Module 2.2.1
Management of the HIV-positive person with respiratory symptoms: TB- diagnostics

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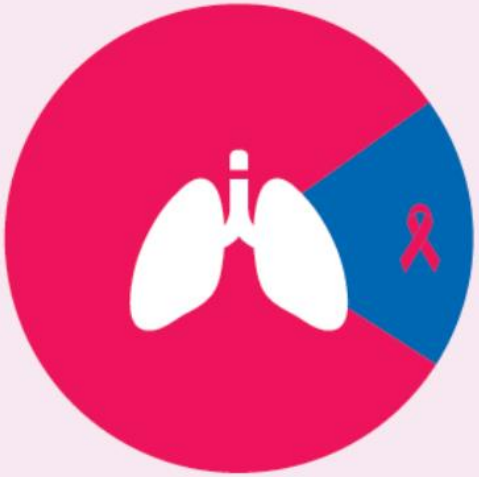
Learning Outcomes

- **Upon completion of this module, clinicians will be able to:**
  - Understand the risk of active TB in PLHIV
  - Understand the changes to TB screening/ testing for PLHIV
  - Describe the TB-NAAT algorithms
  - Describe the uLAM algorithm for patients with AHD

Outline

- Background

TUBERCULOSIS IS THE TOP INFECTIOUS KILLER IN THE WORLD



IN 2018

1.5 MILLION* PEOPLE DIED FROM TB

INCLUDING
251 000 PEOPLE
WITH HIV

TB is the leading killer of people with HIV and
a major cause of deaths related to antimicrobial resistance

*The 95% uncertainty intervals are 1.4-1.6 million for TB deaths and 223 000 - 281 000 for TB/HIV deaths.

END TB

World Health Organization

TUBERCULOSIS IS THE LEADING KILLER OF PEOPLE WITH HIV

IN 2018, THERE WERE 251 000 DEATHS FROM TB AMONG PEOPLE WITH HIV*

862 000* PEOPLE WITH **HIV** FELL ILL WITH **TB**

ONLY **56%** OF THEM WERE DIAGNOSED WITH BOTH HIV AND TB

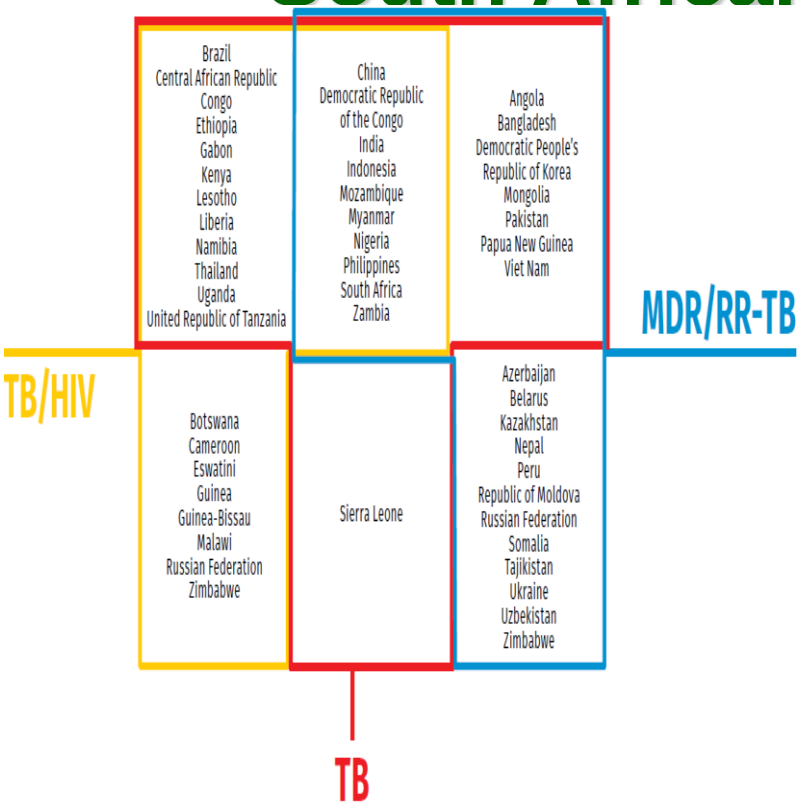
End preventable deaths by ensuring early access to TB treatment, life-saving antiretroviral therapy and TB preventive treatment

*The 95% uncertainty intervals are 223 000 – 281 000 for deaths and 776 000 – 952 000 for incidence.

END TB

World Health Organization

South African epidemiology



Estimates of TB burden*, 2021

	Number	(Rate per 100 000 population)
Total TB incidence	304 000 (207 000-421 000)	513 (348-709)
HIV-positive TB incidence	163 000 (111 000-225 000)	274 (186-379)
MDR/RR-TB incidence**	21 000 (13 000-29 000)	35 (21-49)
HIV-negative TB mortality	23 000 (22 000-24 000)	38 (36-40)
HIV-positive TB mortality	33 000 (11 000-65 000)	55 (19-109)

Estimated proportion of TB cases with MDR/RR-TB*, 2021

New cases	4.1% (3.9-4.2)
Previously treated cases	28% (27-29)

Poll 1

1. The risk of developing active TB among PLHIV who have CD4+ counts >350 and are virally suppressed is _____when compared to the risk among similar HIV negative individuals?
   a. Equivalent
   b. Higher
   c. Lower

TB in PLHIV

- An estimated 50-60% of HIV positive people infected with TB will go on to develop active disease
- TB can occur at any point in the course of progression of HIV infection
- The risk of TB is increased even in the first year of HIV infection (with CD4+ counts >350)
- **ART reduces risk of developing TB, but does NOT totally eliminate it: Risk of TB >4x in those with CD4+>700 vs general population**

Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. **Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community**. *PLoS One*. 2012;**7**(3):e34156.

- ***TPT crucial in reducing this risk***

Poll 2

1. TB/HIV coinfected clients have _____mortality risk when compared to HIV negative people with TB (PWTB)?
    a. Equivalent
    b. Higher
    c. Lower
    d. It depends

TB/HIV co-infection outcomes

- **TB/HIV co-infected clients may have increased mortality due to**
  - rapid TB disease progression
  - late diagnosis and treatment
- **For those on TB treatment:** Co-infected higher mortality than HIV neg**- no stratification by ART status**
- Other studies e.g. Schippell et al: Risk ratio of mortality in people with RR-TB**: similar to HIV neg people if on ART & HIV controlled**

- **Suboptimal diagnostics contribute to poor outcomes from HIV-associated tuberculosis**

