



# HIV and Latent Tuberculosis Infection (LTBI)

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# Continuing Education Disclosure

- The speakers do not have any financial relationships with commercial entities to disclose.

# Objectives:

At the end of this presentation, participants will be able to:

1

Describe the global and US epidemiology of tuberculosis (TB) and HIV

2

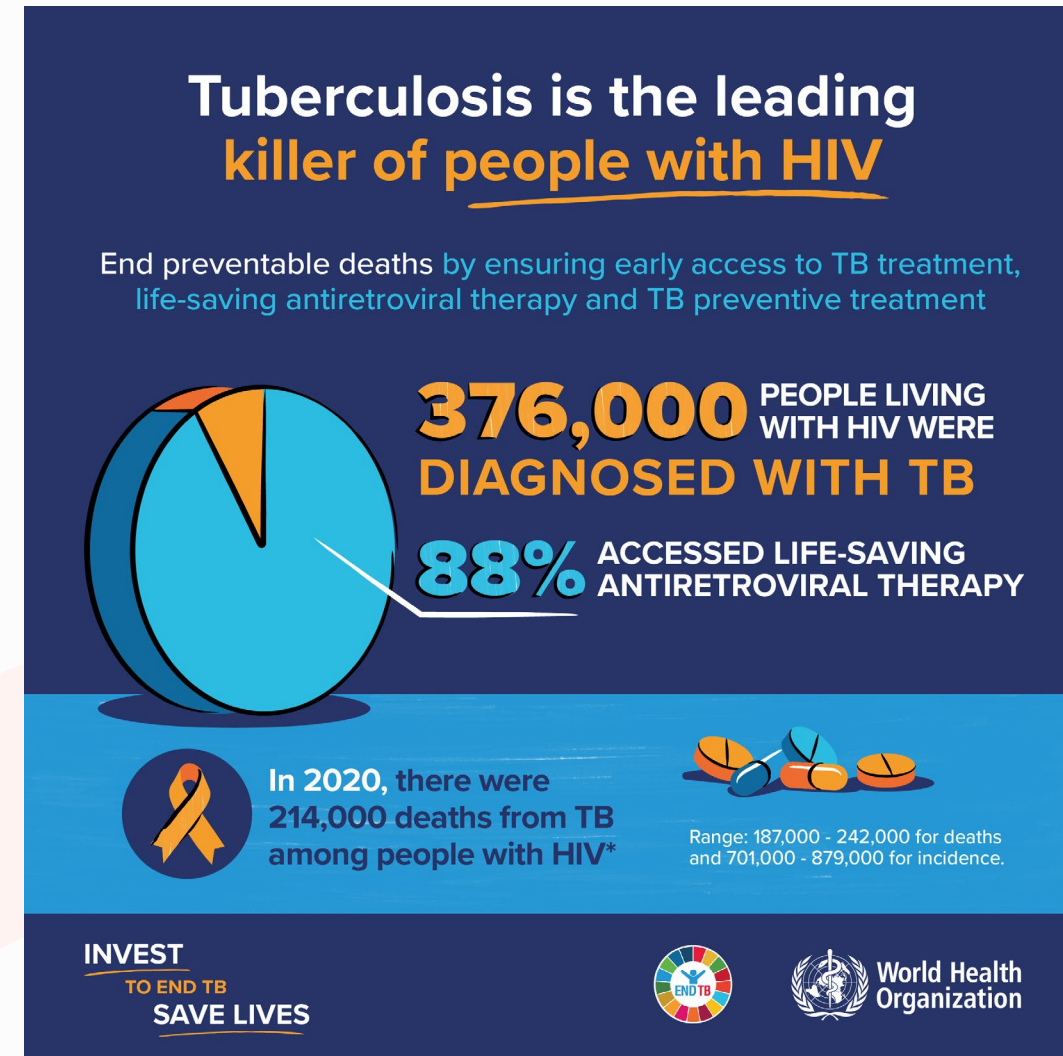
Identify appropriate tests to assess for LTBI in people with HIV (PWH)

3

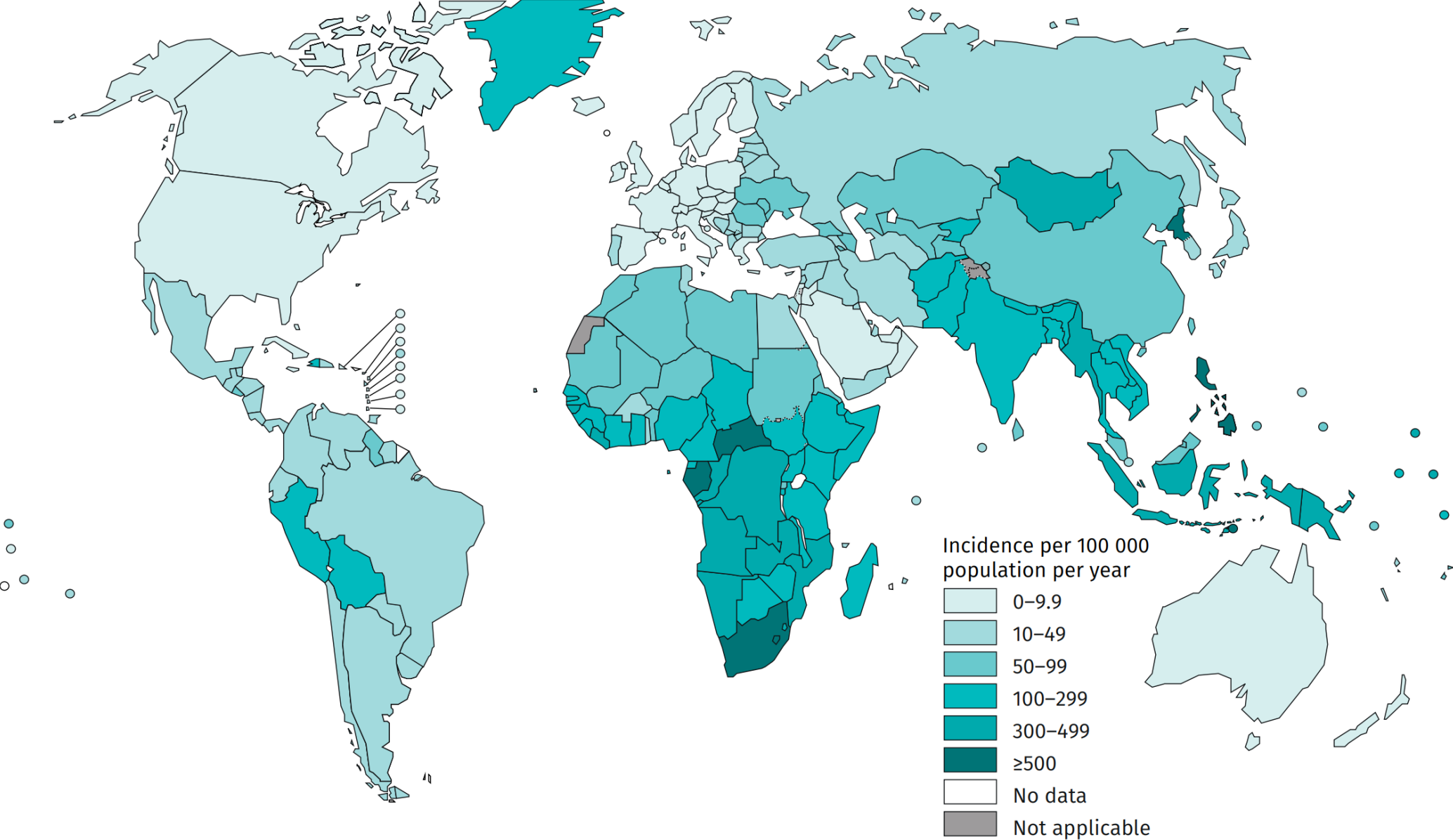
Determine an appropriate treatment regimen for LTBI in PWH

