UNIVERSITY OF KWAZULU-NATAL ™
INYUVESI YAKWAZULU-NATALI

Tuberculosis in Advanced HIV Disease: Navigating the Clinical Minefield

AWACC
29 October 2026

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Outline

- Overview of AHD
- TB in the context of advanced HIV disease
- Illustrative case - challenges of PTB in AHD
- Retention during TB treatment cascade
- Asymptomatic TB
- Tools to diagnose TB
- Treatment and monitoring algorithm
- Illustrative case – value of monitoring

Introduction

- Access to ART - decreased HIV associated morbidity and mortality.
- **One in five newly diagnosed HIV**
- **Growing number returning to care**

→ **present with AHD**

- AHD are at **higher risk of death** , even after ART initiation
- Most common causes of death:
  - TB
  - CM
  - Severe Bacterial infections

How do you identifying AHD

Defined by the severity of immune deficiency:

- CD4 ≤ 200
- WHO clinical stage 3 or 4 condition.

Wide spectrum of clinical presentation:

- Clinically well or asymptomatic.
- Unwell - not warranting urgent admission.
- Severely ill with danger signs

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for >1 month
- Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anaemia
- (haemoglobin<8 g/dL)
- Neutropenia (neutrophils <500 cells/μL)
- Chronic thrombocytopenia (platelets <50,000 cells/μL)

Stage 3

Stage 4

- HIV wasting syndrome, as defined by the CDC (see Table 1, above)
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month orvisceral herpes at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extra pulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extra pulmonary (including meningitis)
- Disseminated non-Tuberculosis mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent non-typhoidal Salmonella bacteraemia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

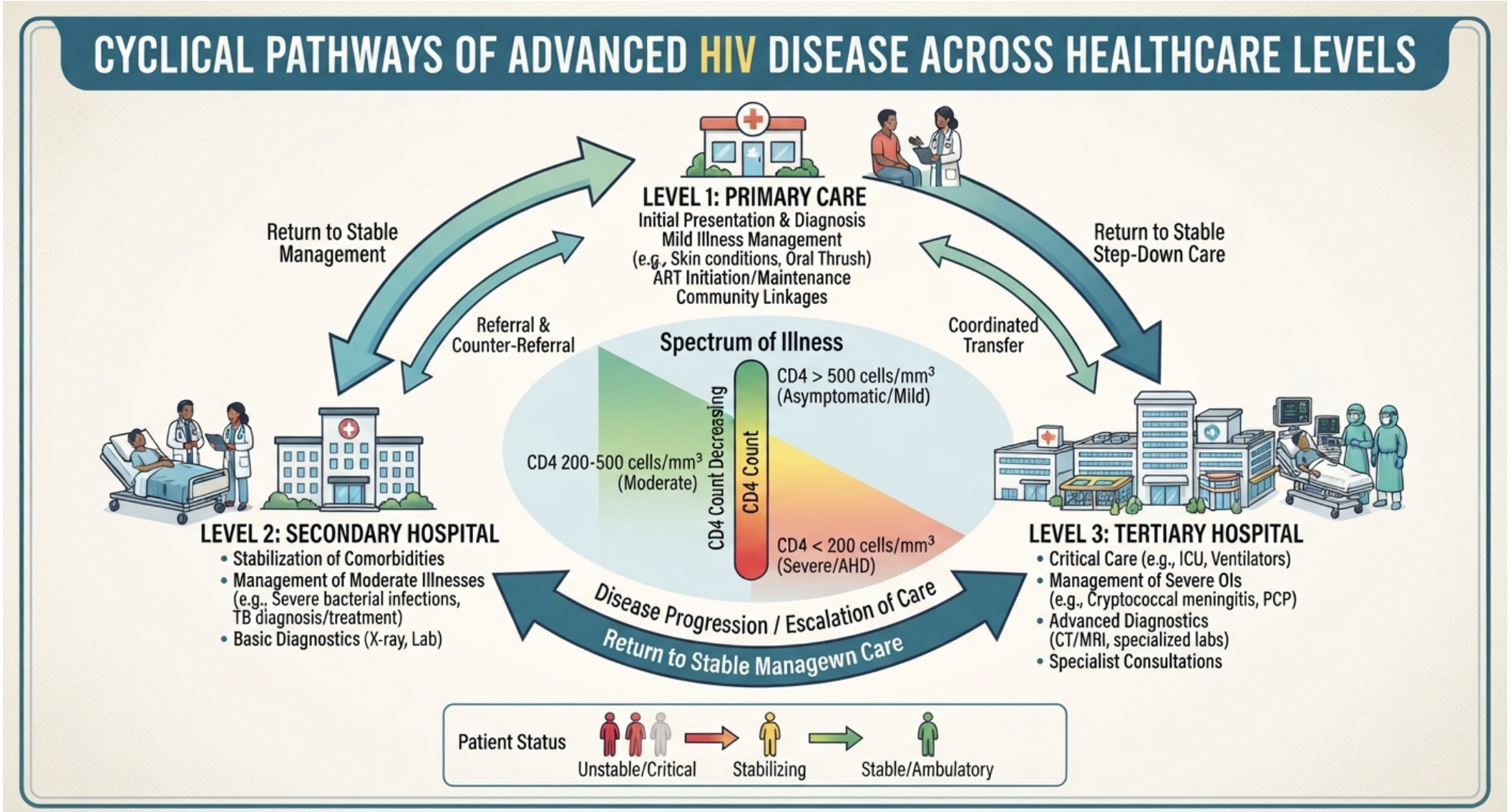
Who is at high risk for AHD

- Newly diagnosed HIV
- PLHIV that are clinically unwell irrespective of ART
- VL > 1000 c/mL
- Returning after >3/12 of treatment interruption

Who is at high risk for AHD

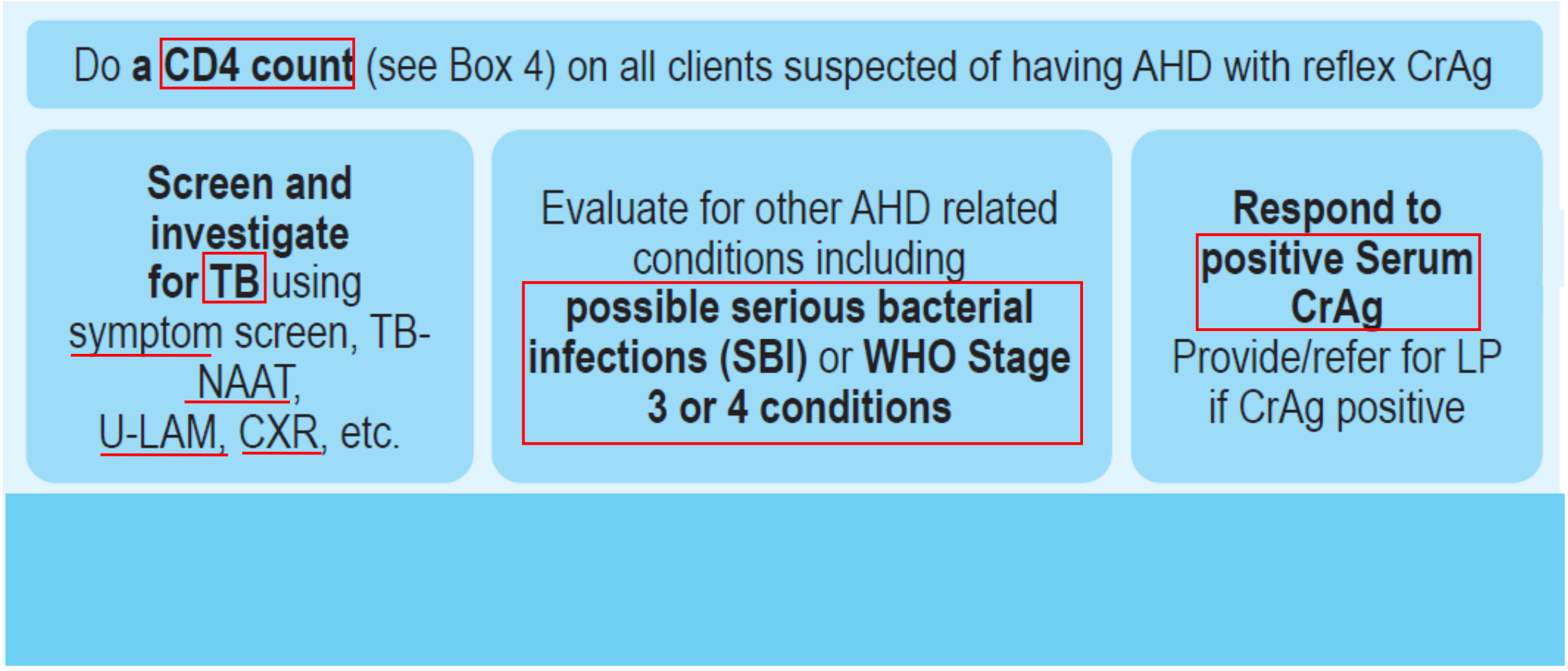
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All Categories of HCW and All levels of Health care facilities need to be familiar with diagnosing AHD



Assessment for AHD

- Newly diagnosed HIV
- PLHIV that are clinically unwell irrespective of ART
- VL > 1000 c/mL
- Returning after >3/12 of treatment interruption





41 yo female:

- Fatigue, lassitude
- LOA, LOW

Source Sputum

Description Not Stated

DIRECT PREP: AFB (TB MICRO)

AURAMINE O (DIRECT PREP) — Not observed

Mycobacterial culture

HIV-1/2 (4th Gen) — **REACTIVE**

HIV-1/2 (4th Gen) Confirm — **REACTIVE**

Organism 1 — **Mycobacterium tuberculosis complex detected**

*

Mycobact tuberculosis complex Rifampicin sensitive
VERY Low

	M TB
Rifampicin	S

trapping or lobar collapse.
No pleural effusions or hilar lymphadenopathy.