Poll 3

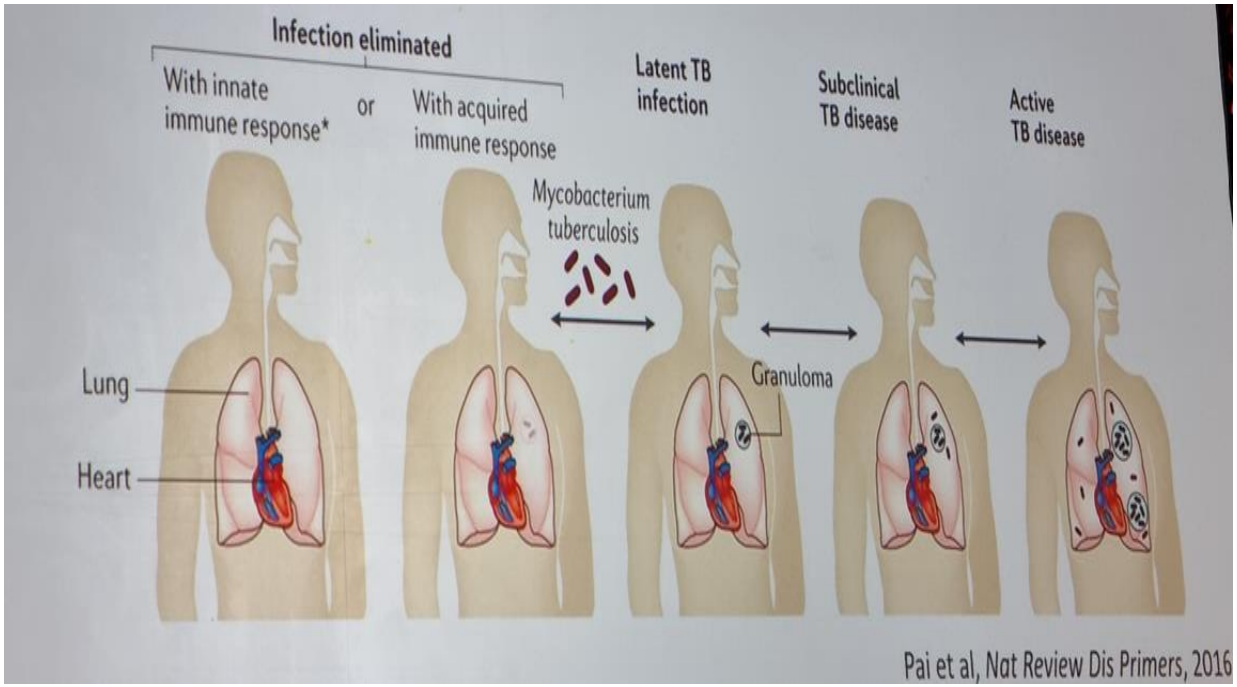
3. There are TWO fairly static states of TB infection, i.e. Latent TB (no symptoms) and Clinical (Active) TB disease

a. True

b. False

c. Not sure

TB infection states



Sub-clinical TB disease

- Disease due to Mtb that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected by CXR or microbiologic assays.

  -Drain et al, Clin Microbiol Reviews, 2018

-Infectious

-Drive transmission

-?Treat for how long

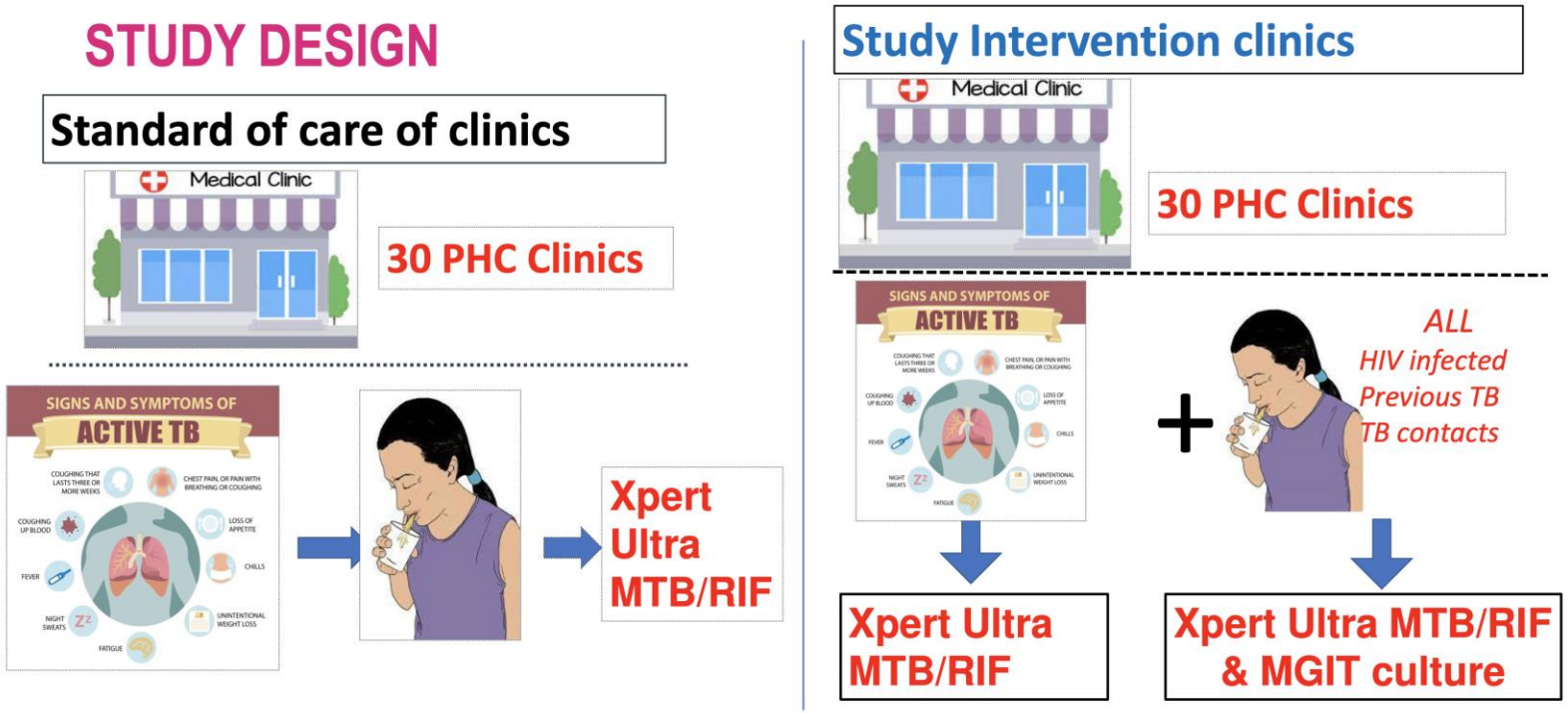
Therefore: Expand TB screening beyond W4SS

- DCXR with CAD
- TUTT

Poll 4

4. Which of the following is TRUE about the TUTT strategy?
    a. TUTT= Targeted Universal TB Treatment
    b. The target groups must only be tested for TB when they have TB symptoms
    c. The target groups must not be screened for TB but must be tested for TB at all their visits.
    d. The target groups include PLHIV, Close contacts of people with TB, and people previously treated for TB in the last 2 years.

