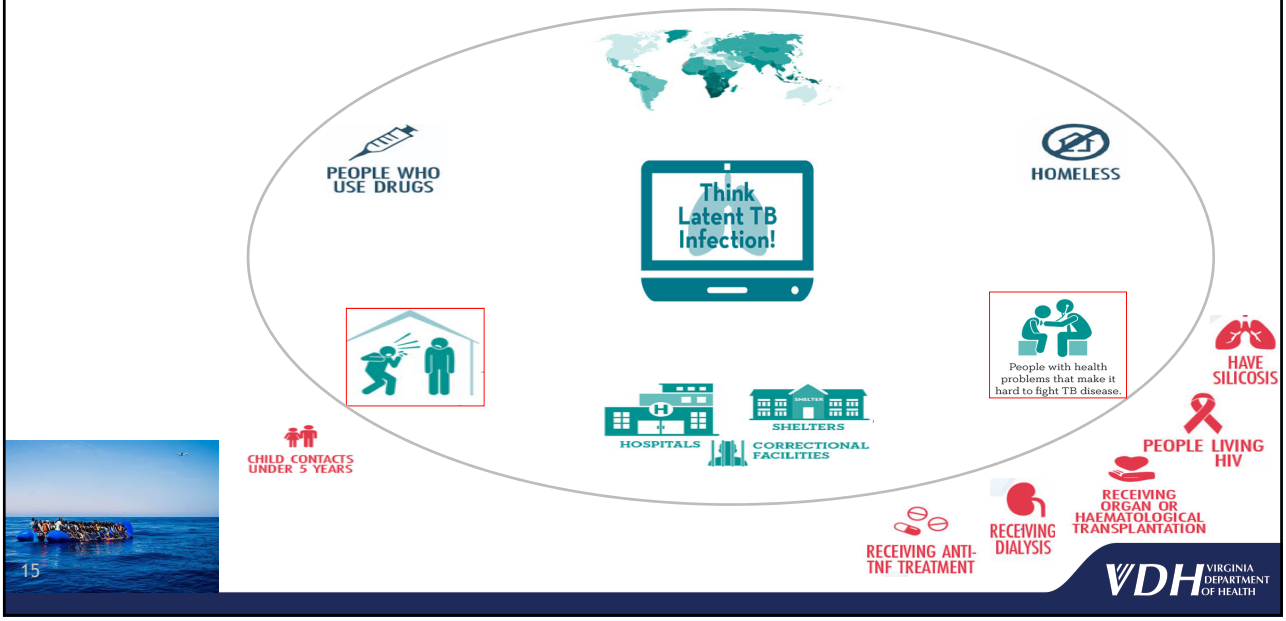
Process of finding/treating those at high risk for LTBI entails:

- Conducting a risk assessment
  - Symptom review
  - LTBI risk
  - Risk for progression to TB if infected
- TB testing
  - IGRA or TST
  - Clinical evaluation to exclude TB disease if test results positive
- LTBI treatment initiation

What is the purpose of a TB risk assessment?

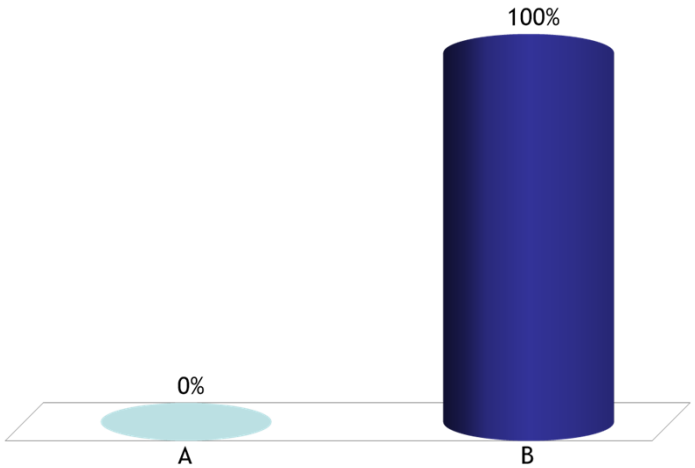
25

GROUPS AT RISK FOR LTBI OR FOR PROGRESSION TO TB ONCE INFECTED



True or False: "Not all individuals who complete a TB screening will need a TB test"