# Tuberculosis (TB)

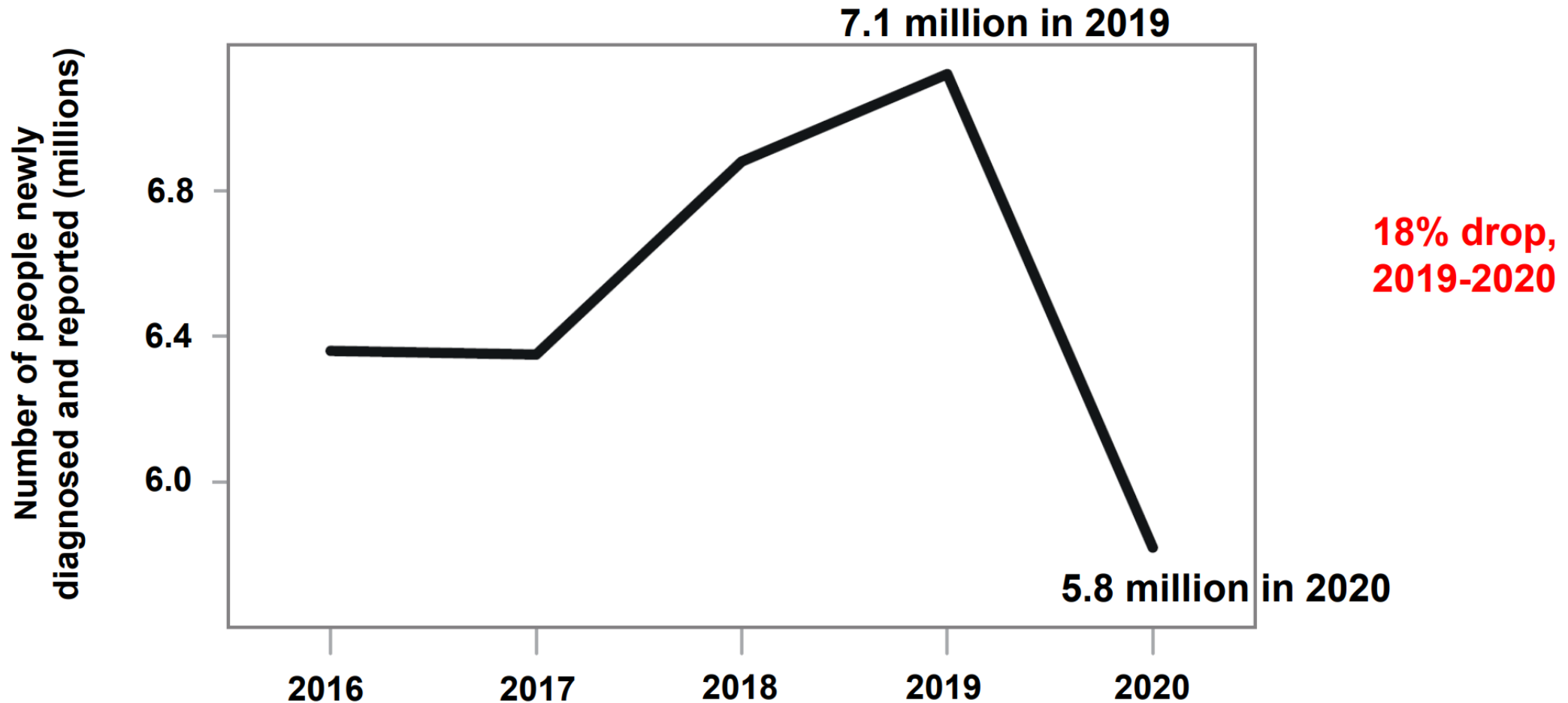
- In 2020, an estimated 10 million people fell ill with TB worldwide
- 1.5 million people died from TB in 2020, including 214 000 people with HIV
- Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19
- Nearly 2 billion people are infected with TB
- TB is curable and preventable



# Estimated TB incidence rates, 2020



# Reported Global TB Incidence, 2020



# WIDER IMPACT OF COVID-19 PANDEMIC ON GLOBAL HEALTH

1.4 million additional  
TB deaths by 2025

## Tuberculosis



382,000 additional  
malaria deaths in 2020

## Malaria



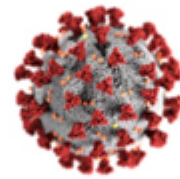
## HIV

673,000 additional  
HIV-related deaths in  
Africa in 2020



## Maternal & Child Health

2.3 million child deaths  
and 113,000 maternal  
deaths over 12 months



## Routine Immunisation

80 million children at risk of  
vaccine-preventable diseases



## Non-Communicable Diseases

Cancer treatment  
disrupted in 42% of  
countries



## Reproductive Health

Up to 15 million unintended  
pregnancies



## Poverty

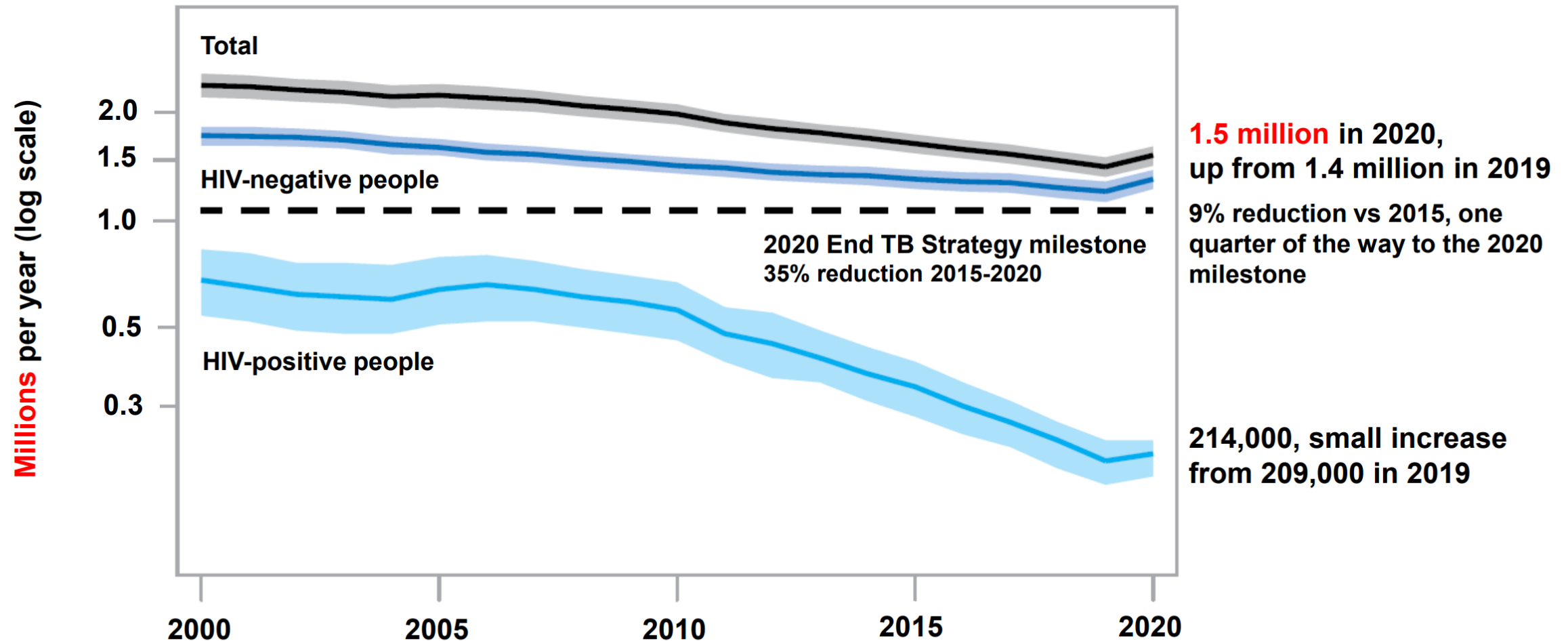
Deepest global recession  
since  
World War II