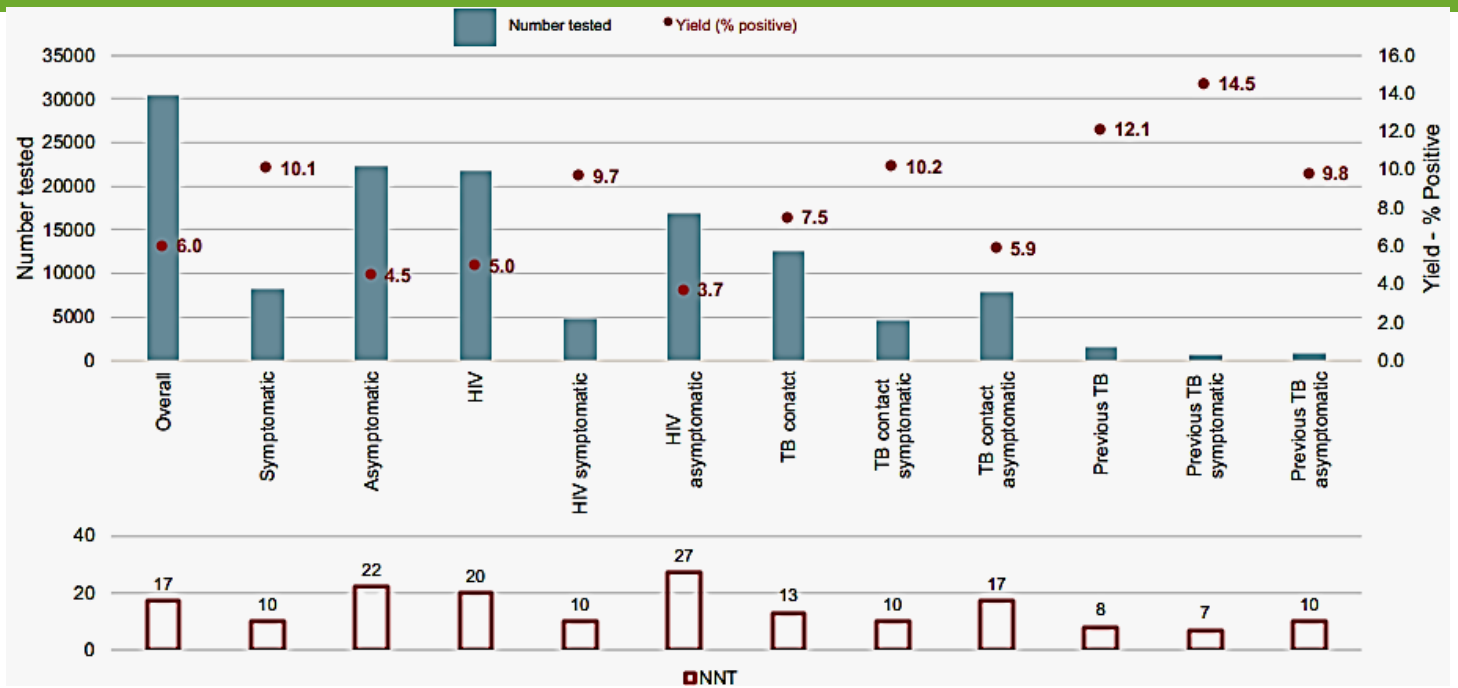
Targeted Universal Testing for TB (TUTT)



Martinson et al. A Cluster Randomized Trial of Systematic Targeted Universal Testing for Tuberculosis in Primary Care Clinics of South Africa (The TUTT Study). Available at SSRN: https://ssrn.com/abstract=4092970

Targeted Universal TB Testing (TUTT) study

RESULTS: YIELD BY RISK FACTOR AND SYMPTOMS



Universal TB testing for patients at high risk for TB using Xpert and culture irrespective of the presence of TB symptoms resulted in a 6% overall yield in laboratory confirmed TB.

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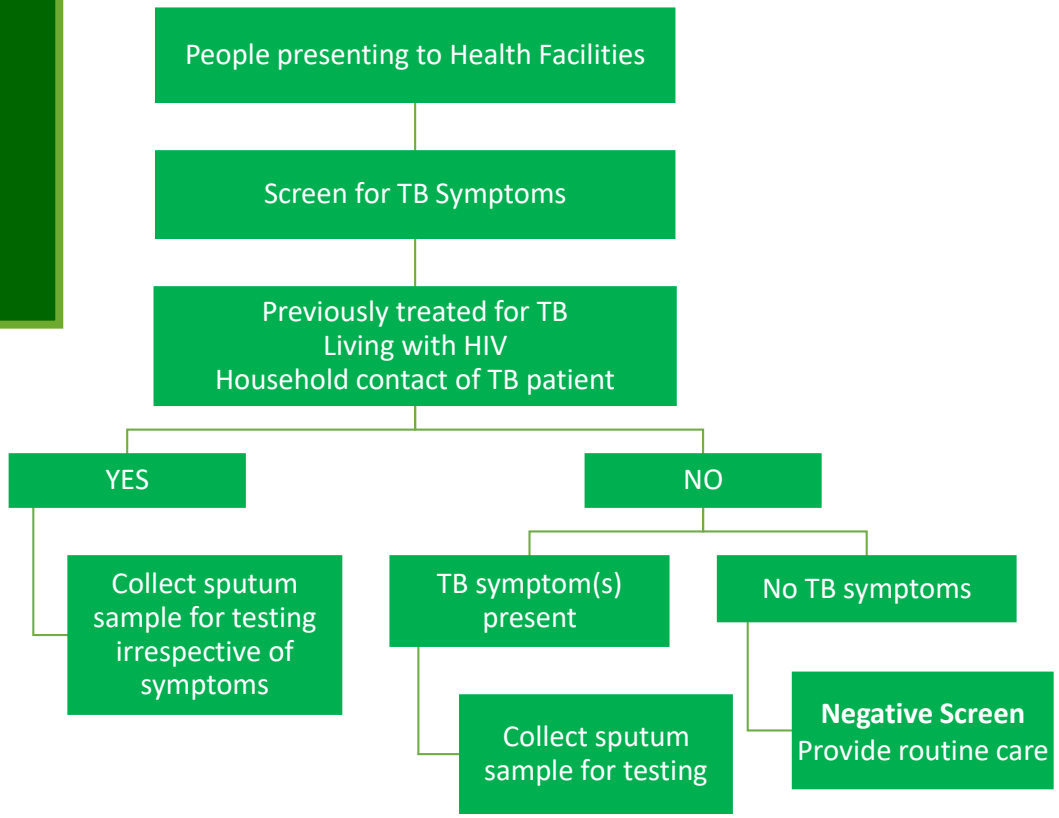
TUTT Study Conclusions

- Systematic screening with Xpert & culture found more PWTB in clinics
  - Overall: 6%
  - PLHIV: 5%
- Clinics are diagnosing 8% fewer patients with TB year on-year under the standard of care
- The TUTT intervention resulted in a 17% net increase in finding PWTB per clinic per month as compared to the standard of care clinics.
- Systematic screening with Xpert is recommended in sub-populations at high risk of TB

Health Facility TB Screening Algorithm



Poll 5

4. Which of these statements about TUTT in PLHIV is FALSE- according to the TB screening and Testing SOP?
    a. All newly diagnosed adults and adolescents should have their sputum sent for TB testing with Xpert Ultra irrespective of TB symptoms
    b. All newly diagnosed PLHIV with a baseline CD4+ count less than 200 should be tested with urine TB LAM irrespective of TB symptoms
    c. All pregnant women (PWLIV) should be tested for TB at Antenatal Care enrolment
    d. TUTT should be conducted annually, linked to viral load monitoring visits.