A. False
✓ B. True



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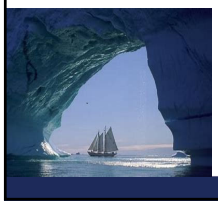
A GLANCE BACK AT 2000 LTBI TREATMENT RECOMMENDATIONS

Drugs	Duration (mo)	Interval	Rating* (Evidence)† HIV-	HIV+
Isoniazid	9	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin-pyrazinamide	2	Daily	B (II)	A (I)
	2-3	Twice weekly	C (II)	C (I)
Rifampin	4	Daily	B (II)	B (III)

* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.

† I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.



Treatment of latent tuberculosis infection

Treatment of latent tuberculosis infection (LTBI) is an important component of TB elimination programs. To note, countries with a low incidence of TB have new cases emerge as a result of reactivation of LTBI.

Meta-analysis, randomized clinical trials

1962–2014

53 studies were evaluated and compared. Odds ratios were calculated for the prevention of active TB comparing numerous medications with placebo.

Key

INH = isoniazid
EMB = ethambutol
RMP = rifampicin
RFB = rifabutin
RPT = rifapentine
PZA = pyrazinamide

Regimen	Odds Ratio (95% CI)
No treatment	1.82 (1.05-3.05)
INH 3-4 months	0.94 (0.53-1.56)
INH 6 months	0.64 (0.48-0.83)
INH 9 months	0.94 (0.40-2.10)
INH 12-72 months	0.52 (0.41-0.66)
RFB-INH	0.28 (0.05-1.49)
RFB-INH (high)	0.31 (0.06-1.59)
RPT-INH	0.61 (0.29-1.22)
RMP	0.41 (0.18-0.86)
RMP-INH 1 month	1.07 (0.36-2.79)
RMP-INH 3-4 months	0.52 (0.34-0.79)
RMP-INH-PZA	0.34 (0.18-0.62)
RMP-PZA	0.55 (0.33-0.92)
INH-EMB	0.91 (0.32-2.42)

Among different LTBI treatment regimens, various therapies containing rifamycins for 3 months or more were efficacious at preventing TB, potentially more so than INH alone. These regimens may be effective alternatives to INH monotherapy under current guidelines. Clinicians should take cost, toxicity and efficacy into account to make informed decisions on which treatment plan is best suited to the individual patient.

Stagg HR, Zenner D, Harris RJ, et al. Ann Intern Med. 2014;161:419-28.

Focus after 2000 Guidelines on efficacy studies of new drugs & comparisons of shorter & longer regimens

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In the past year, what treatment regimen did you often/most prescribe/favor for clients diagnosed with LTBI?

A. Daily INH (9 months)
B. Twice weekly INH (9 months by DOT)
C. Daily INH (6 months)
D. Twice weekly INH (6 months by DOT)
E. Rifampin (4 months)
F. INH-RPT 12 weekly dose (3 months)
G. INH-RIF (3 months)

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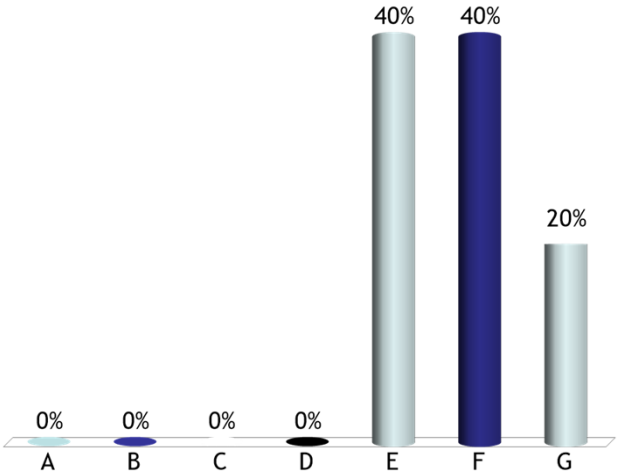