# Global number of TB deaths increased in 2020

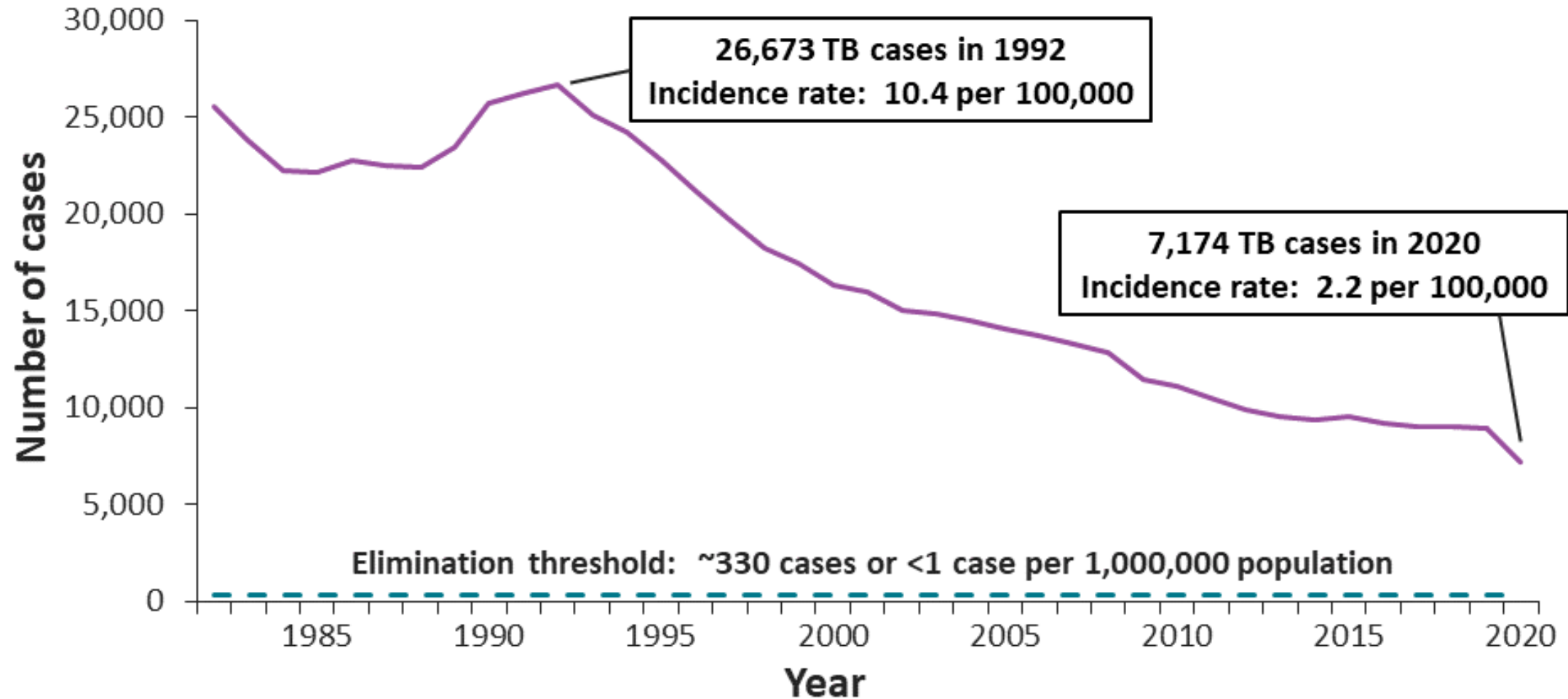
first year-on-year increase since 2005, back to the level of 2017