Frequency of testing

1. General population
    - Only when they present with any TB symptom or chest x-ray changes suggestive of TB
2. People living with HIV
    - At the time of HIV diagnosis
    - On enrolment in Antenatal care for pregnant women
    - Annually for PLHIV on treatment linked to VL monitoring follow up visits
    - At re-engagement to care after >/=90 days of missed appointment (Think Tank)
3. Household contacts of people diagnosed with TB
    - After each exposure to a person with a confirmed TB diagnosis
4. People previously treated for TB
    - Annually for a period of two years

Poll 6

4. Which of the following statements is true about TB diagnostic testing?
    a. Direct LPA testing on pleural fluid is recommended to confirm Pleural TB
    b. Direct LPA testing on sputum is recommended when the Xpert MTB/Rif result is negative
    c. The Xpert Ultra MTB/Rif test can only be performed on sputum
    d. The Xpert Ultra MTB/Rif test can be performed on a variety of samples including, sputum, CSF, pleural fluid, and stool

TB TESTING PLATFORMS

GENEXPERT (CEPHEID)	 
COBAS MTB and COBAS MTB RIF/INH (ROCHE)	   a b
BD MAX MDR-TB (BECTON DICKINSON)	

Available Tests

- **LPAs discontinued (Direct LPAs were only validated for sputum & less sensitive than GXP)**
- No reference to Xpert as first line test but **TB-NAAT**
- Cobas and BD Max conducted on **sputum only**
- Xpert conducted on sputum, gastric washings/aspirates, lymph node biopsies or fine needle aspirates, tissue biopsies, Fluids (joint, pleural, ascitic, peritoneal, pus collection) and cerebro-spinal fluid (CSF) – ? stool, urine
- Results reported as RS, RR, HR, MDR TB
- Major change is **Hr-TB diagnosis upfront**, requiring appropriate management at point of diagnosis
- Patients with RR/MDR-TB will be referred to treatment initiation unit

Management of patient with respiratory symptoms

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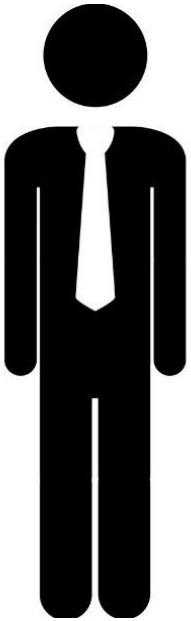
Case Study 1



29 year old man

- Diagnosed with HIV three years ago
- ART-naive, CD4: 195 cells/uL

Presents with

- Cough for 5 days
- Fever
- Progressive dyspnoea

What is your differential diagnosis?

- **Poll 7**

Case 1: What is the differential diagnosis?

a. Bacterial pneumonia
b. TB
c. PCP/PJP
d. Viral pneumonia
e. All of the above

- **What should you do next?**

Differential Diagnosis

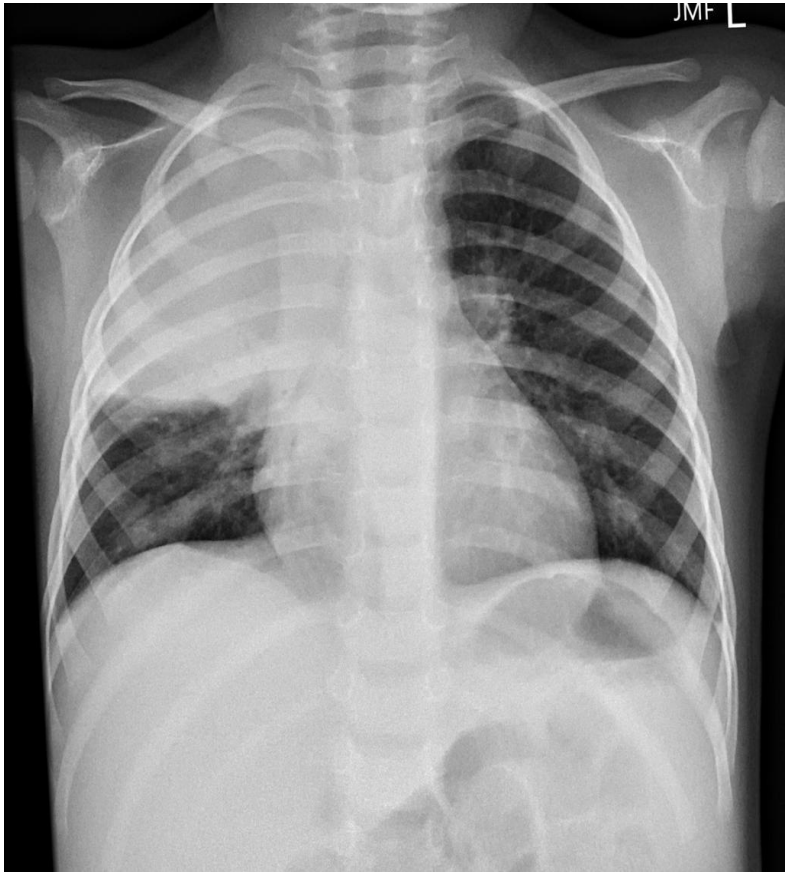
- Bacterial pneumonia
- Tuberculosis
- PCP/PJP
- Viral (may rank higher in Pandemics)
- Fungal
  - Cryptococcal
  - Dimorphic
- Kaposi Sarcoma
- Non-tuberculous Mycobacterium (NTM)
- Other
  - Lymphoma
  - Lymphocytic interstitial pneumonia (LIP)
  - Pulmonary hypertension

Very Common

Less Common

What is your differential diagnosis?

- Examination:
- RR 32/min, BP 110/70 mmHg
- Temp 38° C
- Bronchial breathing and crackles: right upper zone
- CXR on the right
- **Poll 8**



Poll 8

4. Case CXR: The following statement is TRUE?
    a. The most likely diagnosis is a Bacterial CAP, so the patient must be started on antibiotics and not be investigated for TB
    b. This is typical of PCP/PJP
    c. Bacterial CAP is very likely, but starting the patient on antibiotics, then performing urine LAM testing and taking sputum for Xpert MTB/Rif is the best course of action
    d. Bacterial CAP is very likely, but starting the patient on antibiotics and taking sputum for Xpert MTB/Rif is the best course of action