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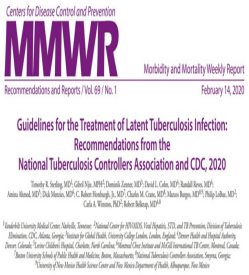
THE NTCA/CDC 2020 UPDATED LTBI TREATMENT GUIDELINES:


Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 69 / No. 1 February 14, 2020
Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

- Systematic literature review by a CDC-NTCA committee
- Recommend the most effective & least toxic LTBI treatment regimens
- Recommend shorter treatment regimens that favor treatment completion
- Present the recommended treatment regimens in order of preference
- Recommend treatment regimens comprising
  - three preferred rifamycin-based regimens and
  - two alternative monotherapy regimens with daily isoniazid
- Encourage healthcare providers to prescribe these preferred shorter & more convenient regimens, when possible

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EVIDENCE-BASED REVIEW: 'GRADE' CRITERIA APPLICATION

	Strong Recommendation ("We recommend . . .")	Conditional Recommendation ("We suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action and only a small minority would not.	The majority individuals in this situation would want the suggested course of action, but a sizeable minority would not.
For clinicians	**The overwhelming majority of individuals** should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy-making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

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ELEMENTS OF 2020 UPDATED LTBI TREATMENT RECOMMENDATIONS IN ORDER OF PREFERENCE

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.

* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.

† No evidence reported in HIV-positive persons.

§ Strong recommendation for those persons unable to take a preferred regimen (e.g., due to drug intolerability or drug-drug interactions).

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THE 2020 UPDATED LTBI TREATMENT REGIMENS AT A GLANCE

Latent Tuberculosis Infection Treatment Regimens

Treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). CDC and the National Tuberculosis Controllers Association preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.

Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV*), and potential for drug–drug interactions.

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	ISONIAZID† AND RIFAPENTINE†† (3HP)	3 months	Once weekly	12	**Adults and children aged ≥12 yrs** INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum 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 ≥50.0 kg; 900 mg maximum
					Children aged 2–11 yrs INH†: 25 mg/kg; 900 mg maximum RPT††: See above
	RIFAMPIN§ (4R)	4 months	Daily	120	**Adults:** 10 mg/kg; 600 mg maximum
					Children: 15–20 mg/kg¶; 600 mg maximum
	ISONIAZID† AND RIFAMPIN§ (3HR)	3 months	Daily	90	**Adults** INH†: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum
					Children INH†: 10-20 mg/kg¶; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum
Alternative	ISONIAZID† (6H/9H)	6 months	Daily	180	**Adults** Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
			Twice weekly¶	52	
		9 months	Daily	270	**Children** Daily: 10-20 mg/kg¶; 300 mg maximum Twice weekly: 20–40 mg/kg¶; 900 mg maximum
			Twice weekly¶	76	

*For persons with HIV/AIDS, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview.
†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.
‖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 Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–83).
#The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

CDC LTBI Treatment Guidelines

Find TB. Treat TB. Working together to eliminate TB.

NOTE: It is imperative to rule out active TB disease in all persons prior to initiating treatment for LTBI

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PREFERRED RIFAMYCIN-BASED REGIMENS*

- Three preferred rifamycin-based regimens in preference order are:
  - 3 months of once-weekly isoniazid plus rifapentine **(3HP)**
  - 4 months of daily **rifampin** (4R)
  - 3 months of daily isoniazid plus rifampin **(3HR**)
- Preference based on effectiveness, safety, and high treatment completion rates.
- Should not be used for patients for whom rifamycins contraindicated
  - (including those taking medications with significant drug-drug interactions with rifamycin).