Cardiac and mediastinal contours are normal.
Major airways are normal in appearance.
Pulmonary vasculature appears normal.

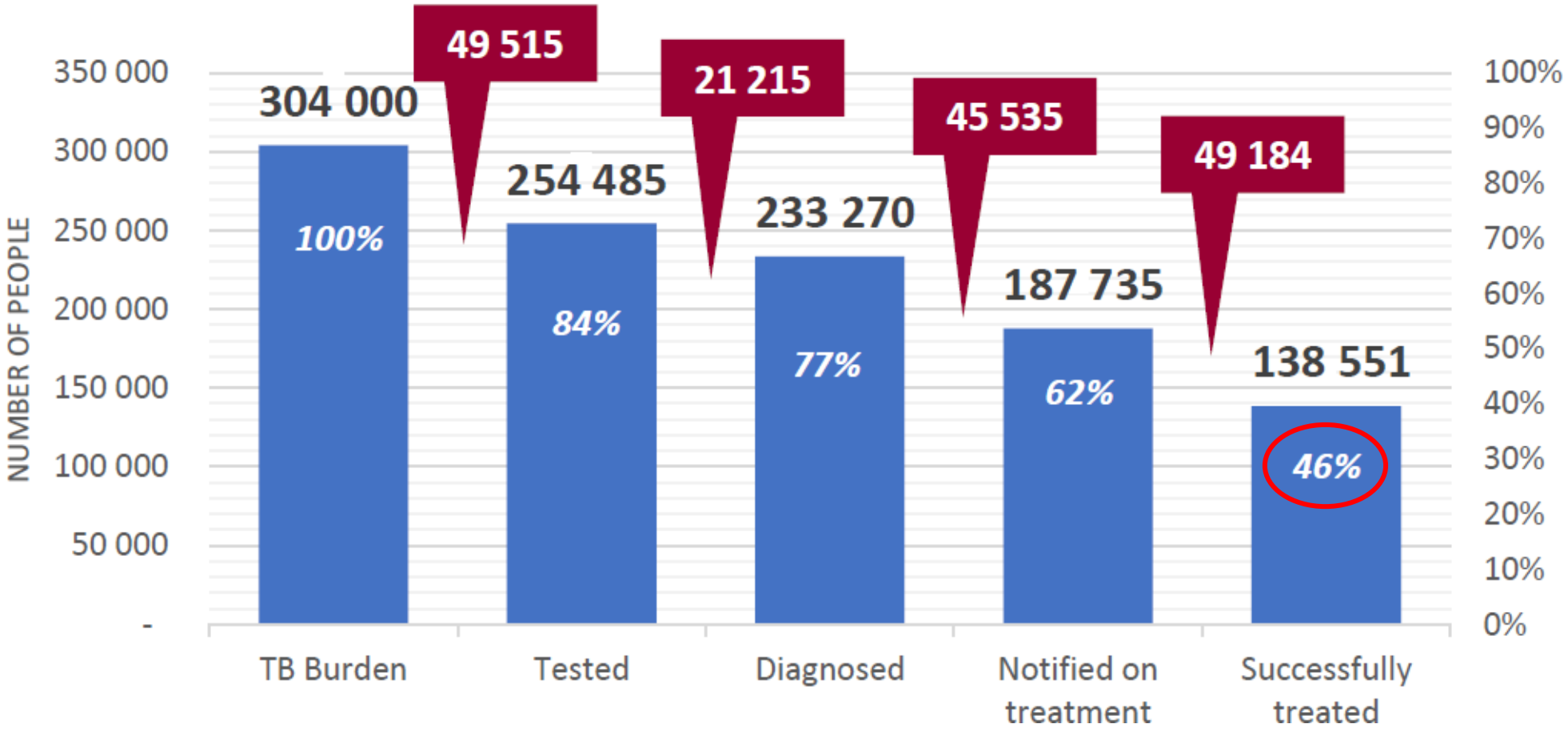
National TB prevalence survey, 2017-19



Estimated prevalence **bacteriologically confirmed PTB** ≥15 yrs - 852/10^5 vs. 4/10^5

How are we doing with treatment?
TB care cascade, 2021

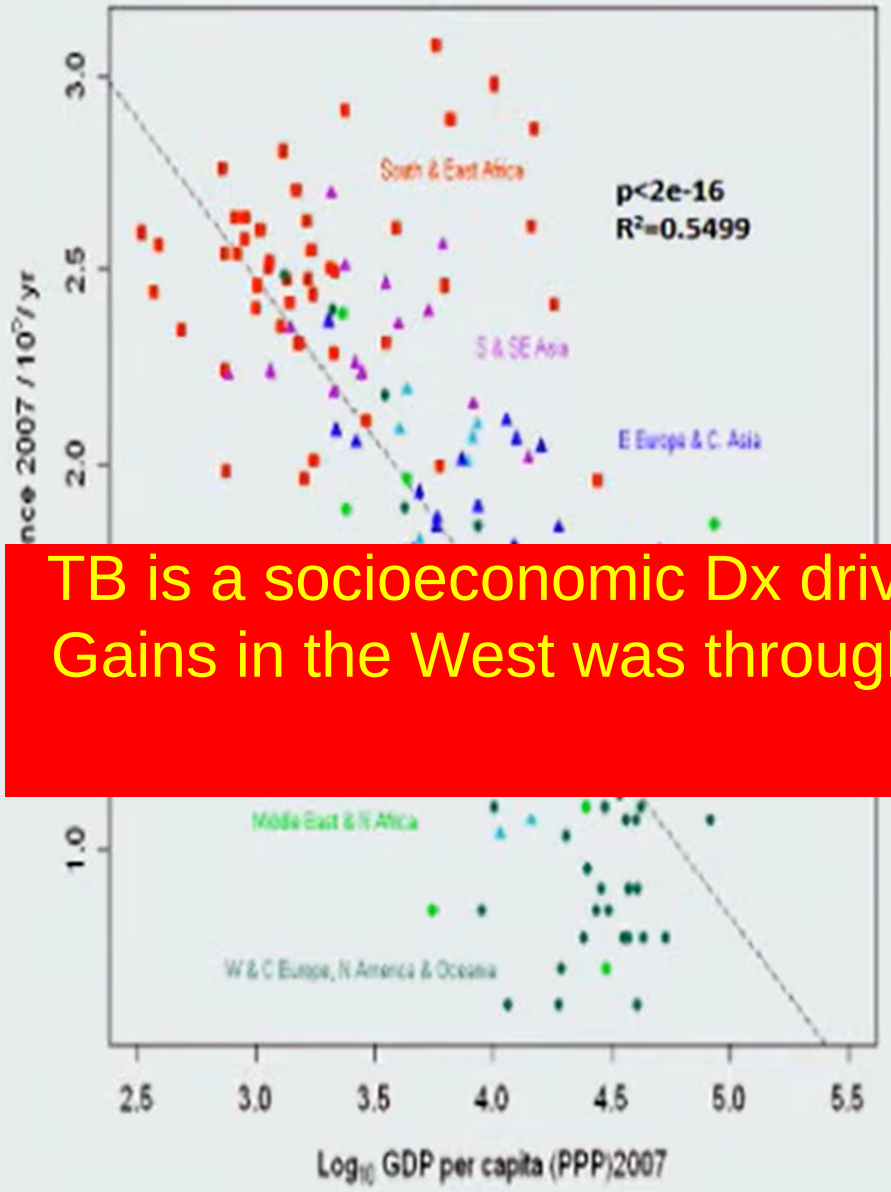
Significant attrition along care cascade- Under half successfully treated.