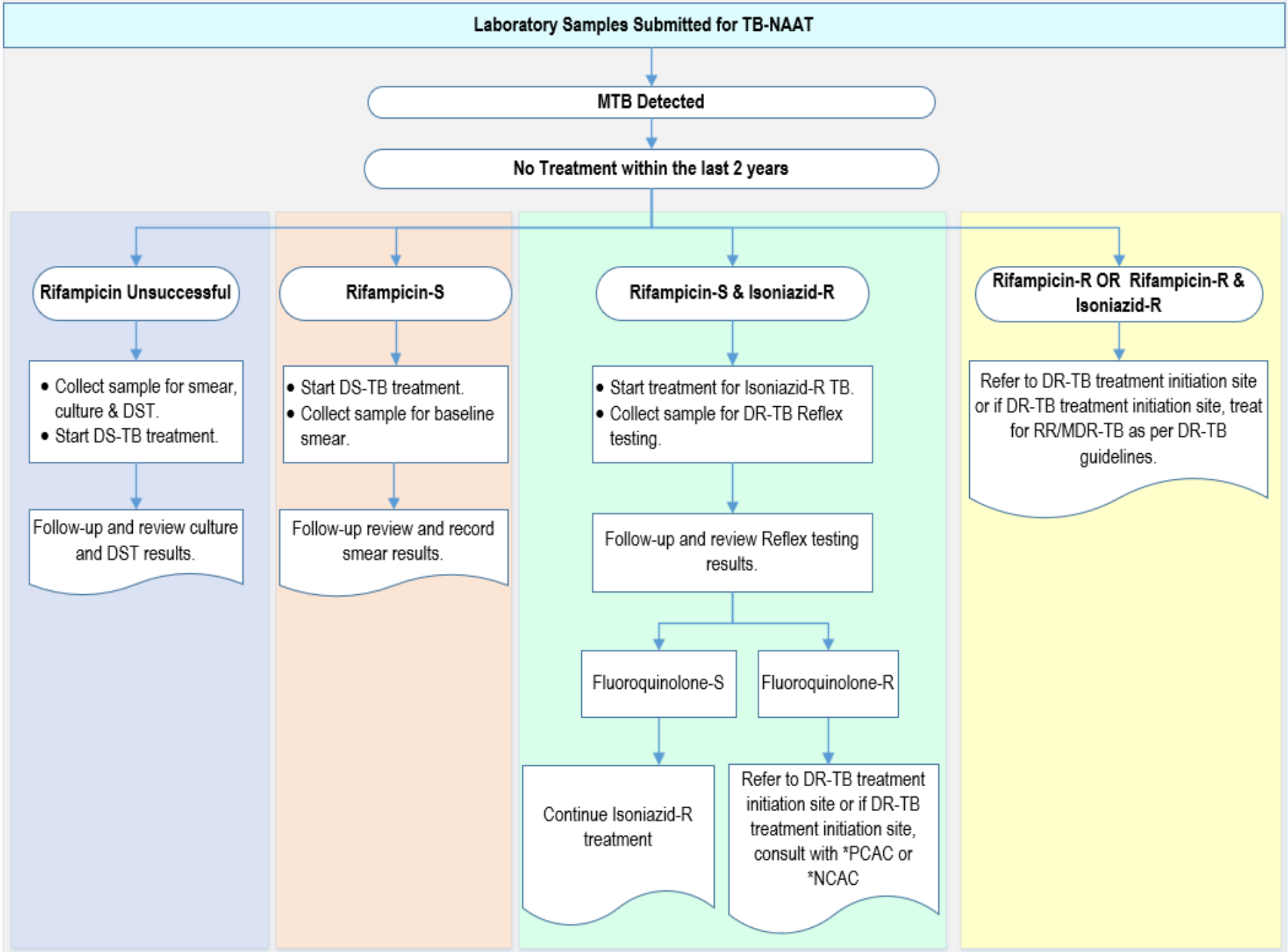
Respiratory Symptoms and HIV

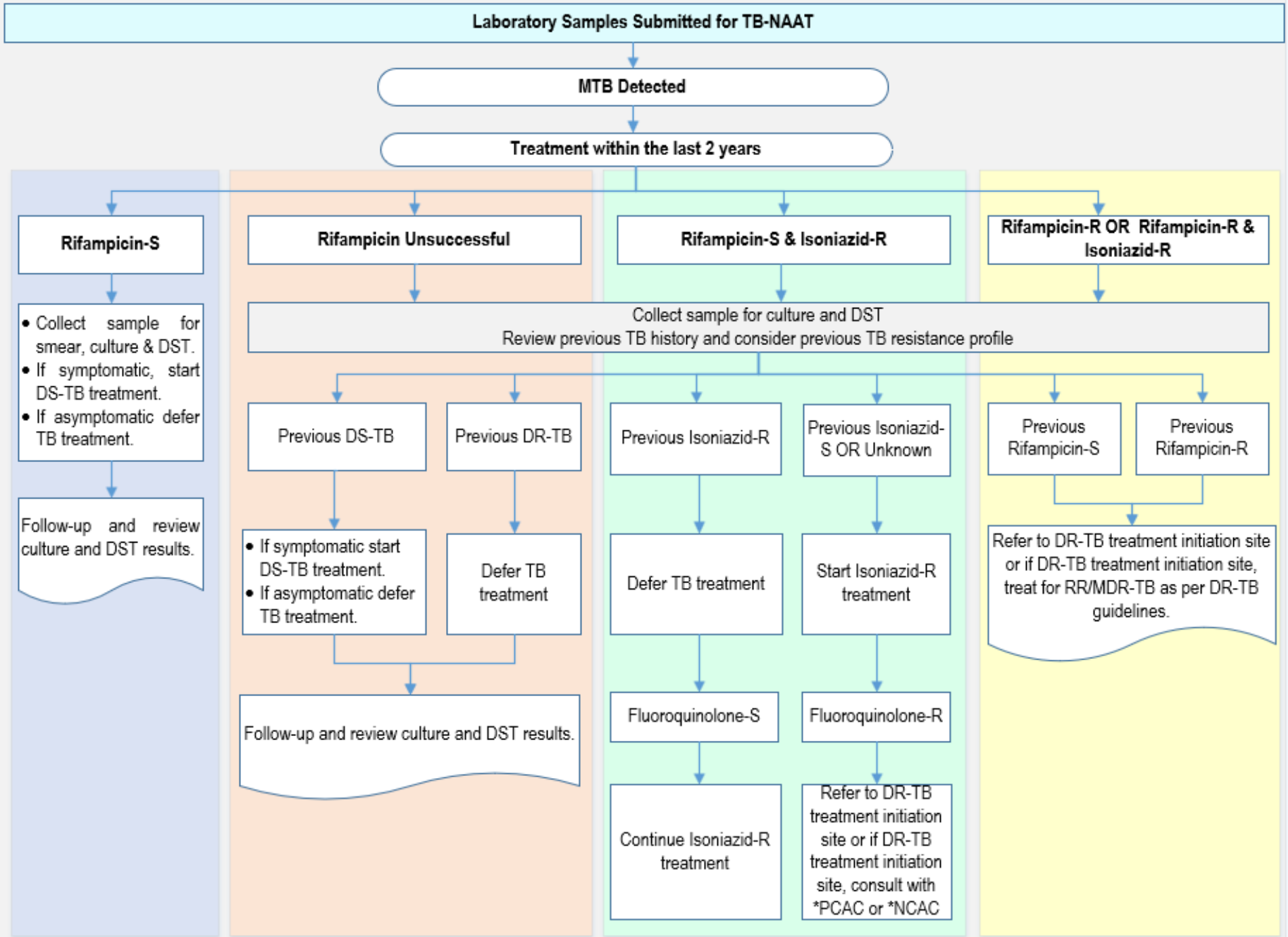
- Very common
- **Difficulties:**
  - Not easy to distinguish clinically
  - Diagnostics not ideal
  - Patients may have more than one problem