TB second only to COVID-19 as cause of death from single infectious agent

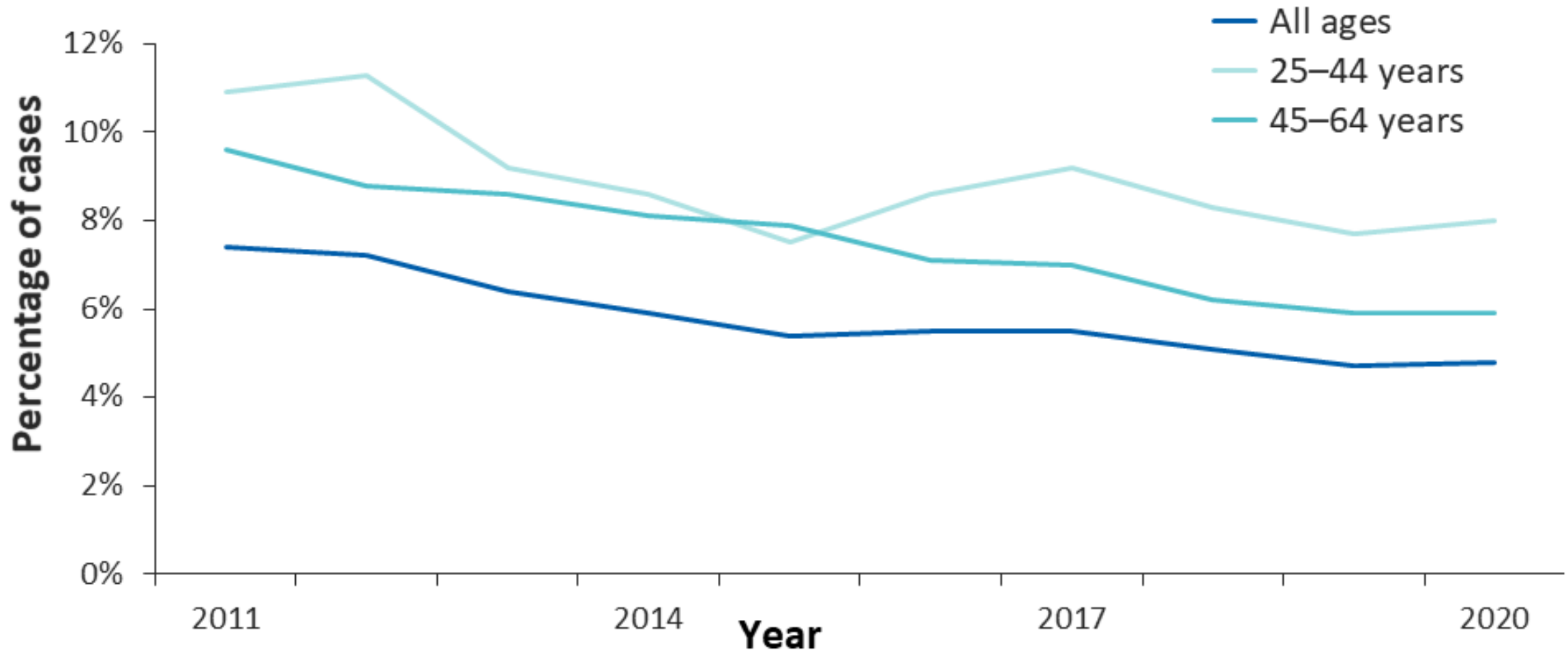




# Progress Towards TB Elimination, United States, 1982–2020



# Percentage of HIV Coinfection by Age among Persons with TB, United States, 2011–2020

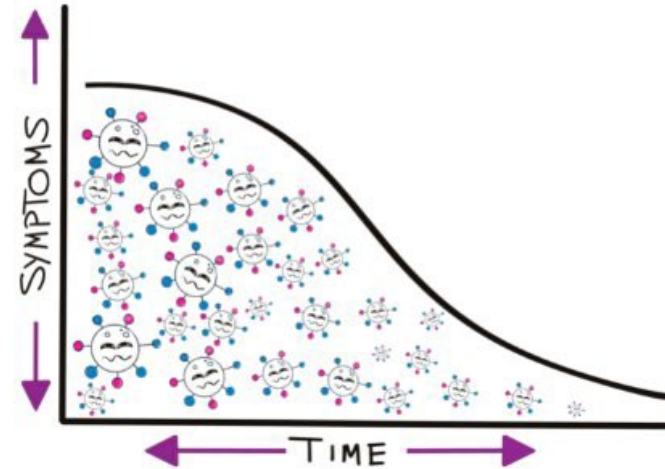
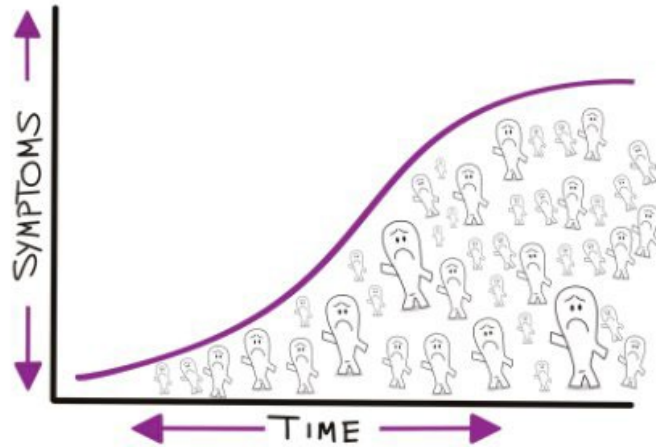


# TB in the US: 2021

- 7860 reported TB cases (rate 2.4/100,000)
- Up to 13 million people in the US are living with LTBI
- During 2021 TB incidence increased among both US-born and non-US-born persons

# Think TB: Not every cough is COVID

COVID-19 symptoms last between  
1-2 weeks for most people  
- getting better over time



TB symptoms begin slowly -  
getting worse over time



Manchester Health & Care  
Commissioning  
A partnership between  
Manchester City Council  
and NHS Manchester CCG

**BHA** for equality  
in health  
and social care



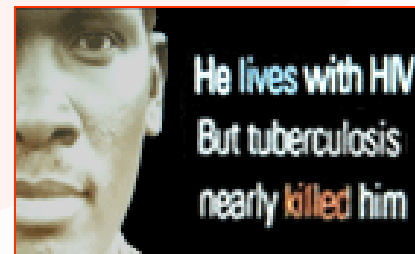
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**TB ANYWHERE IS  
EVERYWHERE**

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# HIV and Tuberculosis

- HIV increases the risk of TB reactivation enormously  
TST+, HIV-  $\Rightarrow$  lifetime risk  $\sim$ 10%
- TST+, HIV+  $\Rightarrow$  YEARLY risk  $\sim$ 10%
- A deadly duo



# Effect of HIV on TB

- Risk of TB increases after HIV seroconversion due to depletion of TB-specific T-helper cells
- Risk of TB progressively increases with declining immunity
- HIV is a risk factor for accelerated progression following TB exposure



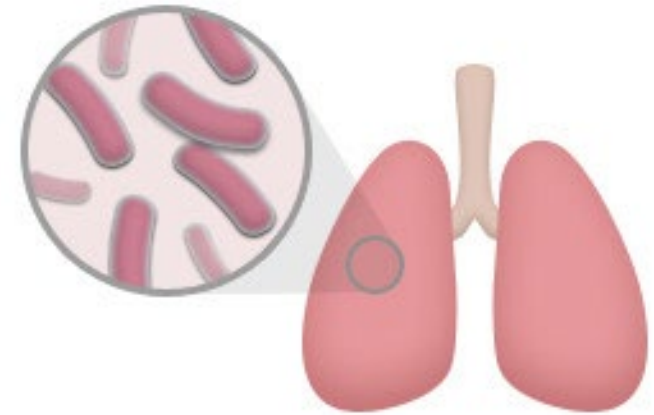
## **The Connection between TB and HIV (the AIDS virus)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Centers for Disease Control  
and Prevention



# Effect of TB on HIV

- TB increases the risk of progression to AIDS or death
- Multiple theories as to why this may happen: increased HIV viremia in those with TB disease, increased CD4 activation



**TUBERCULOSIS REMAINS A SERIOUS THREAT FOR PEOPLE LIVING WITH HIV/AIDS BECAUSE TB AND HIV INFECTION CAN WORK TOGETHER TO MAKE YOU VERY SICK.**



# TB Prevention in HIV

- Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease
- HIV-related TB incidence has declined more rapidly than the rate of active TB in the general population, in part due to the widespread use of ART
- Even with the beneficial effects of ART, the risk of TB disease among persons with HIV infection remains greater than that of the general population