Cannot treat our way out of TB epidemic

National TB Recovery Plan

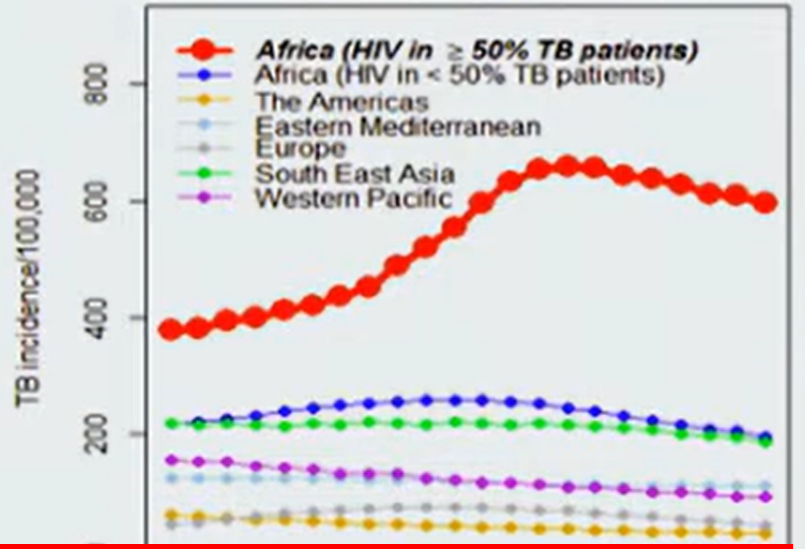
1. Poverty



2. Broken health systems



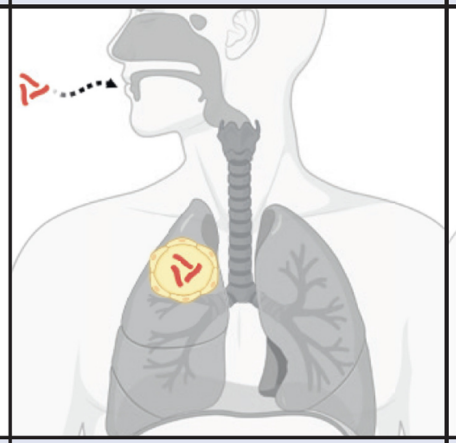
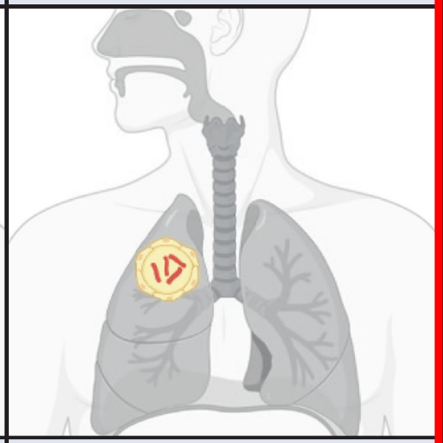
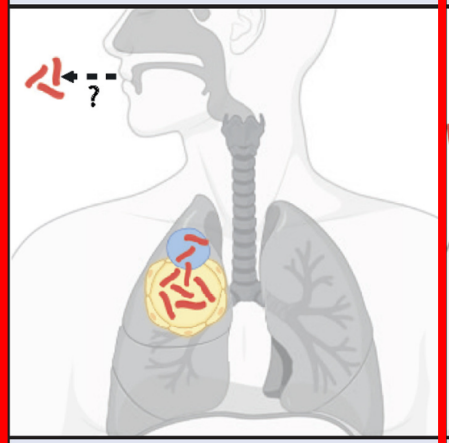
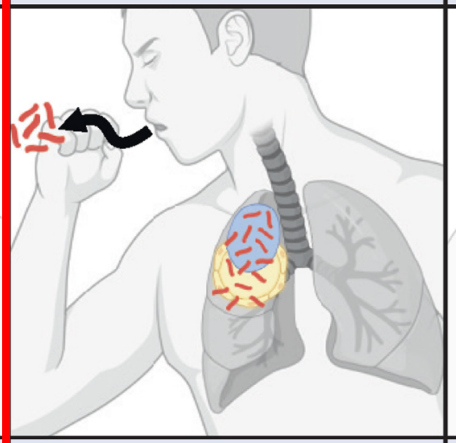
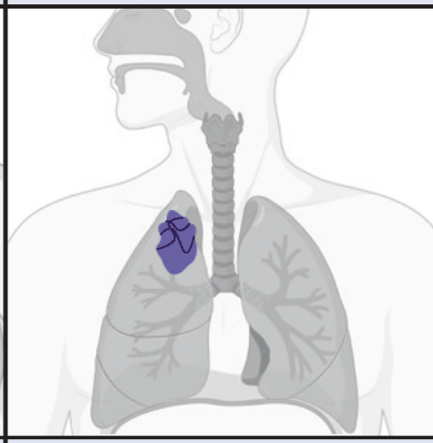
3. HIV infection (esp. Africa)



TB is a socioeconomic Dx driven by poverty, overcrowding, and poor living conditions
Gains in the West was through focused improvement in poverty, living conditions and health care systems



Different States of PTB

Biophenotype	Tuberculosis infection (MET-A-NAD or LTBI)	Asymptomatic tuberculosis (incipient)	Asymptomatic tuberculosis (subclinical)	Symptomatic tuberculosis (active tuberculosis disease)	After tuberculosis lung disease
Illustration					
Symptoms	Absent	Absent	Absent	Present	Present
Microbial burden	+	++	+++	+++++	Absent or +
Imaging—chest radiograph	Normal	Usually normal	Often abnormal (maybe normal)	Abnormal	Abnormal
Tuberculosis DNA in sputum or oral sample	Negative	Likely negative	Positive	Positive	Could be positive
Infectiousness	No	Possible (but unknown)	Probable (but unknown)	High risk (might be non-infectious)	No

Asymptomatic Tuberculosis Across the Disease Spectrum: A Scoping Review of Epidemiology, Diagnosis, and Public Health Implications

Beatriz Barreto Duarte,[1,2,3] Jerrold Ellner,[4] Alicia D. Wright,[5] Mark Hatherill,[4] Amita Gupta,[6,7] Timothy R. Sterling,[5] Rajita Bhavaraju,[8] and Bruno B. Andrade[1,2,3,6,7]

Challenges to control TB: Find and Treat

- Control strategies prioritized symptomatic cases
- Community based active screening- 30%-50% bacteriologically confirmed TB cases occur in asymptomatic subjects
- A substantial proportion smear positive - role in transmission
- Huge burden on the public health response
- To find them you have to do **active** case finding

Following should be investigated for TB **regardless of TB symptoms**

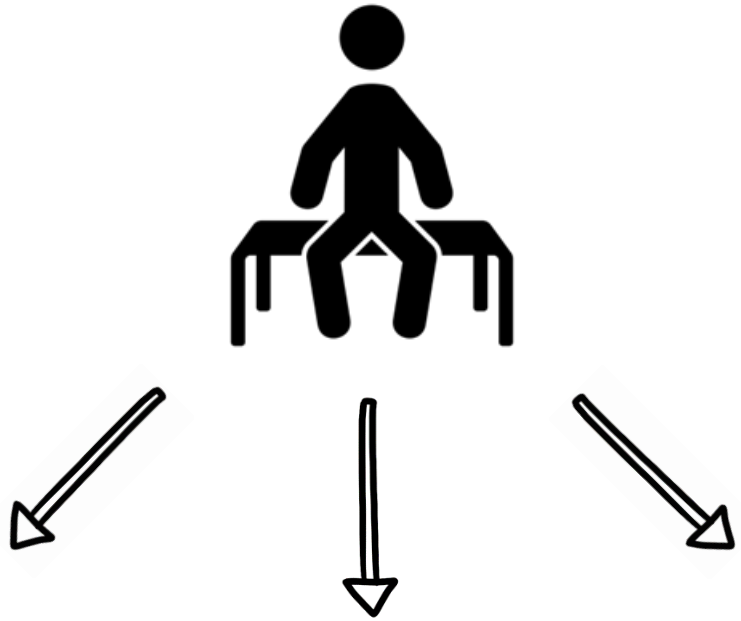
- At HIV diagnosis
- Confirmed or suspected AHD
- New TB exposure
- At annual clinical review on ART – align with annual VL
- HIV-positive with new pregnancy irrespective of ART