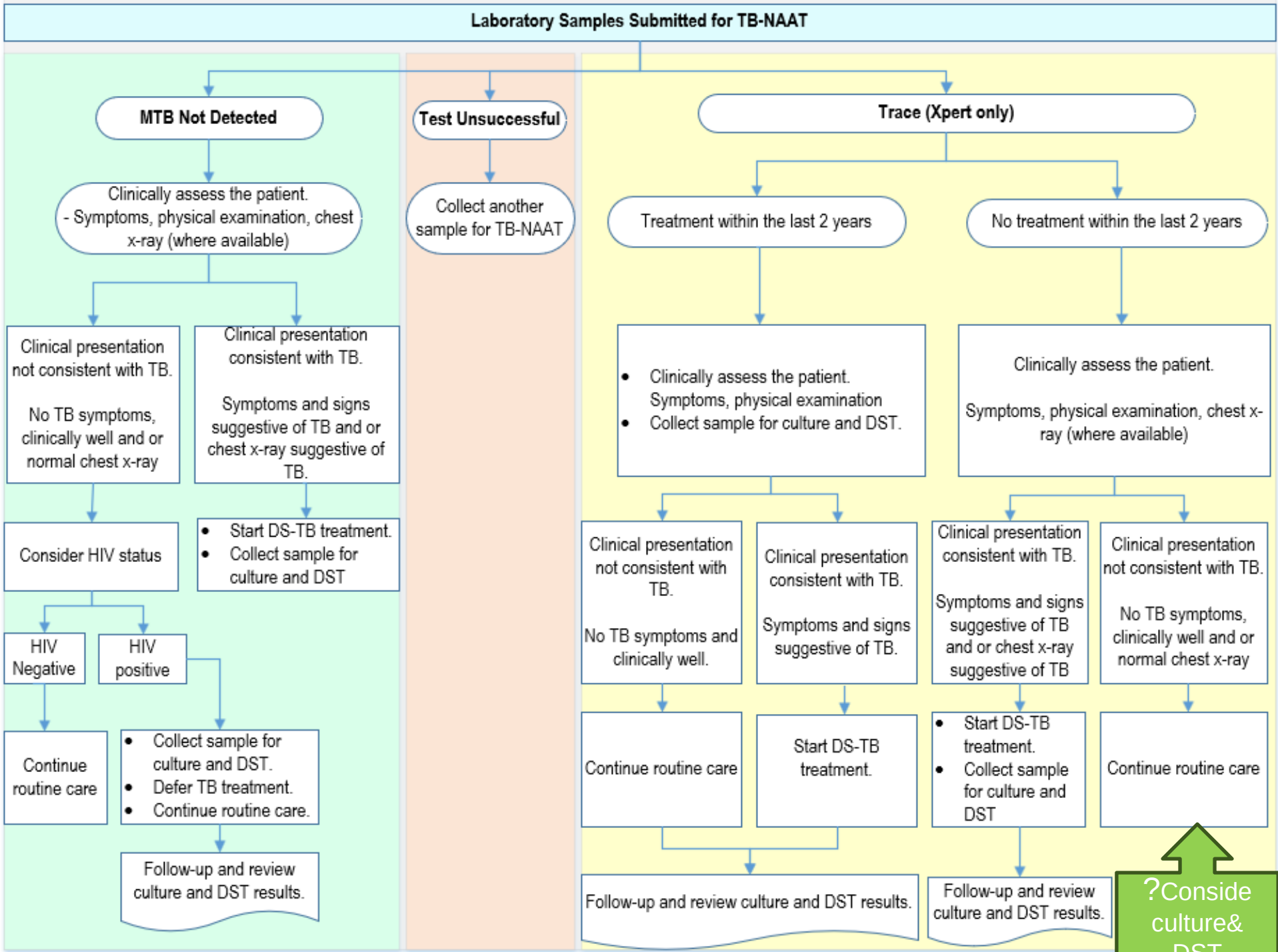
Poll 9

Regarding MTB/Rif results in Case 1, which of these is TRUE?

a. A negative sputum MTB/Rif result, must be followed by a TB culture & DST
b. A sputum positive MTB/Rif result always indicates active TB, and TB treatment must be promptly initiated.
c. A sputum 'trace positive' result always indicates past TB, and must be ignored
d. A sputum negative result always excludes pulmonary TB


Laboratory Samples Submitted for TB-NAAT
MTB Detected
No Treatment within the last 2 years
Rifampicin Unsuccessful
• Collect sample for smear, culture & DST.
• Start DS-TB treatment.
Follow-up and review culture and DST results.
Rifampicin-S
• Start DS-TB treatment.
• Collect sample for baseline smear.
Follow-up review and record smear results.
Rifampicin-S & Isoniazid-R
• Start treatment for Isoniazid-R TB.
• Collect sample for DR-TB Reflex testing.
Follow-up and review Reflex testing results.
Fluoroquinolone-S
Fluoroquinolone-R
Continue Isoniazid-R treatment
Refer to DR-TB treatment initiation site or if DR-TB treatment initiation site, consult with *PCAC or *NCAC
Rifampicin-R OR Rifampicin-R & Isoniazid-R
Refer to DR-TB treatment initiation site or if DR-TB treatment initiation site, treat for RR/MDR-TB as per DR-TB guidelines.


Laboratory Samples Submitted for TB-NAAT
MTB Detected
Treatment within the last 2 years
Rifampicin-S
Rifampicin Unsuccessful
Rifampicin-S & Isoniazid-R
Rifampicin-R OR Rifampicin-R & Isoniazid-R
• Collect sample for smear, culture & DST.
• If symptomatic, start DS-TB treatment.
• If asymptomatic defer TB treatment.
Follow-up and review culture and DST results.
Collect sample for culture and DST
Review previous TB history and consider previous TB resistance profile
Previous DS-TB
Previous DR-TB
Previous Isoniazid-R
Previous Isoniazid-S OR Unknown
Previous Rifampicin-S
Previous Rifampicin-R
• If symptomatic start DS-TB treatment.
• If asymptomatic defer TB treatment.
Defer TB treatment
Defer TB treatment
Start Isoniazid-R treatment
Refer to DR-TB treatment initiation site or if DR-TB treatment initiation site, treat for RR/MDR-TB as per DR-TB guidelines.
Follow-up and review culture and DST results.
Fluoroquinolone-S
Fluoroquinolone-R
Continue Isoniazid-R treatment
Refer to DR-TB treatment initiation site or if DR-TB treatment initiation site, consult with *PCAC or *NCAC


Laboratory Samples Submitted for TB-NAAT
MTB Not Detected
Test Unsuccessful
Trace (Xpert only)
Clinically assess the patient.
- Symptoms, physical examination, chest x-ray (where available)
Collect another sample for TB-NAAT
Treatment within the last 2 years
No treatment within the last 2 years
Clinical presentation not consistent with TB.
No TB symptoms, clinically well and or normal chest x-ray
Clinical presentation consistent with TB.
Symptoms and signs suggestive of TB and or chest x-ray suggestive of TB.
Clinically assess the patient.
Symptoms and signs suggestive of TB.
Collect sample for culture and DST.
Clinically assess the patient.
Symptoms, physical examination, chest x-ray (where available)
Consider HIV status
Start DS-TB treatment.
Collect sample for culture and DST
Clinical presentation not consistent with TB.
No TB symptoms and clinically well.
Clinical presentation consistent with TB.
Symptoms and signs suggestive of TB.
Clinical presentation consistent with TB.
Symptoms and signs suggestive of TB and or chest x-ray suggestive of TB
Clinical presentation not consistent with TB.
No TB symptoms, clinically well and or normal chest x-ray
HIV Negative
HIV positive
Continue routine care
Collect sample for culture and DST.
Defer TB treatment.
Continue routine care.
Start DS-TB treatment.
Start DS-TB treatment.
Collect sample for culture and DST
Continue routine care
Continue routine care
Follow-up and review culture and DST results.
Follow-up and review culture and DST results.
Follow-up and review culture and DST results.
?Conside culture&

Case Study 2

44 year old male, newly diagnosed HIV positive at this visit

Presents with 10 day hx of non-productive cough

- Difficulty breathing
- Weight loss > 5%
- RR 30/min
- Temp 38.4°C
- Pulse 124bpm
- BP 100/68 mmHg
- Cannot walk unaided

Poll 10

Which of these is true about LF-LAM testing recommendations in South Africa?