(*A rifamycin-based regimen includes either rifampin or rifapentine)

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PREFERRED REGIMEN 1: 3HP

- 3-month regimen of 12 once-a-week doses of isoniazid (INH) and rifapentine (RPT) is **1st preferred regimen**
- Recommended for people ≥ 2yrs old
- Persons on HIV/AIDS antiretroviral medications with acceptable drug-drug interactions with RPT
- NOT recommended for the following individuals:
  - Children younger than 2 years of age
  - People with HIV/AIDS taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly RPT
  - People presumed to be infected with INH- or RIF-resistant *M. tuberculosis*
  - Pregnant women or women expecting to become pregnant during the 3-month regimen period

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PREFERRED REGIMEN 2 : 4R

- 4-month regimen of rifampin (RIF), given daily is the **2nd preferred regimen**
- Should be completed within 6 months
- Recommended for HIV-negative adults and children of all ages
- Especially recommended for people who cannot tolerate INH or who have been exposed to INH-resistant TB
- Should not be used to treat HIV-infected people taking some combinations of antiretroviral therapy
- When rifampin (RIF) cannot be used, sometimes another drug, rifabutin (RBT), may be substituted

PREFERRED REGIMEN 3: 3HR

- 3-month regimen of INH and RIF given daily is the **3rd preferred regimen**
- Recommended short-course for adults and children of all ages
- Recommended for HIV-negative and also for HIV-positive patients as drug interactions allow.

ALTERNATIVE ISONIAZID MONOTHERAPY REGIMENS

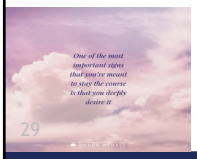
- Two alternative isoniazid monotherapy treatment regimens are the **4th preferred regimen**
- Regimens of 6 or 9 months daily isoniazid with 6 months considered first
- Are as efficacious as rifamycin-based shorter-course regimens
- Higher toxicity risk
- Lower treatment completion rates
- Effectiveness decreased by higher toxicity risk/lower treatment completion rates.

ALTERNATIVE ISONIAZID MONOTHERAPY REGIMENS

- Alternative regimens of 6 or 9 months daily INH when short-course treatment not an option
- 6H strongly recommended for HIV-negative adults & children of all ages
- 6H also a treatment option for HIV-positive adults & children of all ages
- 9H rated another option for HIV-negative/positive adults & children of all ages
- Daily self-administered treatments. May also be given twice weekly by DOT

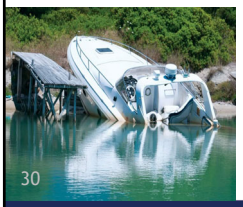
NTCA/CDC 2020 RECOMMENDED LTBI TREATMENT COMPLETION TIMEFRAMES

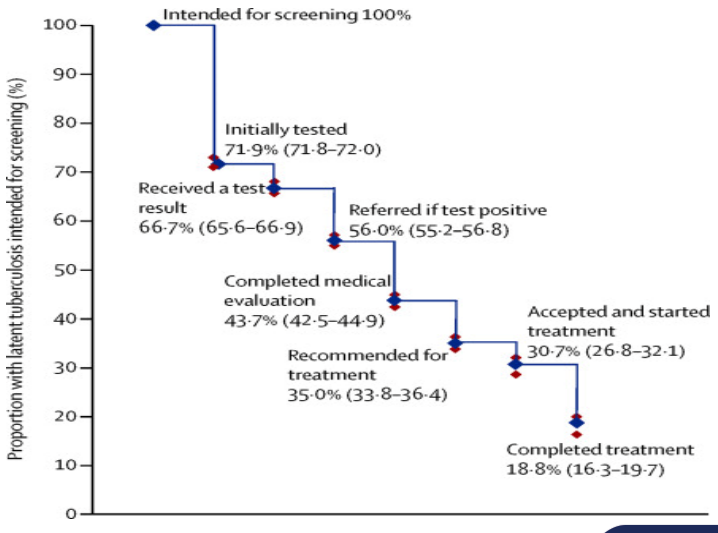
Regimen	Duration	Doses	Complete Within
INH-RPT (#1 preferred)	3 months	11-12	16 weeks
Rifampin (#2 preferred)	4 months	120	6 months
INH-RIF (#3 preferred)	3 months	90	4 months
Daily INH (Alternative)	6 months	180	9 months
Twice weekly INH (Alternative)	6 months	52 DOT	9 months
Daily INH (Alternative)	9 months	270	12 months
Twice weekly INH(Alternative)	9 months	76 DOT	12 months