Tools to diagnose PTB

Essentially six tools available

	TB Investigation	Purpose
Tests for TB Infection	**Tuberculin Skin Test (TST)**	Confirmation of TB Infection when TB exposure status is unknown (and no previous positive TST or history of TB disease)
Investigations to make the diagnosis of TB Disease	**Chest X-ray and other imaging**	To identify radiological changes in lungs & adjacent structures (or other organ systems is EPTB suspected) suggestive of TB disease and other non-TB-related abnormalities.
	TB Nucleic Acid Amplification Tests (TB-NAAT)	Bacteriological confirmation of TB. Identification of rifampicin resistance* If Rif-resistance is detected, DR-TB reflex testing should be done to detect resistance to isoniazid (INH) and second-line drugs
	TB Culture	Bacteriological confirmation of TB, especially if initial NAAT negative Allows for DST (using TB-NAAT off the cultured isolate)
	Sputum Smear Microscopy	Not a routine or priority investigation in younger children who are seldom sputum smear positive for acid-fast bacilli (AFB) To monitor treatment response in older children and adolescents who were initially smear-positive on sputum Smear-positivity on sputum in a child suggests cavitary lung disease and severe TB disease
	Urine-LAM	To facilitate the diagnosis of TB in symptomatic CLHIV who meet the eligibility criteria for testing

Goals of TB treatment, care & support

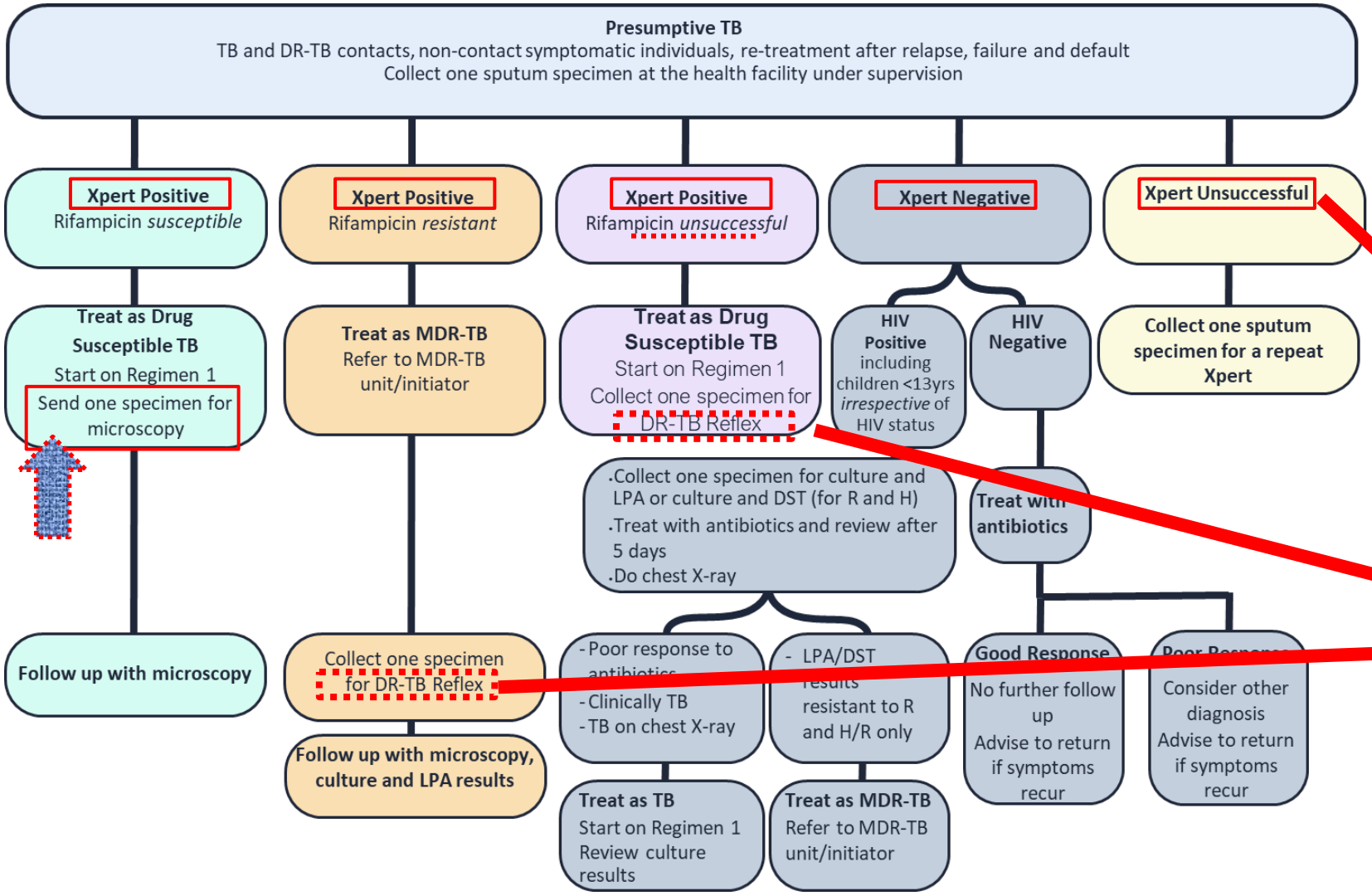


Cure patient

Minimise risk of death & disability

Reduce transmission

How molecular testing fits into Standard TB diagnostic algorithm



Smear:
LOD: 10000-100,000

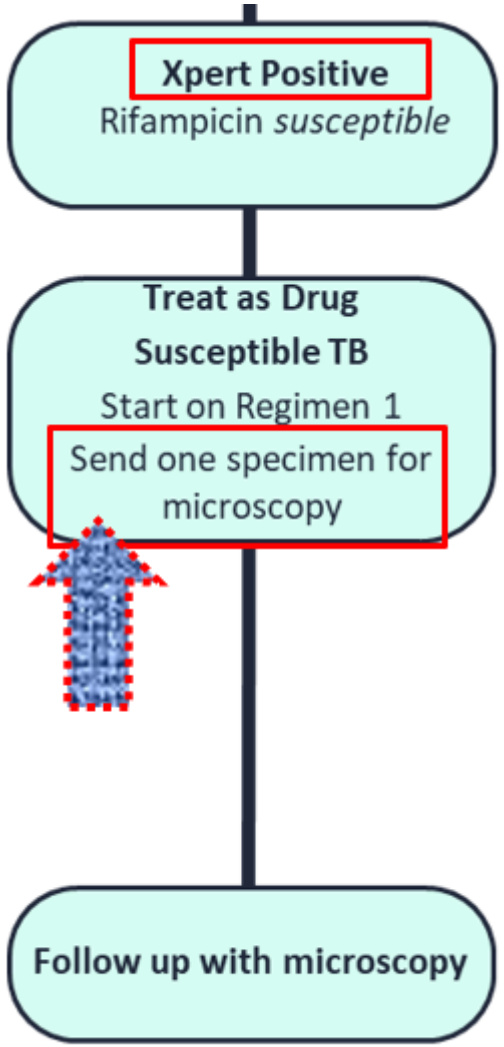
Culture:
LOD: 10 to 100

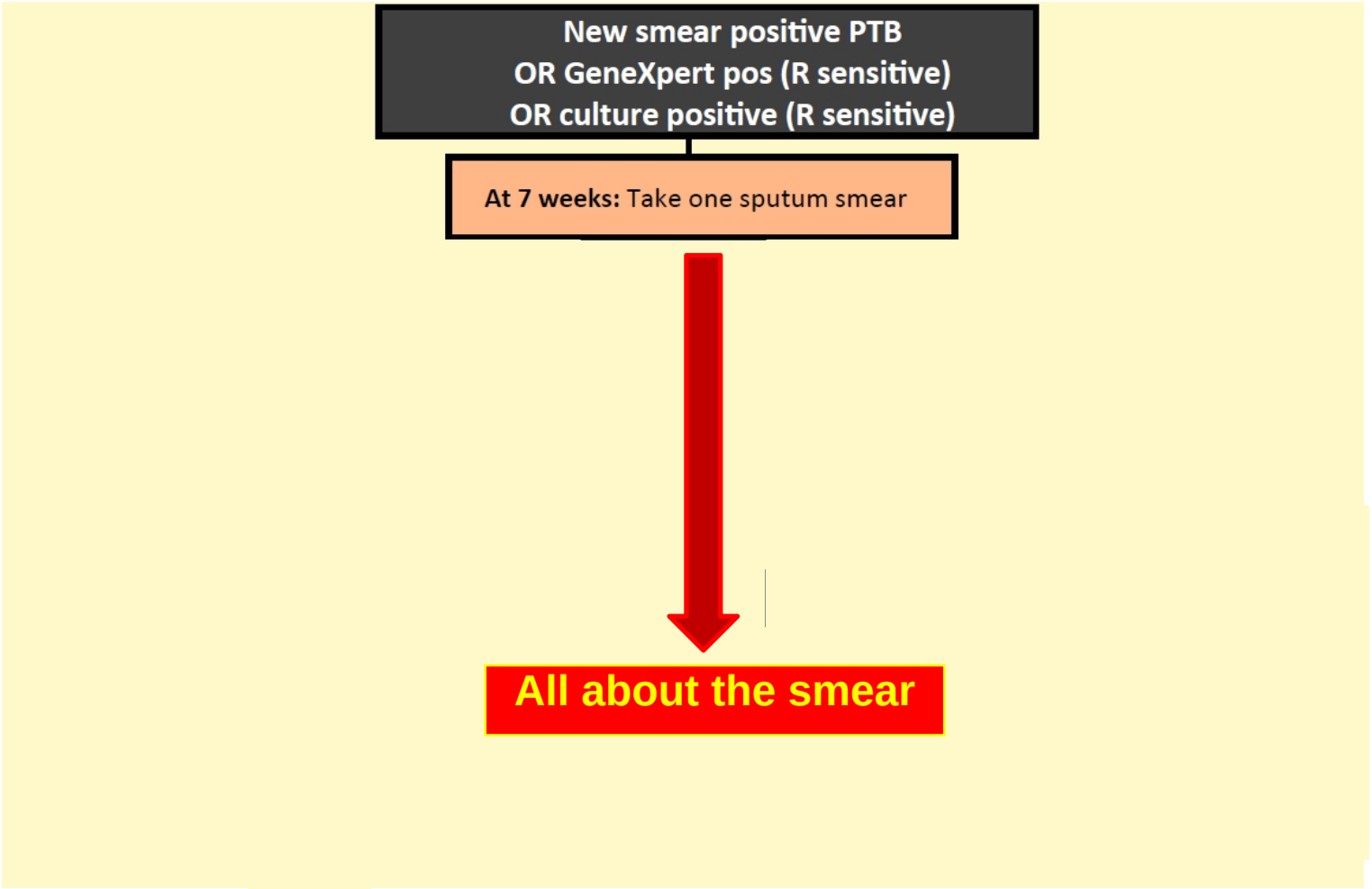
Xpert Ultra:
LOD for MTB: 16 CFU
LOD for RIF sensitivity: 105 CFU!

