HIV and Latent Tuberculosis Infection (LTBI)

L. Beth Gadkowski MD MPH MS
University of Florida

1

Continuing Education Disclosure

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

2

Objectives:

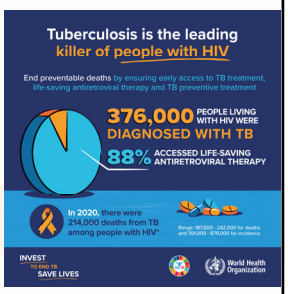
At the end of this presentation, participants will be able to:

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

3

Tuberculosis (TB)

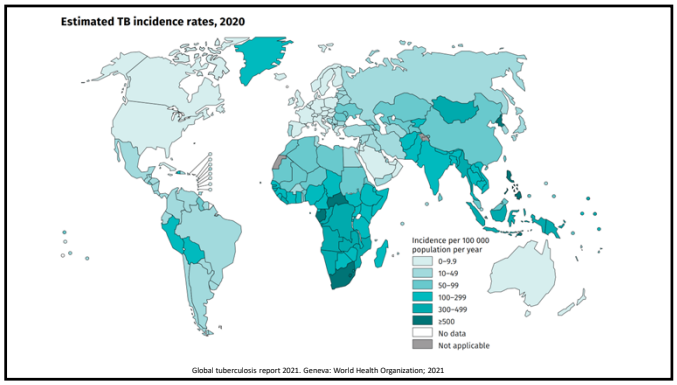
- In 2020, an estimated 10 million people fell ill with TB worldwide
- 1.5 million people died from TB in 2020, including 214 000 people with HIV
- Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19
- Nearly 2 billion people are infected with TB
-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



AETC Southeast

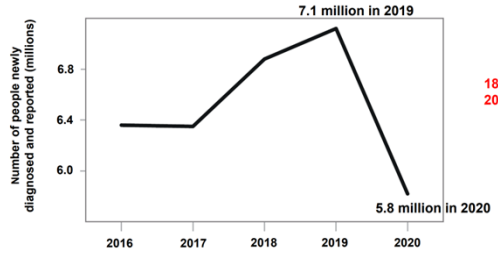
https://www.cdc.gov/globalhivtb/index.html

4



5

Reported Global TB Incidence, 2020

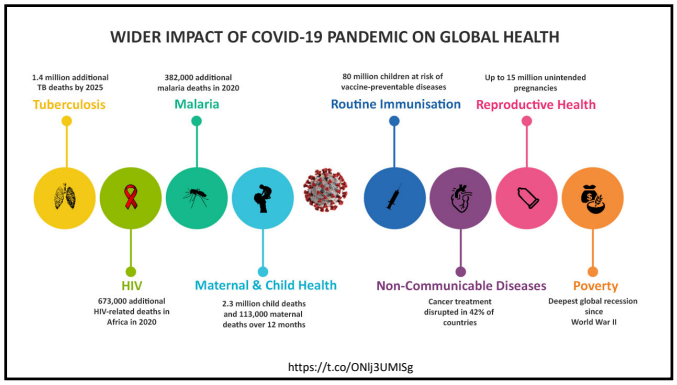


18% drop, 2019-2020

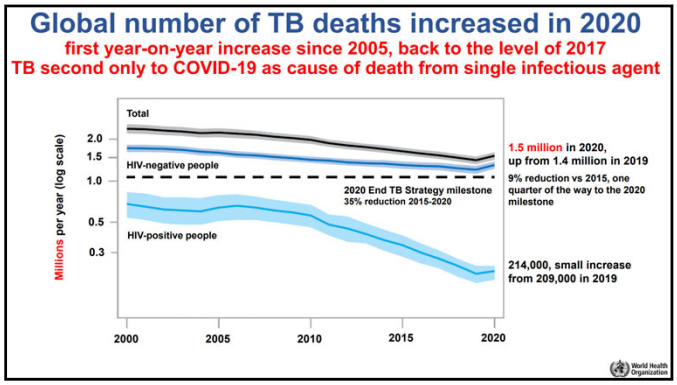
World Health Organization

AETC Southeast

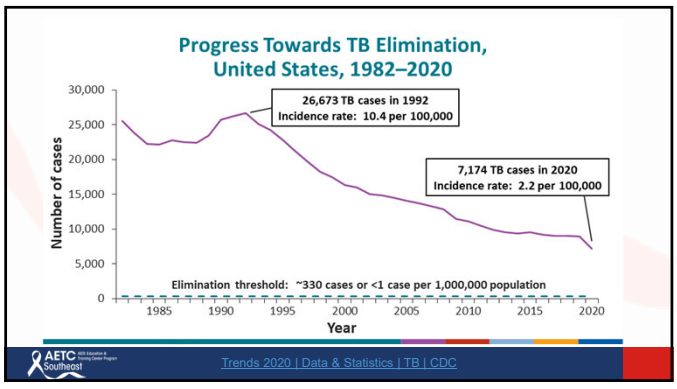
6


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
80 million children at risk of vaccine-preventable diseases
Routine Immunisation
Up to 15 million unintended pregnancies
Reproductive Health
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
Non-Communicable Diseases
Cancer treatment disrupted in 42% of countries
Poverty
Deepest global recession since World War II
https://t.co/ONlj3UMISg