a. All adult PLHIV with a negative TB screen, and unable to produce sputum, should undergo LAM testing at HIV diagnosis.
b. Urine TB LAM should NEVER be performed on the day of HIV diagnosis.
c. A positive LAM test confirms DS-TB
d. All PLHIV admitted to medical wards and not known to have active TB, need to undergo LAM testing

What to do if sputum not obtainable

1. **Induced sputum-**
   - Nebulisation: Hypertonic/ N-saline with bronchodilator
   - Chest physiotherapy

2. Chest X-ray

3. +/- Urine LF-LAM (do in inpatients/ CD4+ count < 200/ seriously ill PLHIV)

- Severely sick, regardless of CD4+ count: RR> 30/min; Temp >39; HR>120bpm; BMI<18.5; cannot walk unaided
- CD4+ <200

Shown to reduce TB deaths: all-cause mortality at 8w by 17%

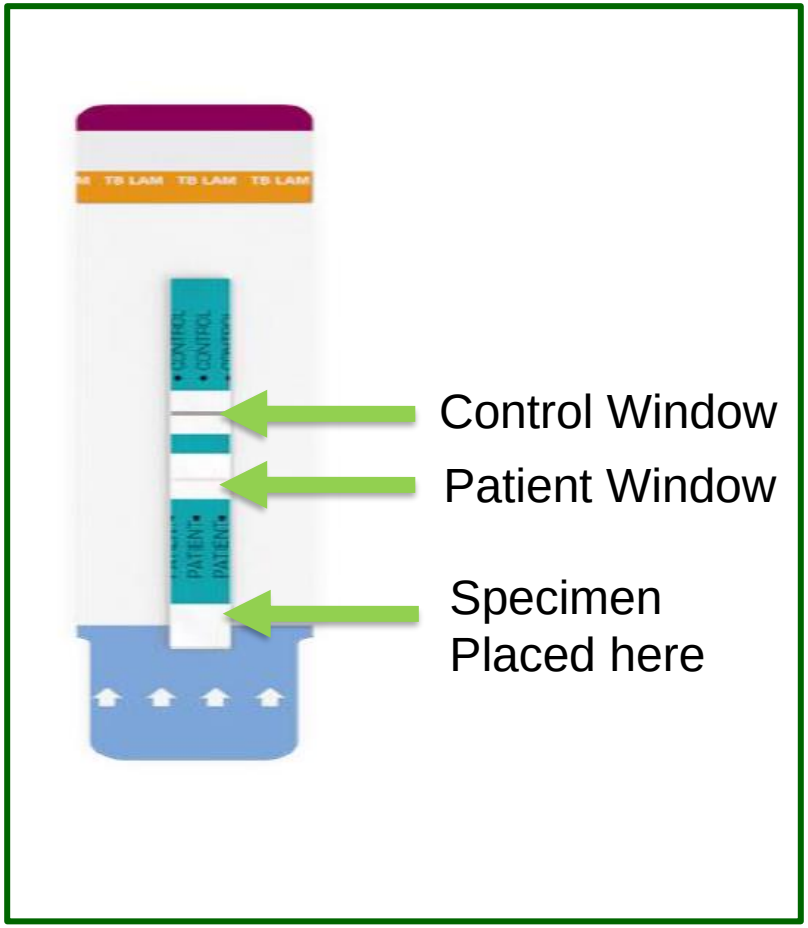
Peter JG et al- randomized clinical trial of 2,000 hospitalized people with HIV in South Africa, Tanzania, Zambia, and Zimbabwe

Diagnostic challenges in AHD

- **Diagnosis of TB in people with advanced HIV using sputum-based tests is challenging**
  - High % extra-pulmonary TB
  - paucibacillary pulmonary TB
  - ➢ Molecular tests less sensitive; long TAT of TB culture
  - inability of such patients to expectorate sputum.

  - **Enter urine LF-LAM**

Urine lipoarabinomannan (LAM) assay

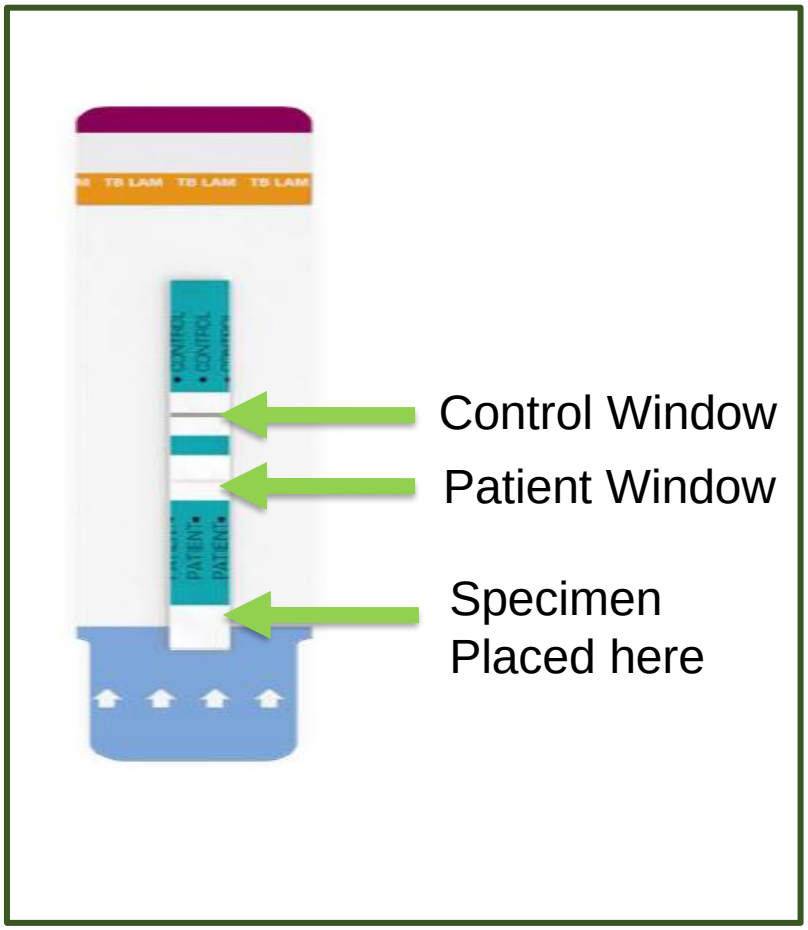


- Bedside test using urine
- Detects TB antigen (LAM is component of mycobacterial cell wall)
- Easy to perform (mid-stream urine; inspect after 25 min)
- Sensitivity increases as CD4+ cell count declines – should be used in hospitalized PLHIV (medical condition) or those with CD4+ <200, or seriously ill