"DR-TB Reflex DST Testing"

1. Smear
2. Xpert MTB/XDR: **INH/FQ/AG**
3. Culture
4. Phenotypic DST - BDQ/LZD

Monitoring on treatment: 7weeks (2 months)





Monitoring on treatment: 8 weeks

Sputum smear - Wk 7

Negative

Continue SOC

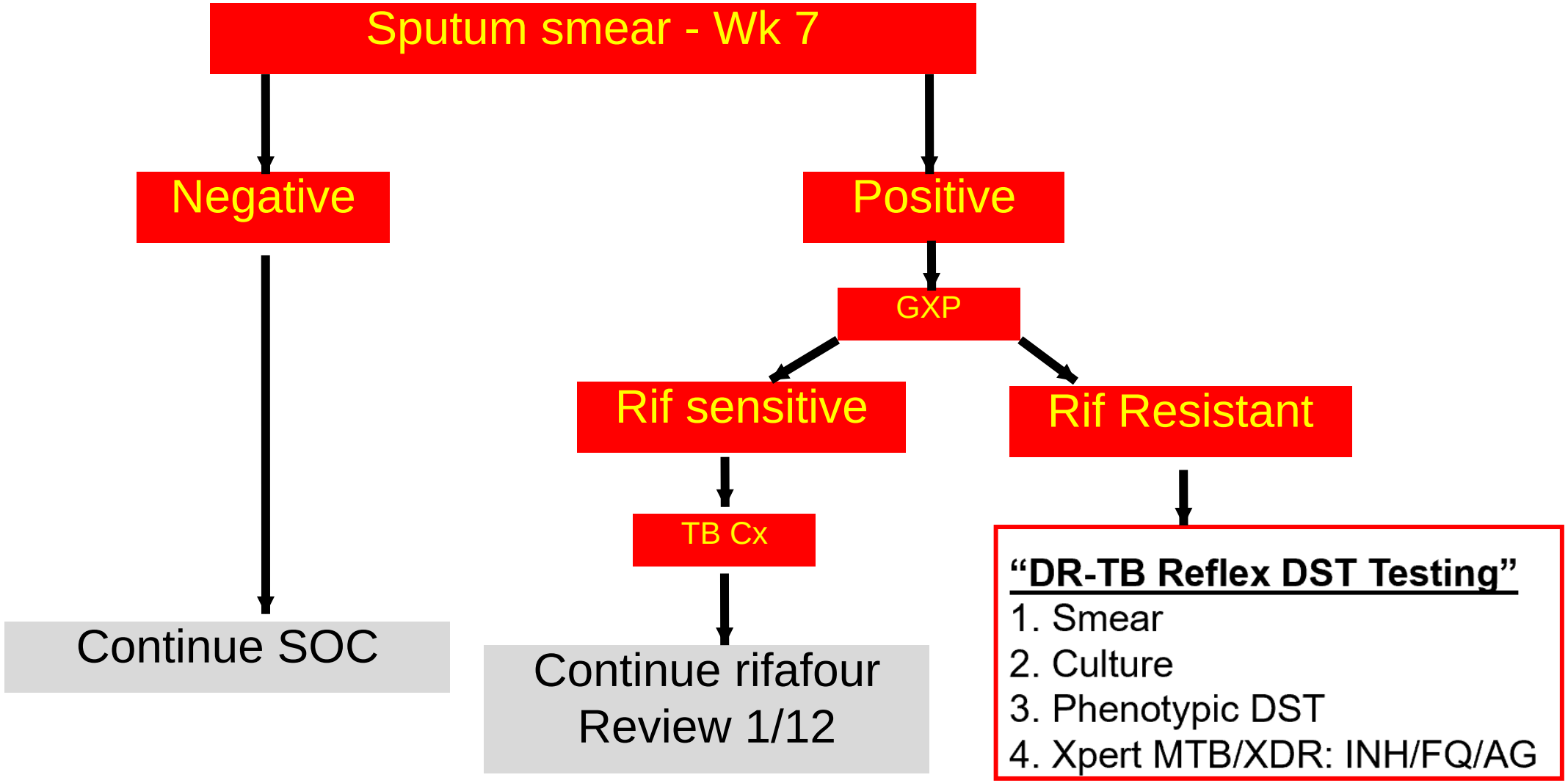
Positive



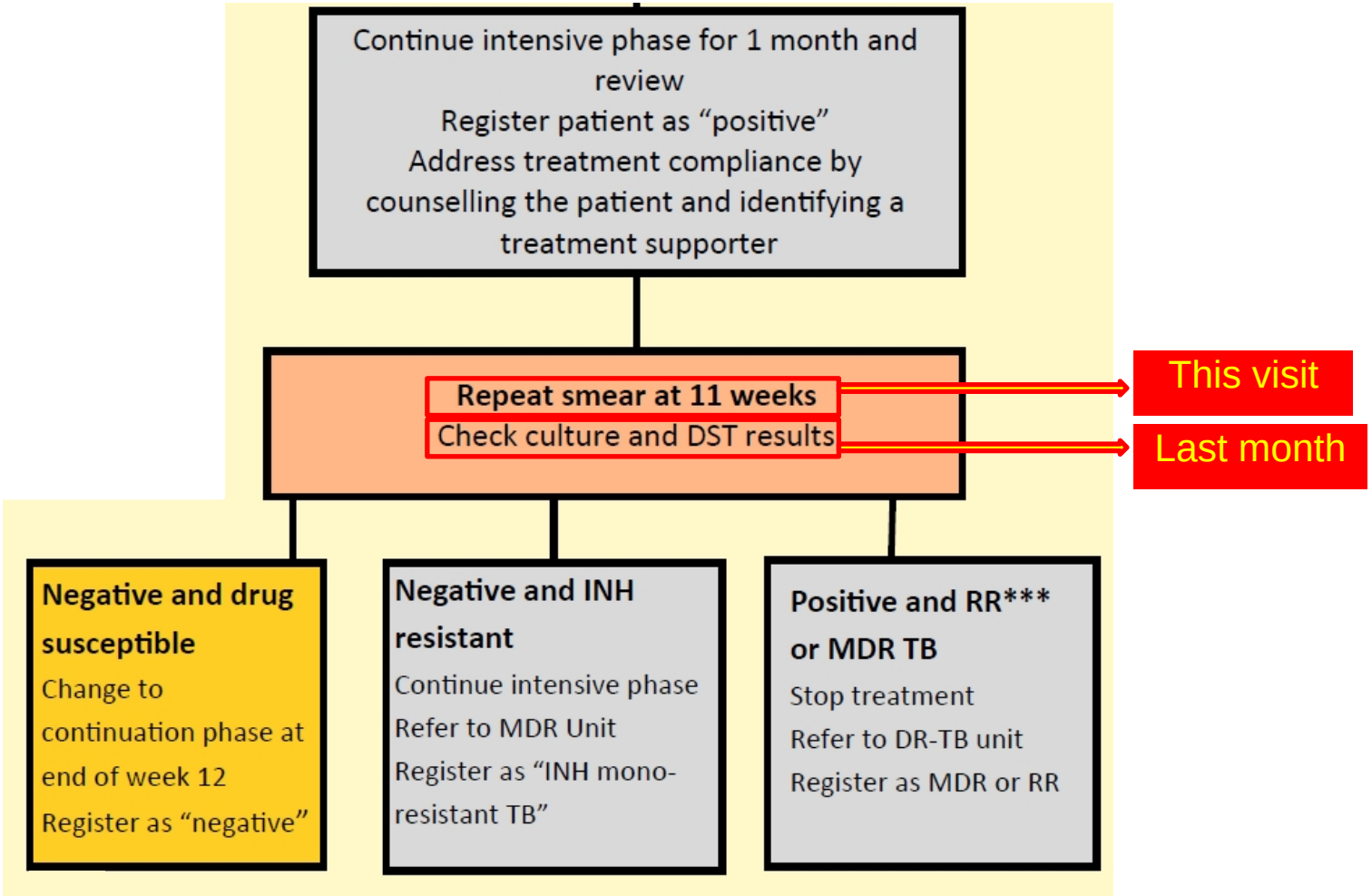
Potential causes of AFB non-conversion

Problem	Considerations & action
Correct Medication	check script – check drugs
Drug doses	Check dosage appropriate for weight
Adherence	Enhanced adherence counselling + treatment supporter – drug toxicites
Absorption	Check for symptoms, signs or laboratory markers of malabsorption
Drug-drug interactions	Check concomitant medications
Slow smear conversion	Clinical examination/chest X-ray – **extensive disease & cavitation (high bacillary load) can lead to delayed conversion**
Non-tuberculous mycobacteria (NTM)	Check baseline Xpert ultra, culture – repeat Xpert-ultra
Microscopy/lab issues	Non-viable organisms can still be observed on microscopy; false positive smears (reader error); clinic or lab specimen labelling errors (double check patient details)
Drug resistance	Check baseline Xpert ± culture/DST - **send spot sputum for Xpert ultra and/or culture/DST**

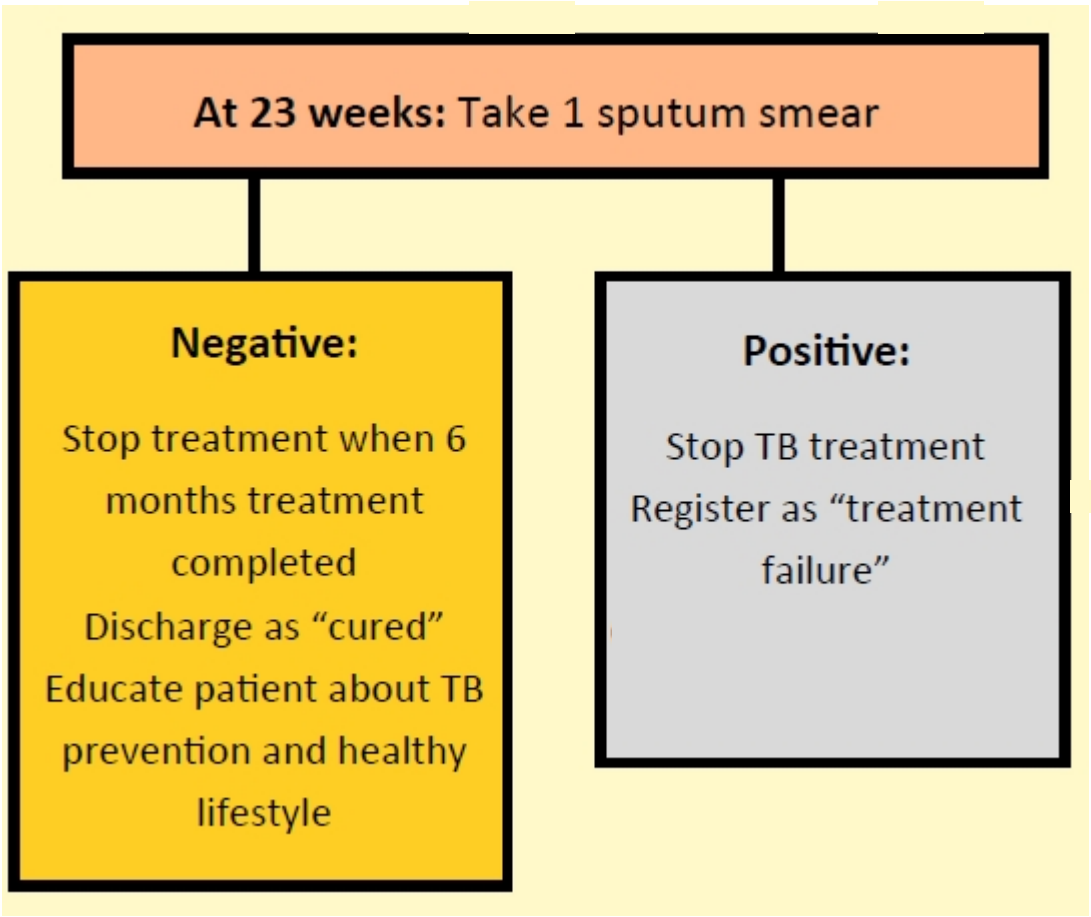