7

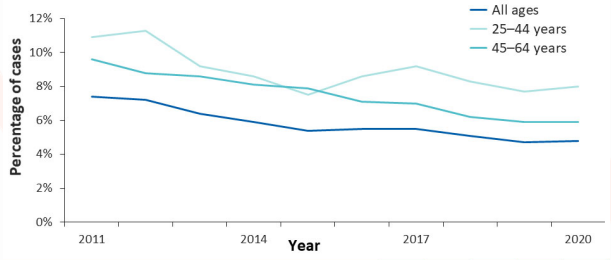

Global number of TB deaths increased in 2020
first year-on-year increase since 2005, back to the level of 2017
TB second only to COVID-19 as cause of death from single infectious agent
Millions per year (log scale)
2.0
1.5
1.0
0.5
0.3
Total
HIV-negative people
2020 End TB Strategy milestone
35% reduction 2015-2020
HIV-positive people
2000
2005
2010
2015
2020
1.5 million in 2020, up from 1.4 million in 2019
9% reduction vs 2015, one quarter of the way to the 2020 milestone
214,000, small increase from 209,000 in 2019
World Health Organization

8


Progress Towards TB Elimination, United States, 1982–2020
Number of cases
30,000
25,000
20,000
15,000
10,000
5,000
0
26,673 TB cases in 1992
Incidence rate: 10.4 per 100,000
7,174 TB cases in 2020
Incidence rate: 2.2 per 100,000
Elimination threshold: ~330 cases or <1 case per 1,000,000 population
1985
1990
1995
2000
2005
2010
2015
2020
Year
AETC Southeast
Trends 2020 | Data & Statistics | TB | CDC

9

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



Trends 2020 | Data & Statistics | TB | CDC

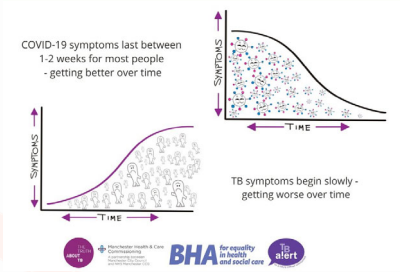
10

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

11

Think TB: Not every cough is COVID



https://www.tbalert.org/about-tb/global-tb-challenges/tb-hiv/

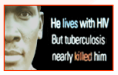
12

TB ANYWHERE IS EVERYWHERE

13

HIV and Tuberculosis

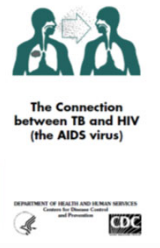
- HIV increases the risk of TB reactivation enormously
  TST+, HIV- ⇒lifetime risk ~10%
- TST+, HIV+⇒YEARLY risk ~10%
- A deadly duo



14

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



15

Effect of TB on HIV

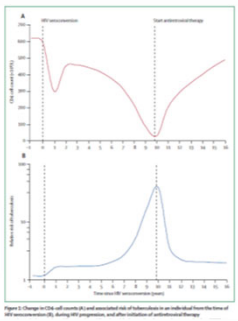
- TB increases the risk of progression to AIDS or death
- Multiple theories as to why this may happen: increased HIV viremia in those with TB disease, increased CD4 activation

AETC Southeast

16

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



AETC Southeast

17

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

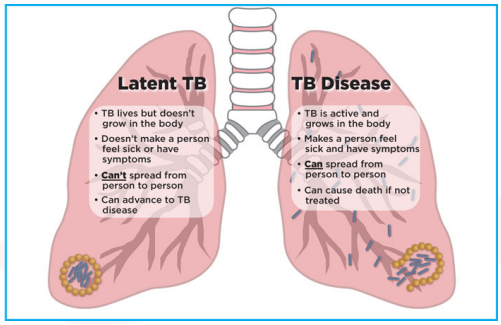
Clinical:

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

AETC Southeast

Winter et al. UTLD (7):713-722 · July 2018

18



19

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)

20

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"

21

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

22

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

23

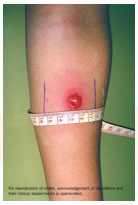
What is your preferred test for TB infection in HIV?