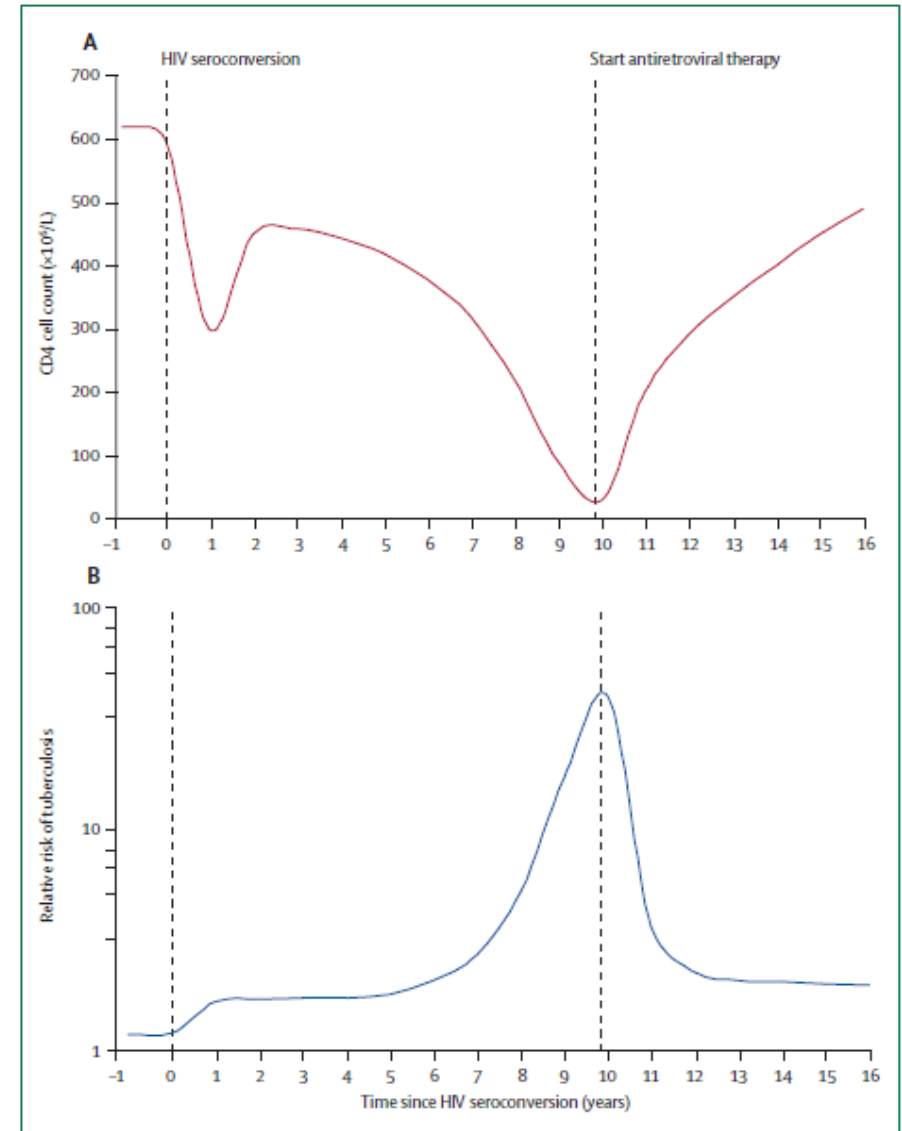


Figure 1: Change in CD4-cell counts (A) and associated risk of tuberculosis in an individual from the time of HIV seroconversion (B), during HIV progression, and after initiation of antiretroviral therapy

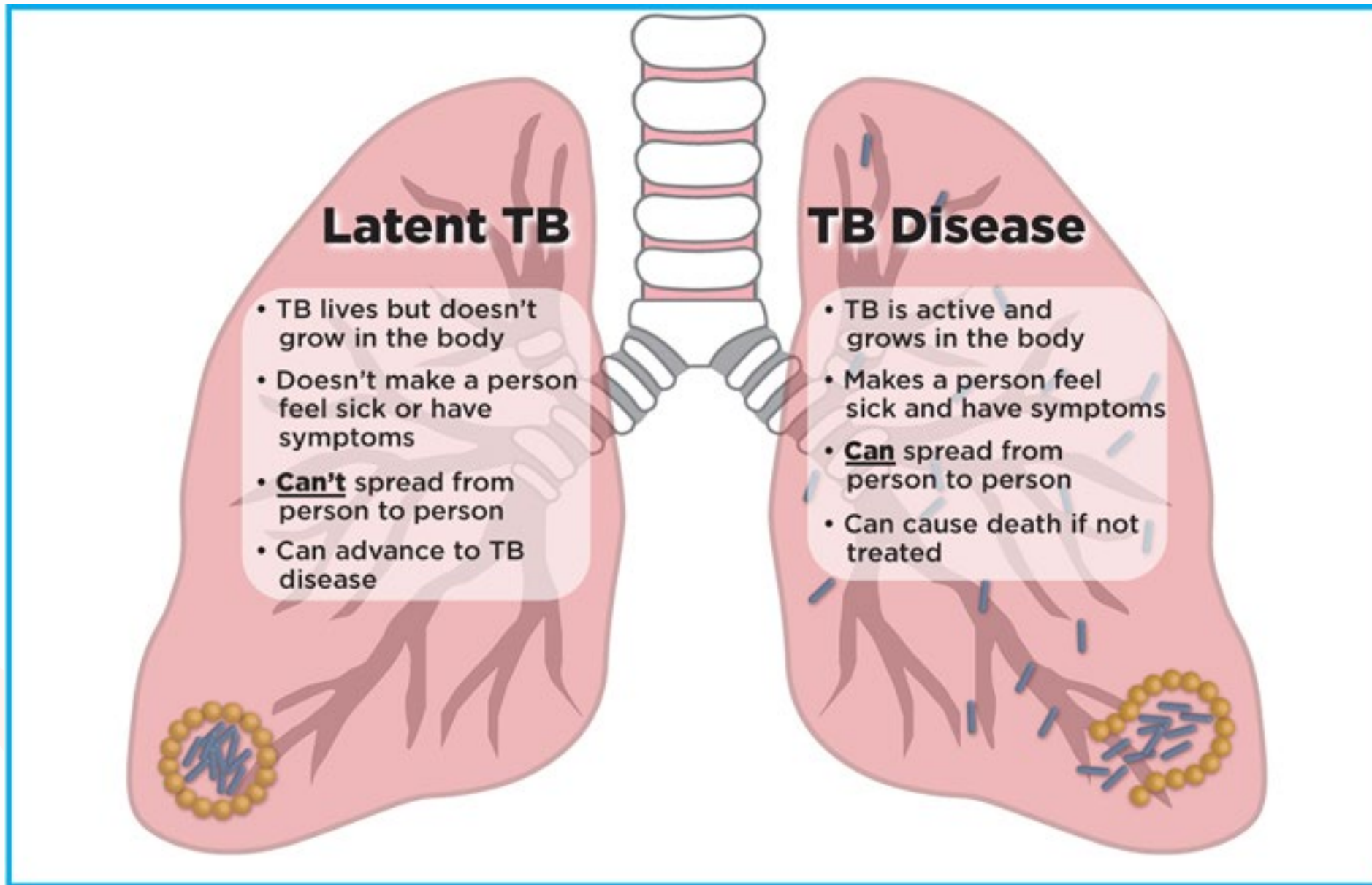
# TB Risk Factors in HIV

## Sociodemographic:

- Black, Asian or Hispanic ethnicity
- Birth or long-term residence in a country with high TB incidence
- HIV acquisition through IDU/ active IDU use
- Homelessness
- Proximity to active TB case

## Clinical:

- Low CD4 count
- High viral load
- Failure of (or late) initiation of ART



# Terminology: TB Infection vs. TB Disease

- Tuberculosis infection (TBI)
- Latent tuberculosis infection (LTBI)
- Inactive tuberculosis
- Tuberculosis disease (newer term)
- Active tuberculosis (older term)
- Active tuberculosis disease (older term)