Monitoring on treatment: 8 weeks



8 Week smear positive: Monitoring at 11 weeks



Monitoring on treatment: 23 weeks



Re-evaluate for causes of non-conversion and proceed as in 2 months

Xpert Ultra:
LOD for MTB: 16 CFU
LOD for RIF sensitivity: 105 CFU!

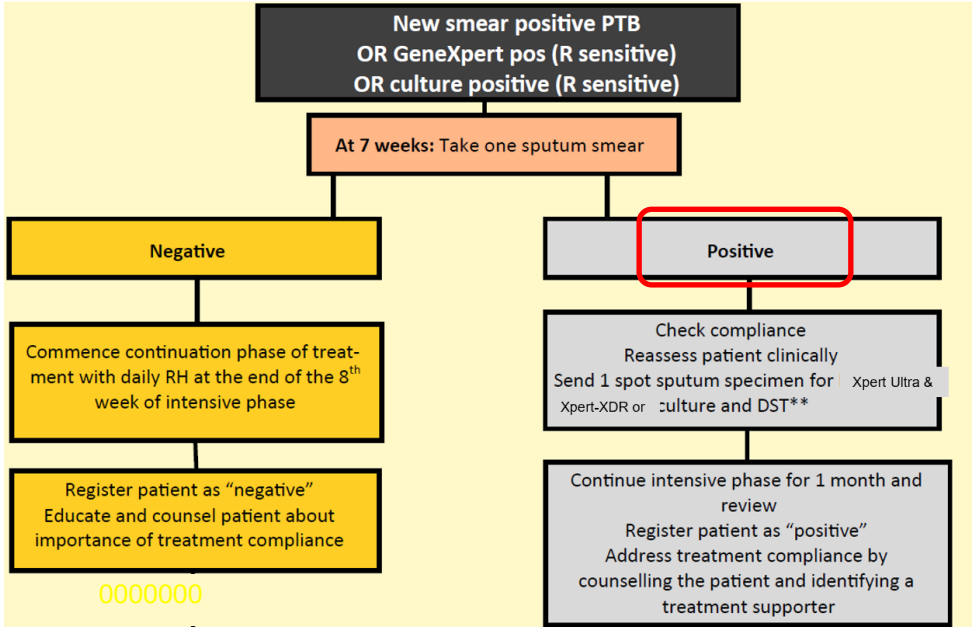
Rif resistance

"DR-TB Reflex DST Testing"
1. Smear
2. Culture
3. Phenotypic DST
4. Xpert MTB/XDR: INH/FQ/AG

Clinical Case

Clinical history

- 21-year-old HIV-infected female
- On ART for 3 months (TDF/3TC/EFV)
- Baseline CD4 220 cells/µL
- 1 month symptoms of TB
- GXP positive - rifampicin sensitive
- Baseline AFB smears +++
- **Referred to IDC for evaluation because 7-week smear positive**



Potential causes of AFB non-conversion

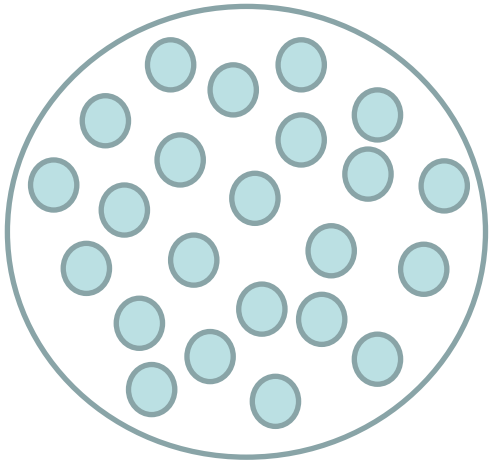
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Non-tuberculous mycobacteria (NTM)	Check baseline Xpert ultra, culture – repeat Xpert-ultra
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Next review - week 8 (1 week later)

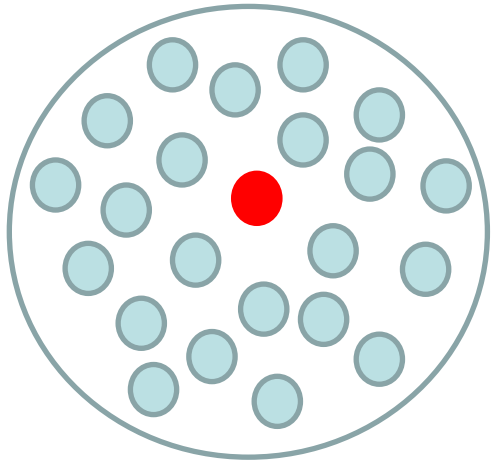
	Xpert ultra	Xpert MTB/XDR
Pre-treatment	RIF sensitive	-
2 months	**RIF resistant**	INH sensitive FQ sensitive

- Consequence of poor monitoring –4 drugs vs. 2 drugs
- How come rifampicin resistance?