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

24

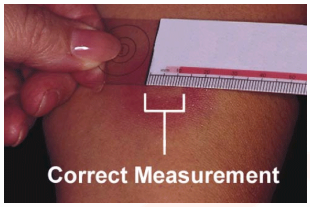
Tuberculin Skin Testing (TST)

- 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

25

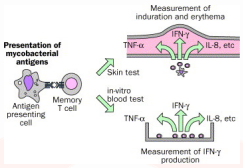


http://depts.washington.edu/hivaids/images/oip/oip_c4_d03.png

26

Blood Tests for TB Infection

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



Lancet 356: 1099 2000

27

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
M. tuberculosis 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

AETC Southeast

https://www.hiv.uw.edu/go/co-occurring-conditions/latent-tuberculosis/core-concept/all#figures

28

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 *M. tuberculosis*	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 **not** 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 **not** cause false-positive result and infection with most nontuberculous mycobacteria does **not** cause false-positive result
A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease	A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease

AETC Southeast

https://www.cdc.gov

29

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/mm3
- Overall estimated LTBI prevalence: 4.7%
- IGRA more sensitive that 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 ETKON Gold In-Tube; TSPOT, T-SPOT.TB; TST, tuberculin skin test.

AETC Southeast

Petit et al. CID 2021;73 (1 October)

30

JYNNEOS Vaccine and TST/IGRA Testing

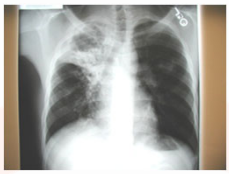
- TB testing with TST or IGRA can be done at the same time as JYNNEOS vaccination and any sequence of vaccination and TB testing may be used
- Since JYNNEOS is a live (non-replicating) virus, If delays in TB testing will not cause substantial burden, a delay of at least 4 weeks after JYNNEOS vaccination 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

9/23/22 CDC Dear Colleague Letter

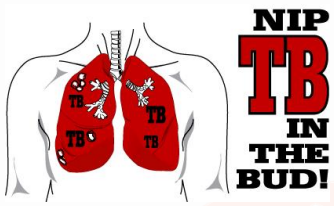
31

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



32



Neither an IGRA nor TST can distinguish LTBI from active tuberculosis!

33

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

34

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

35

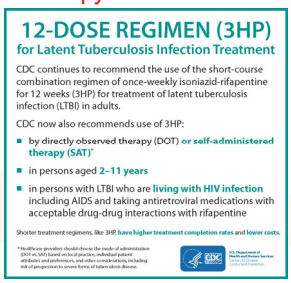
When choosing a TB preventive treatment (TPT) regimen, what is your major consideration?

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

36

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



37

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

Dooley et al. Lancet HIV 2020 Jun;7(6):e401-e409

38

3HP: TB Preventive Therapy in HIV

Drug*	Weekly Dosage	Maximum dose
Isoniazid	15 mg/kg rounded to nearest 50/100mg in patients ≥ 12 years	900 mg
	25 mg/kg rounded to the nearest 50/100 mg in patients 2–11 years	
Rifapentine (Priftin®)	10.0 – 14.0 kg = 300 mg	900 mg
	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

39

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

Dooley KE, Savic R, Gupta A, et al.. Lancet HIV 2020;7:e401–9
Sun HY, Cheng CN, Lin YT, et al.. CROI. Virtual, March 6–10, 2021

40

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

41

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."**

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions

42

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)

Ayle HT et al. PLoS One 2015; 10:e0142290

43

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

44

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

45

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

AETC Southeast

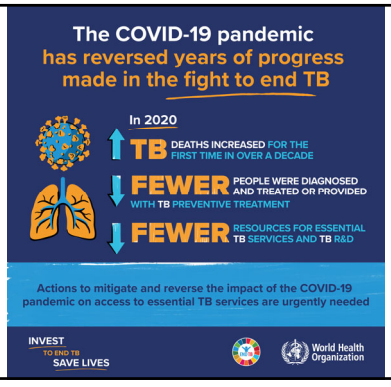
46

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

AETC Southeast

47



48

TB hides in plain sight. Millions of Americans are living with inactive TB.

Inactive TB in the United States

It is estimated that up to 13 million people in the United States live with inactive TB.

Risks of Untreated Inactive TB

Without treatment, 1 in 10 people with inactive TB will get sick with active TB disease, which can spread to others and be deadly.

Prevent TB

If you are diagnosed with inactive TB, there are several short and convenient treatment options available that can help protect you from getting sick with active TB disease.

https://www.cdc.gov/thinktesttreattb/

49

Quantiferon Gold In-Tube Plus

- Mitogen – Positive Control
  Low response may indicate inability to generate IFN-γ
- Nil – Negative Control
  Adjusts for background IFN-γ
- TB1 – Primarily detects CD4 T cell response
- TB2 – Optimized for detection of CD4 and CD8 T cell responses

AETC Southeast

50

Causes of Indeterminate Results

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

AETC Southeast

51

- . 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

52