# Ms. T

- 42 yo presenting to clinic to re-establish HIV care
- She has been out of care for about two years due to COVID-19, during which time she lost her job and was staying intermittently at a shelter, moving around, trying to find work
- She moved to your area about 6 months ago to stay with family, has since found a job at a truck stop and is ready to restart her HIV medications
- She reports being diagnosed in 2014 and has always been on “one pill, once a day”

# How frequently should PWH be evaluated for TB infection?

- A. Annually--regardless of TB exposure risk
- B. At the time of HIV diagnosis and repeat when CD4 is > 200 (if CD4 <200 at time of HIV diagnosis)
- C. Annually –if high risk of repeated or ongoing exposure to TB disease
- D. Answers B and C

# Risk of TB Exposure

- Incarceration
- Housing instability
- Substance use
- Living in a congregate setting
- Travel to TB-endemic areas
- Known or suspected exposures to people with pulmonary TB

# What is your preferred test for TB infection in HIV?

- A. Tuberculin Skin Test (TST)
- B. Interferon gamma release assay (IGRA)
- C. Any test that is available

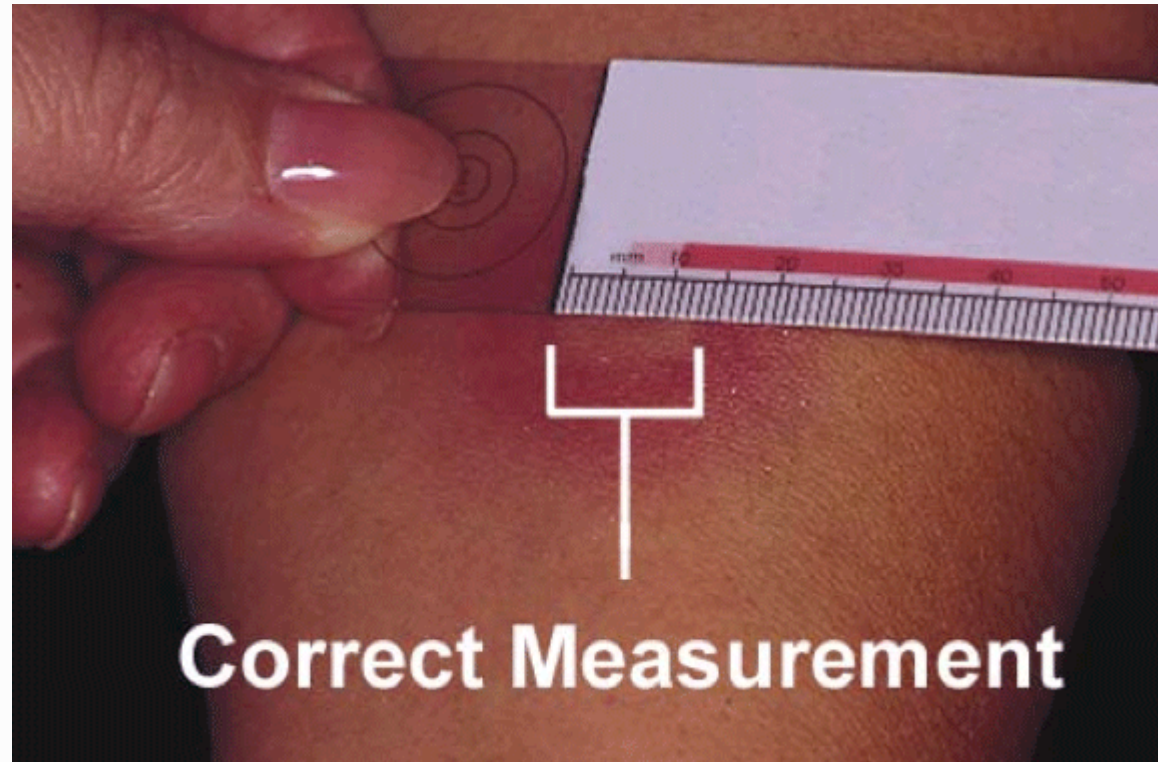


# Tuberculin Skin Testing (TST)

- Inject 0.1 ml of standardized mix of TB proteins (purified protein derivative)
- Given intradermally on volar forearm
- Measure **induration** 48-72 hrs after placement
- Measure in millimeters, not “positive” or “negative”
- Should be interpreted by well-trained health care professional



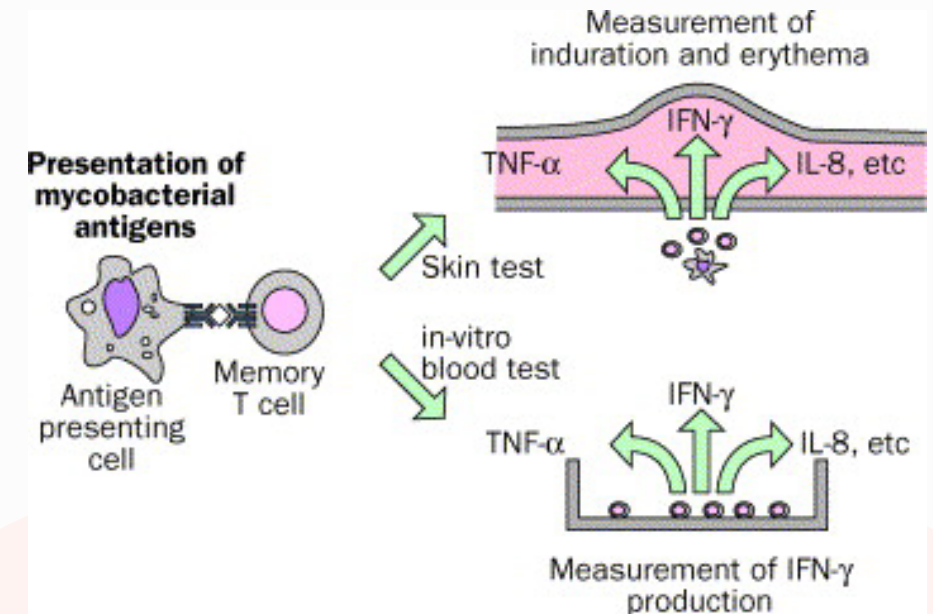
Picture from: [www.info.gov.hk/dh/diseases/CD/TB.htm](http://www.info.gov.hk/dh/diseases/CD/TB.htm)



[http://depts.washington.edu/hivaids/images/oip/oip\\_c4\\_d03.png](http://depts.washington.edu/hivaids/images/oip/oip_c4_d03.png)

# Blood Tests for TB Infection

- Interferon Gamma Release Assays (IGRA)
- Developed in 2001
- Measures the interferon gamma (IFN- $\gamma$ ) released in response to *M.tuberculosis* antigens



## Interferon-Gamma Release Assays (IGRAs)

Feature	Quantiferon-TB Gold Plus	T-SPOT.TB
Format	Process whole blood within 16 hours	Process peripheral blood mononuclear cells (PBMCs) within 8 hours
<i>M. tuberculosis</i> Antigen	Single mixture of synthetic peptides representing ESAT-6 and CFP-10	Separate mixtures of synthetic peptides representing ESAT-6 and CFP-10
Measurement	IFN-gamma concentration	Number of IFN-gamma producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, indeterminate, borderline

Abbreviations: CFP-10 = culture filtrate protein 10; ESAT-6 = early secretory antigenic target-6