Mixed strains & heteroresistance (baseline)



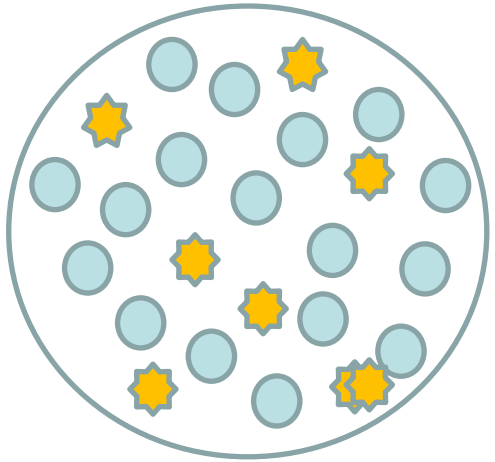
Single strain



Selection by drug pressure

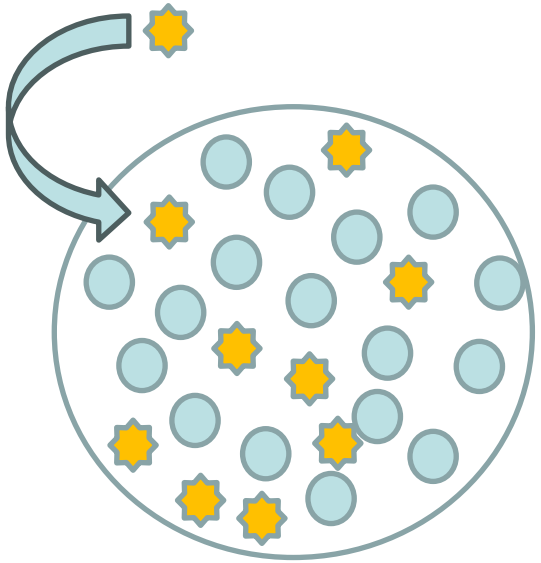
Mixed populations of resistant and susceptible bacilli but otherwise genetically identical strains

Secondary/acquired resistance



Mixed strains

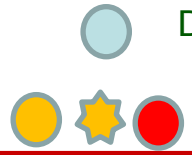
Mixed populations resistant plus susceptible