Test kits are available in hospital pharmacies and depot

Urine lipoarabinomannan (LAM) assay

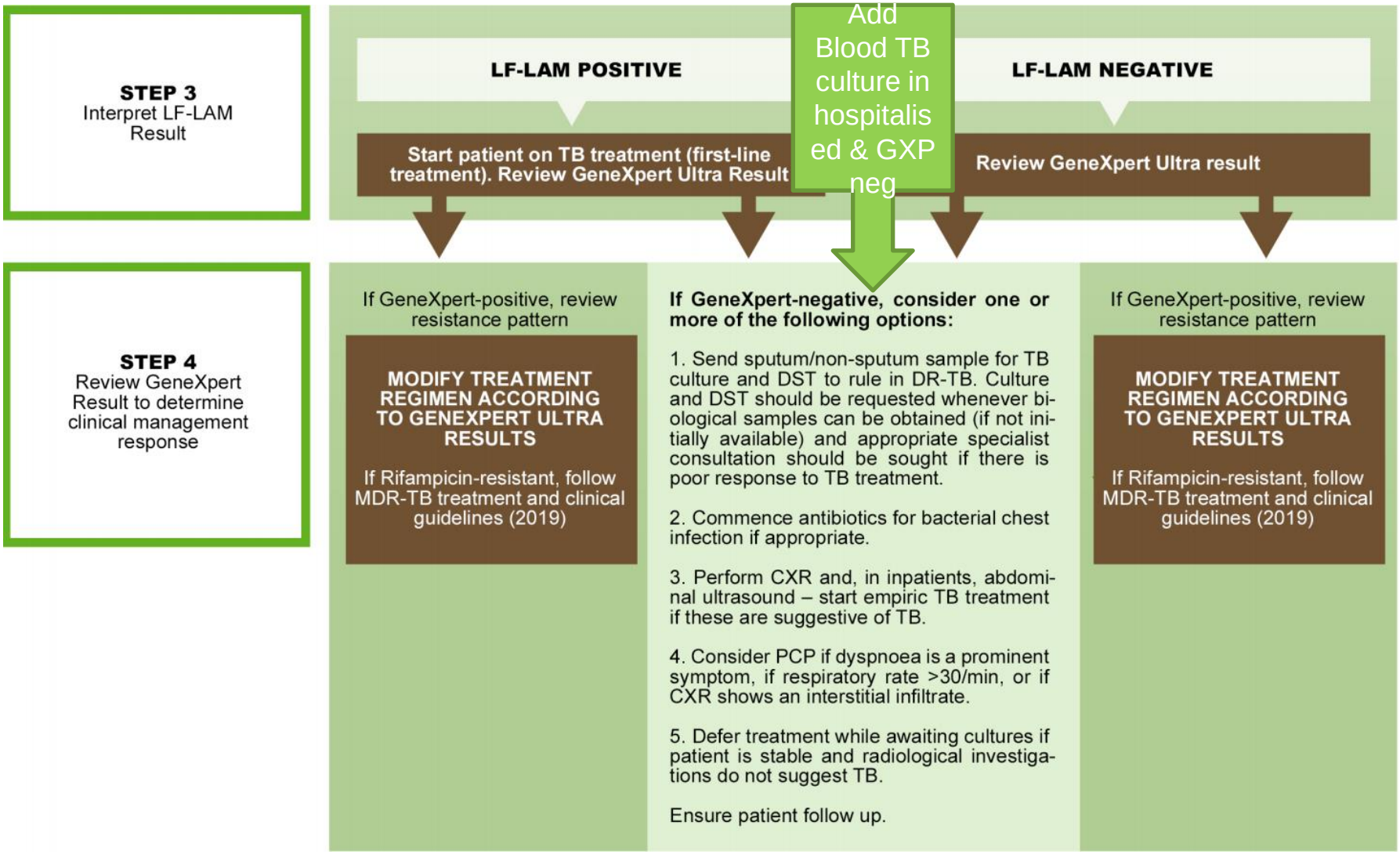
Limitations



- Performance depends on CD4+ cell count
- Negative test does not rule out active TB – further investigations and empirical TB treatment may be required
- Does not detect drug resistance
- Does not differentiate *M. tuberculosis* from non-tuberculous mycobacteria

Expand use of Urine LF-LAM testing for AHD

SETTING	ADMITTED, HOSPITALISED SETTING	CLINIC, OUTPATIENT SETTING, AND PATIENT AMBULATORY AND WITH SIGNS AND SYMPTOMS OF TB
STEP 1 Assess for TB signs and symptoms	All hospitalised patients are considered seriously ill. Proceed with collection of urine LF-LAM irrespective of CD4 count or whether TB is suspected.	**If CD4 count is ≤200 and results are not older than 6 months, perform LF-LAM.** If no CD4 count is available, this should be requested. Patients who have advanced disease and/or are seriously ill should receive LF-LAM. Not eligible for LF-LAM if CD4+ count >200: Do TB-NAAT
STEP 2 Perform LF-LAM test. Where possible, collect sputum and perform GeneXpert concurrently.	1. Collect urine for LF-LAM test 2. Collect sputum or any suitable specimen (e.g. CSF, lymph node aspirate, etc.) for testing on GeneXpert Ultra 3. Conduct additional clinical evaluations for TB (initiate treatment with broad-spectrum antibiotics but not fluoroquinolones for bacterial infections, consider treatment for Pneumocystis pneumonia, conduct chest X-ray (CXR) if available)	


STEP 3
Interpret LF-LAM Result
LF-LAM POSITIVE
LF-LAM NEGATIVE
Add Blood TB culture in hospitalised & GXP neg
Start patient on TB treatment (first-line treatment). Review GeneXpert Ultra Result
Review GeneXpert Ultra result
STEP 4
Review GeneXpert Result to determine clinical management response
If GeneXpert-positive, review resistance pattern
MODIFY TREATMENT REGIMEN ACCORDING TO GENEXPERT ULTRA RESULTS
If Rifampicin-resistant, follow MDR-TB treatment and clinical guidelines (2019)
If GeneXpert-negative, consider one or more of the following options:
1. Send sputum/non-sputum sample for TB culture and DST to rule in DR-TB. Culture and DST should be requested whenever biological samples can be obtained (if not initially available) and appropriate specialist consultation should be sought if there is poor response to TB treatment.
2. Commence antibiotics for bacterial chest infection if appropriate.
3. Perform CXR and, in inpatients, abdominal ultrasound – start empiric TB treatment if these are suggestive of TB.
4. Consider PCP if dyspnoea is a prominent symptom, if respiratory rate >30/min, or if CXR shows an interstitial infiltrate.
5. Defer treatment while awaiting cultures if patient is stable and radiological investigations do not suggest TB.
Ensure patient follow up.
If GeneXpert-positive, review resistance pattern
MODIFY TREATMENT REGIMEN ACCORDING TO GENEXPERT ULTRA RESULTS
If Rifampicin-resistant, follow MDR-TB treatment and clinical guidelines (2019)

Thank You

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- A POCKET GUIDE TO ANTIBIOTIC PRESCRIBING FOR ADULTS IN SOUTH AFRICA, 2015 SEAN WASSERMAN TOM BOYLES MARC MENDELSON
- Treatment decisions and mortality in HIV-positive presumptive smear-negative TB in the Xpert™ MTB/RIF era: a cohort studyHermans SM1,2,3, Babirye JA4, Mbabazi O4, Kakooza F4, Colebunders R5,6, Castelnuovo B4, Sekaggya-Wiltshire C4, Parkes-Ratanshi R4,7, Manabe YC4,8,9.
- Pneumocystis jiroveci Pneumonia (PJP) Overview of Pneumocystis jiroveci Pneumonia (Updated: Apr 24, 2019) author heading Author: Shelley A Gilroy, MD, FIDSA; Chief Editor: Pranatharthi Haran Chandrasekar, MBBS, MD
- SA NDOH: National Consolidated Guidelines-FOR THE MANAGEMENT OF HIV IN ADULTS, ADOLESCENTS, CHILDREN AND INFANTS AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION: Feb 2020
- SA NDOH: Guideline for the Prevention of Mother to Child Transmission of Communicable Infections: Oct 2019

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- National ACC Partners
- Kheth'Impilo
- Right to Care

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