# TST vs. IGRA

TST	IGRA
Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person has been infected with <i>M. tuberculosis</i>	Blood is drawn for testing; test measures the immune response to the TB bacteria in whole blood
Requires two or more patient visits to conduct the test	Requires one patient visit to conduct the test
Results are available 48 to 72 hours later	Results can be available in 24 hours (depending on the batching of specimens by the laboratory and transport)
Can cause boosted reaction	Does <b>not</b> cause boosted reaction
Reading by HCW may be subjective	Laboratory test not affected by HCW perception or bias
BCG vaccination can cause false-positive result	BCG vaccination does <b>not</b> cause false-positive result and infection with most nontuberculous mycobacteria does <b>not</b> cause false-positive result
A negative reaction to the test does <b>not</b> exclude the diagnosis of LTBI or TB disease	A negative reaction to the test does <b>not</b> exclude the diagnosis of LTBI or TB disease

# Is there a best test for LTBI in PWH?

- 1510 US-born PWH evaluated for LTBI with TST, T-SPOT, QFT
- Median self-reported CD4 count: 532 cells/mm<sup>3</sup>
- Overall estimated LTBI prevalence: 4.7%
- IGRA more sensitive than TST

**Table 3. Diagnostic Test Characteristics for US-Born PLWH Estimated Directly From Latent Class Analysis Using Standard US Cutoffs at 4.7% Estimated LTBI Prevalence**

	Sensitivity (95% CrI)	Specificity (95% CrI)	PPV (95% CrI)	NPV (95% CrI)
TST (≥5 mm)	54.2% (45.2–64.3)	96.8% (95.7–97.7)	45.4% (33.3–58.4)	97.7% (96.4–98.7)
QFT (≥0.35 IU/mL)	72.2% (58.7–85.4)	96.5% (95.3–97.6)	50.7% (37.1–65.6)	98.6% (97.4–99.4)
TSPOT (≥8 spots)	51.9% (39.3–66.7)	99.7% (99.3–99.9)	90.0% (77.1–98.1)	97.6% (96.1–98.8)

Abbreviations: CrI, credible interval; LTBI, latent tuberculosis infection; NPV, negative predictive value; PLWH, people living with human immunodeficiency virus; PPV, positive predictive value; QFT, QuantiFERON Gold In-Tube; TSPOT, T-SPOT.TB; TST, tuberculin skin test.

# JYNNEOS Vaccine and TST/IGRA Testing

- TB testing with TST or IGRA can be done at the same time as JYNNEOS vaccination and any sequence of vaccination and TB testing may be used
- Since JYNNEOS is a live (non-replicating) virus, If delays in TB testing will not cause substantial burden, a delay of at least 4 weeks after JYNNEOS vaccination is preferred
- if a delay in TB testing with TST or IGRA for 4 weeks would cause substantial burden (for example, preventing a person from working because of pre-employment screening policies), then TST and IGRA testing should not be delayed

**MONKEYPOX**

## How to administer a JYNNEOS vaccine intradermally



**STEP 3**

Slowly inject 0.1mL intradermally. This should produce a noticeable pale elevation of the skin (wheal).

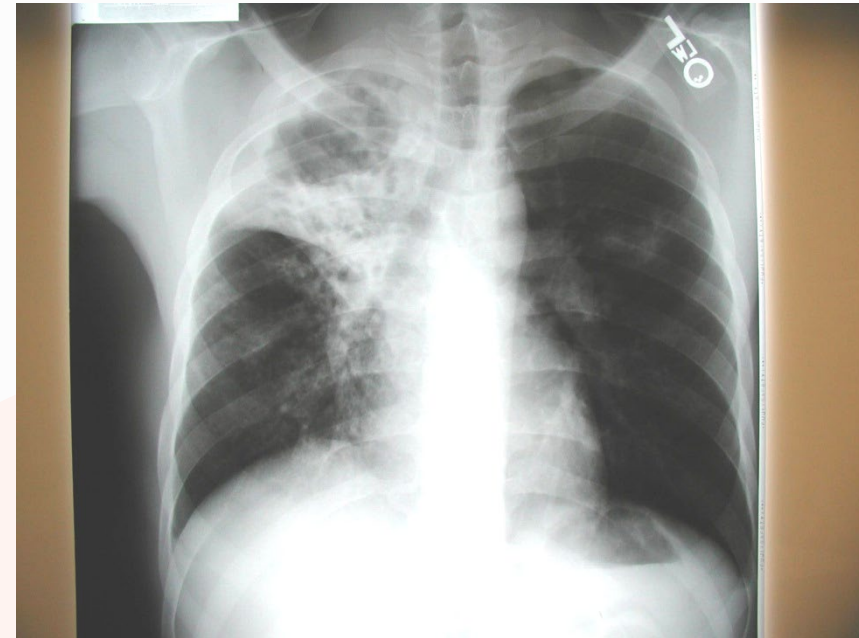
[www.cdc.gov/monkeypox](http://www.cdc.gov/monkeypox)



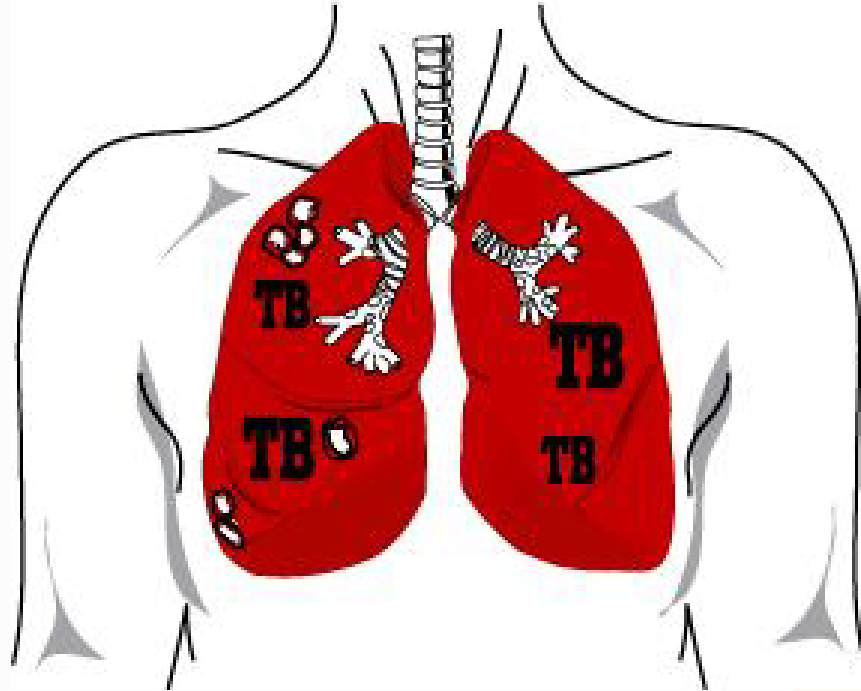
CS 333451 08/09/2022

# Evaluation of LTBI in HIV

- Assess for symptoms: fever, night sweats, weight loss, cough, lymphadenopathy
- CXR
- Assess for extrapulmonary TB:
  - more common in HIV
  - more common when  $CD4 < 200$







**NIP  
TB  
IN  
THE  
BUD!**

**Neither an IGRAs nor TST can  
distinguish LTBI from active  
tuberculosis!**

# Ms. T

- Labs return to show: CD4 320 (20%), VL 25,000
- QFT positive
- Prior records show negative TST/IGRA
- Symptom screen performed: No cough, night sweats, weight loss
- CXR without any findings suspicious for TB disease

# Who to treat for TB infection?

- A. A positive diagnostic test for LTBI and no prior history of treatment for active or latent TB
- B. A negative diagnostic test for LTBI but close contacts of persons with infectious pulmonary TB
- C. All PWH presenting for care, regardless of test result for LTBI
- D. A and B

When choosing a TB preventive treatment (TPT) regimen, what is your major consideration?