Exogenous Infection

Rifampicin resistant strain

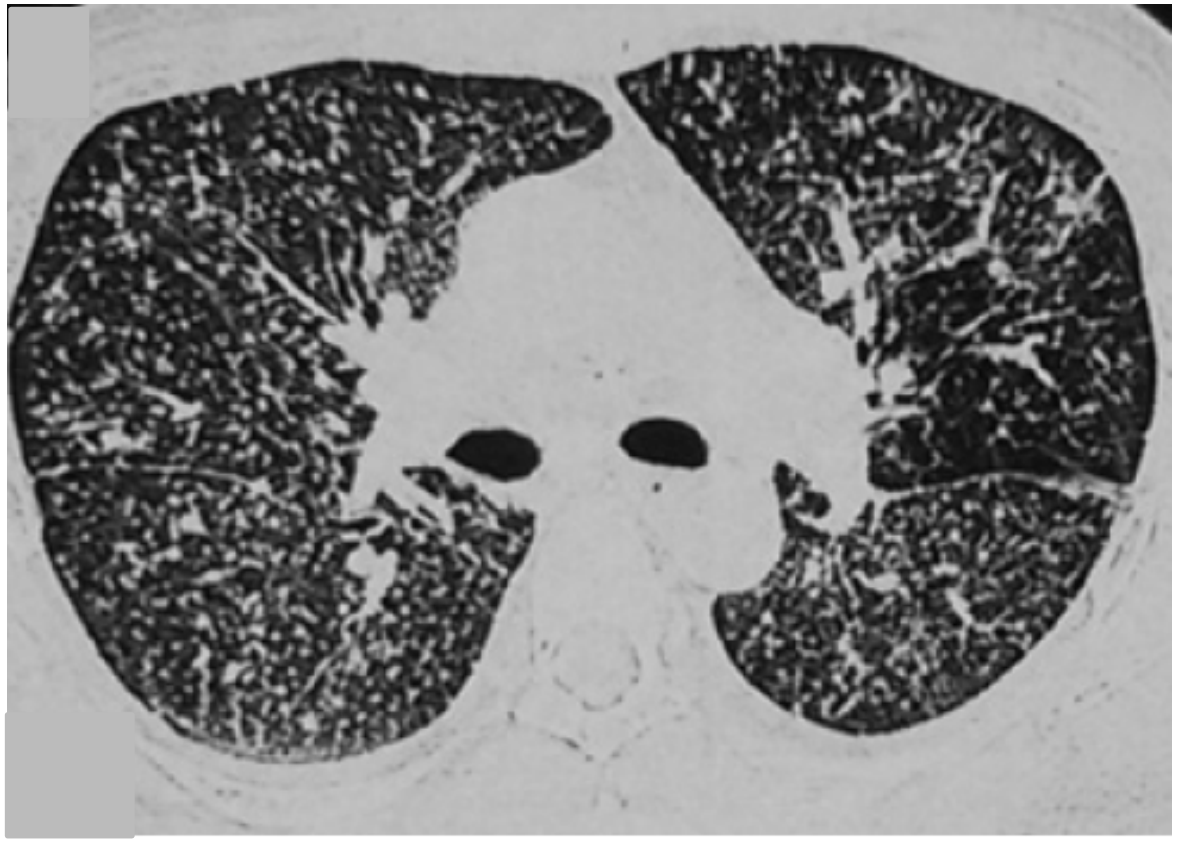
Primary resistance

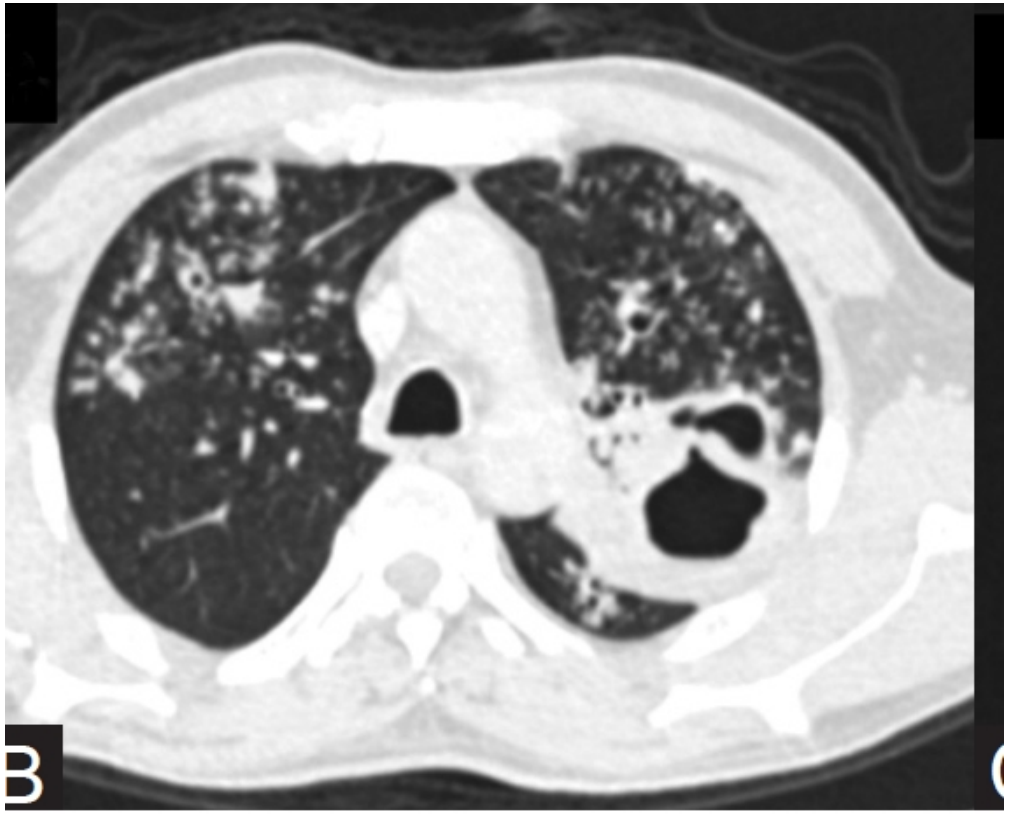


Drug-susceptible bacilli

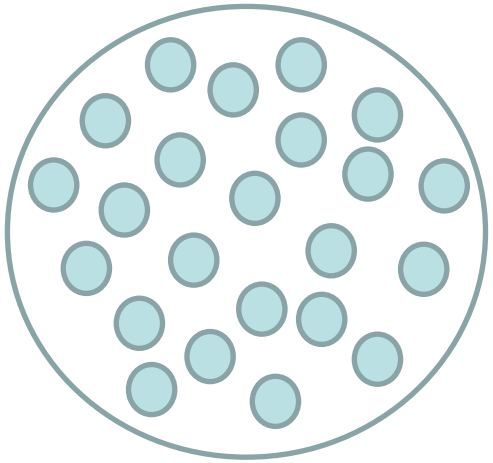
Drug-resistant bacilli

Penetration of drug at site of disease

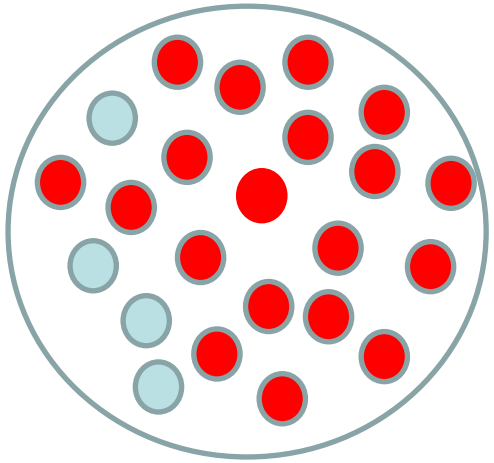




Mixed strains & heteroresistance (2/12)



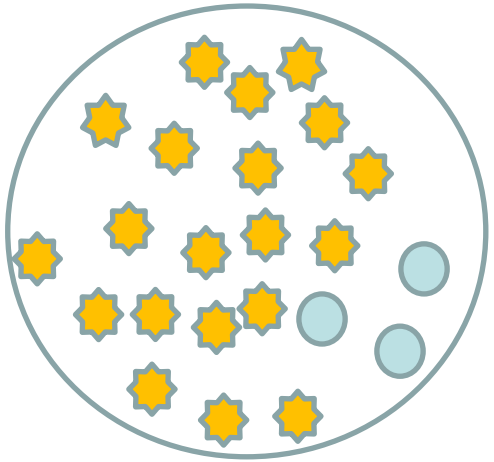
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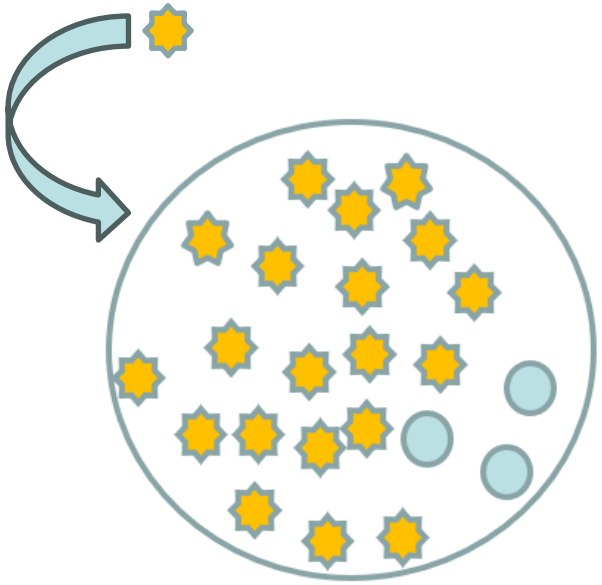
Mixed populations of resistant and susceptible bacilli but otherwise genetically identical strains

Secondary/acquired resistance



Mixed strains

Mixed populations resistant plus susceptible



Exogenous Infection

Rifampicin resistant strain

Primary resistance

Drug-susceptible bacilli

Drug-resistant bacilli

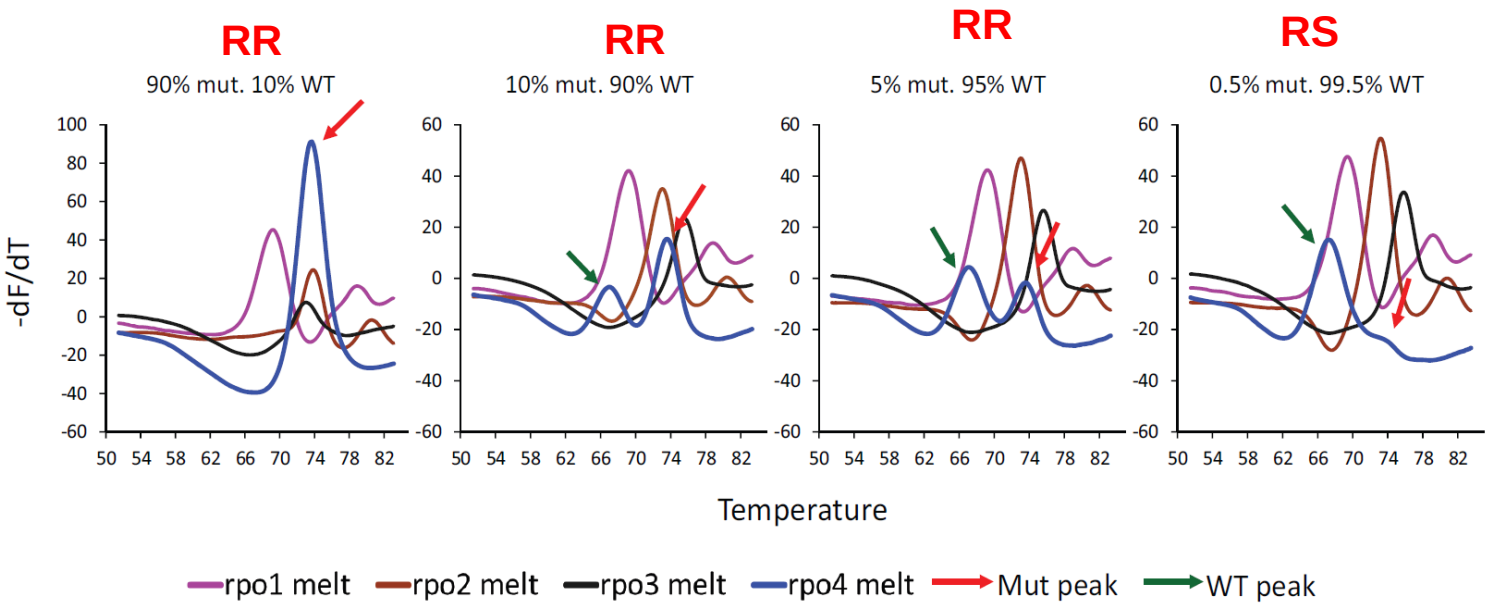
How common are mixed strains?

- Reactivation vs. re-infection (~50/50)
- Low vs High prevalence - force of infection 
- How come secondary resistance? Even with monotherapy? 
- Studies in South Africa have shown up to 20% of TB cases may have mixed strains
- Vigilance important – careful thoughtful monitoring- wise interpretation of diagnostics

AJRCCM 2004; 169: 610-4, AJRCCM 2005; 172: 636-42, J Clin Micro 2011; 49: 385-8

Xpert ultra performance with mixed strains

- All mutations not detected at the same sensitivity -
- In a **mixed** infection – if resistant mutation is in a less sensitive target (need more resistant organism to be detected) assay will “miss” resistant strain
- Depending on the resistance mutation- mixture of Mut : Wt can be 5%-40%.
- **If ultra detects rifampicin S and R - it outputs Rifampicin Resistance**



J Clin Micro 2010; 48: 2495-2501

Key learning points

- AHD is a serious problem despite widespread ART
- All HCW need to develop skills to diagnose AHD
- TB in AHD poses a huge diagnostic challenge
- Molecular tests are important rapid diagnostic tools for detection of resistance
- Algorithmic approach to monitoring is designed to detect patients not responding as expected with tools to pick drug resistance as early as possible.