MAKING A CASE FOR SHORTER-COURSE REGIMENS

LTBI "Cascade of Care"



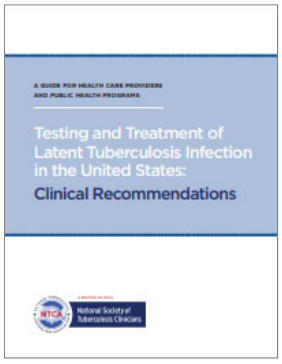


Alsdurf et al *Lancet ID* 2016

LTBI RESOURCES: HOT OFF THE PRESS……

NEW 2021 RESOURCE

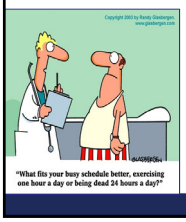
TESTING AND TREATMENT OF LATENT TUBERCULOSIS INFECTION IN THE UNITED STATES: CLINICAL RECOMMENDATIONS



- **'Companion Document'** to 2020 LTBI treatment guidelines
- Developed by NTCA's National Society of TB Clinicians (NSTC)
- A 'living document' with dynamic nature that resides on NTCA website -www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/#.YCAxtHdKiYU
- Practical guidance/clinical expertise to "put 2020 guidelines to work"
- Does not replace clinician clinical judgment

PRACTICAL GUIDANCE

- Determining when to test for LTBI, immunologic test to select/clinical interpretation of results
- Deciding whether to start client on LTBI treatment
- Prescribing correct drugs and dosing for treatment regimens
- Monitoring and managing LTBI Treatment
- Treatment options for specific populations, for example:
  - pregnant, breastfeeding and post partum clients
  - contacts to pan-susceptible and drug-resistant TB
  - LTBI clients with comorbidities that place them at higher risk for progression to TB



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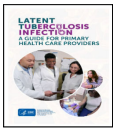
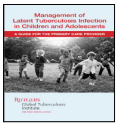
OTHER AVAILABLE LTBI RESOURCES**



Latent Tuberculosis Infection: A Guide for Primary Health Care Providers: www.cdc.gov/tb/publications/ltbi/default.htm

Latent TB Infection Treatment Regimens-Treatment Table www.cdc.gov/tb/topic/treatment/pdf/LTBITreatmentRegimens.pdf



Rutgers Global **Tuberculosis** Institute. **Management of Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider:** 2020 globaltb.njms.rutgers.edu/educationalmaterials/productfolder/ltbichildren

**Links to above resources, in addition to the February 14, 2020 guidelines and other VDH LTBI resources, can be found on the VDH TB Program webpage www.vdh.virginia.gov/tuberculosis/tb-infection-ltbi/

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2020 UPDATED LTBI TREATMENT GUIDELINES SUMMARY

- Why act on recommendations?
  - Preferred regimens have excellent tolerability and efficacy, shorter treatment duration, and higher completion rates
  - Alternative regimens have excellent efficacy but longer treatment duration and lower completion rates
  - Assertion that shorter regimens have higher treatment completion rates is evidence-based
  - Both category regimens have similar efficacy
  - Shorter regimens therefore more effective due to higher completion rates

REFERENCES

American Thoracic Society. CDC targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47).

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.rr6901a1external icon.

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection ATS/CDC Statement Committee on Latent Tuberculosis Infection Membership List, June 2000

Testing and treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations, 2021 www.tbcontrollers.org/resources/ltbi/clinical_recommendations

Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection, MMWR, June 29, 2018;67(25):723-726.

Young, L. Tuberculosis Epidemiology: A Global, National and Virginia Update. March, 2020

Questions

A Q&A document will be provided to all attendees after the session.

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