- A. Duration of therapy—shorter is better
- B. Potential side effects
- C. Drug interactions with HIV medications



# Preferred Drugs for TB Preventive Therapy in HIV

- **3HP:** Rifapentine (P) orally once weekly plus isoniazid (H) orally plus pyridoxine 50 mg once weekly for 12 weeks
- Shorter treatment course associated with higher completion rates
- Better tolerated than isoniazid monotherapy

## 12-DOSE REGIMEN (3HP) for Latent Tuberculosis Infection Treatment

CDC continues to recommend the use of the short-course combination regimen of once-weekly isoniazid-rifapentine for 12 weeks (3HP) for treatment of latent tuberculosis infection (LTBI) in adults.

CDC now also recommends use of 3HP:

- by directly observed therapy (DOT) **or self-administered therapy (SAT)\***
- in persons aged **2–11 years**
- in persons with LTBI who are **living with HIV infection** including AIDS and taking antiretroviral medications with acceptable drug-drug interactions with rifapentine

Shorter treatment regimens, like 3HP, **have higher treatment completion rates** and **lower costs**.

\* Healthcare providers should choose the mode of administration (DOT vs. SAT) based on local practice, individual patient attributes and preferences, and other considerations, including risk of progression to severe forms of tuberculosis disease.





U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

# 3HP: TB Preventive Therapy in HIV

Recommended only for *virally-suppressed patients* receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based antiretroviral (ARV) regimen

DOLPHIN study: rifapentine decreased dolutegravir exposure by 26% but trough concentrations remained above 90% MIC in all but one participant and all maintained an undetectable viral load

# 3HP: TB Preventive Therapy in HIV

Drug*	Weekly Dosage	Maximum dose
<b>Isoniazid</b> 	15 mg/kg rounded to nearest 50/100mg in patients ≥ 12 years	<b>900 mg</b>
	25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years	
<b>Rifapentine (Priftin®)</b> 	10.0 - 14.0 kg = 300 mg	<b>900 mg</b>
	14.1 - 25.0 kg = 450 mg	
	25.1 - 32.0 kg = 600 mg	
	32.1 - 49.9 kg = 750 mg	

- Use of tenofovir alafenamide currently not recommended with rifapentine
- Preferred ARV backbone: TDF/FTC, ABC/3TC

# Bictegravir (BIC) and Rifapentine (RPT)

- A study evaluating once-weekly RPT with BIC/TAF/FTC showed BIC concentrations reduced an average of 40%-57%
- A study evaluating BIC/TAF/FTC in combination with daily RPT also showed significant reductions in BIC concentrations, resulting in low-level viremia during LTBI therapy



## *Preferred Drugs: TB Preventive Therapy in HIV*

- **3HR:** Isoniazid 300 mg PO daily plus rifampin (R) 600 mg PO daily plus pyridoxine 25-50 mg daily for 3 months
- In RCT of 3HR vs 6 months isoniazid in 2736 PWH not on ART showed comparable incidence of TB after 15 months follow-up
- Shorter course therapy

# 3HR: TB Preventive Therapy in HIV

- Rifampin is not recommended for use with doravirine, etravirine, rilpivirine, bictegravir, cabotegravir, elvitegravir-cobicistat, or any HIV protease inhibitor
- With rifampin:
  - increase dolutegravir to 50 mg PO BID
  - increase raltegravir to 800 mg PO BID
- Preferred backbone: TDF/FTC, ABC/3TC
- Rifampin and TAF: “**Do not coadminister unless benefits outweigh risks.**”

# Alternative Drugs: TB Preventive Therapy in HIV

- **Isoniazid (H):** 300 mg PO daily plus pyridoxine 25-50 mg PO daily for 6-9 months
- Systemic review comparing INH to placebo among PWH showed 35% risk reduction of active TB, with pooled relative risk reduction of 52% among those TST+
- Suboptimal completion rates ( 47-53% for 9 months, 45-63% for 6 months)

# Alternative Drugs: TB Preventive Therapy in HIV

- **4R:** Rifampin 600 mg PO daily for 4 months
  - Lack of trial data in PWH
- **1HP:** Isoniazid 300 mg PO daily plus rifapentine PO daily plus pyridoxine 25-50 mg PO daily for 4 weeks
  - BRIEF-TB study evaluated PWH in mostly high TB burden settings, on efavirez- or nevirapine-based regimens
  - High completion rates (97%) and 21% were TST positive

# Ms. T

- TB preventive treatment options were reviewed
- She preferred to take one pill a day for 6-9 months along with her HIV medications
- She felt that she could take both medications daily without any issues
- She was started on BIC/TAF/FTC one pill daily along with isoniazid 300 mg by mouth daily and pyridoxine 25 mg by mouth daily

# Monitoring During TB Preventive Therapy

- Evaluate monthly to assess adherence with medications, possible drug toxicity
- Hepatotoxicity more common with isoniazid → check LFTS prior to initiation and repeat if abnormal
- Assess for new medications, alcohol consumption
- If serum AST/ALT >5 X ULN without symptoms or 3X ULN with symptoms stop medications
- Effects of LTBI therapy can include: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesia of hands/feet, persistent fatigue, weakness, fever lasting 3 or more days, abdominal tenderness, easy bruising or bleeding, arthralgias

# Resources

- National HIV Curriculum: Co-Occurring Conditions, Latent Tuberculosis Infection  
<https://www.hiv.uw.edu/go/co-occurring-conditions/latent-tuberculosis/core-concept/all>
- CDC Latent TB Infection Resources  
<https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm>
- Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV  
<https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections>

# Quantiferon Gold In-Tube Plus

## Mitogen – Positive Control

Low response may indicate inability to generate IFN- $\gamma$

## Nil – Negative Control

Adjusts for background IFN- $\gamma$

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses





# Causes of Indeterminate Results

- Low mitogen:
  - Low T-lymphocyte count
  - Reduced T-lymphocyte activity
  - Inability of T-lymphocytes to produce IFN- $\gamma$
- High nil (control) values:
  - Presence of heterophile antibodies
  - Intrinsic IFN- $\gamma$  production
- Improper specimen transport/handling or technical factors:
  - Delayed transport can affect lymphocyte variability
  - Incomplete washing of an enzyme-linked immunosorbent assay plate

- . However, it is important to note that RBT-containing treatment regimens have not been studied (in clinical trials or otherwise) and their efficacy for the treatment of LTBI is speculative. In addition, all PIs markedly increase serum concentrations of RBT, requiring special attention to RBT dosing in these settings to avoid dose-related toxicities, such as hepatitis, uveitis, and neutropenia [50]. Nonetheless, one could consider using RBT in place of RIF as preferable to no LTBI treatment in cases where LTBI treatment is urgent and there are no alternative LTBI treatment options owing to drug interactions with companion drugs or other barriers