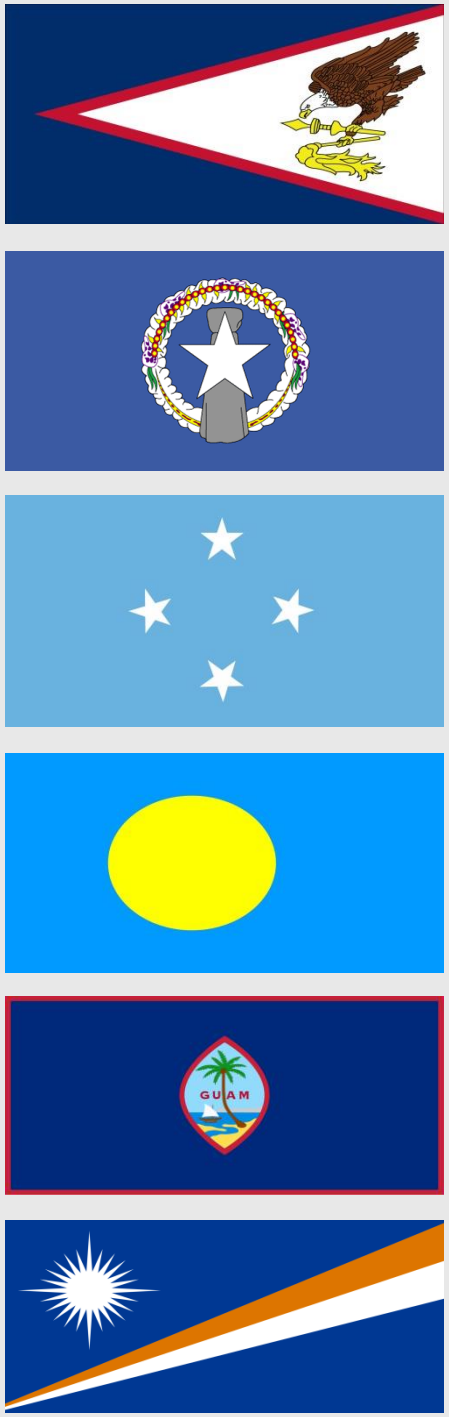
Patient Monitoring of TB Treatment



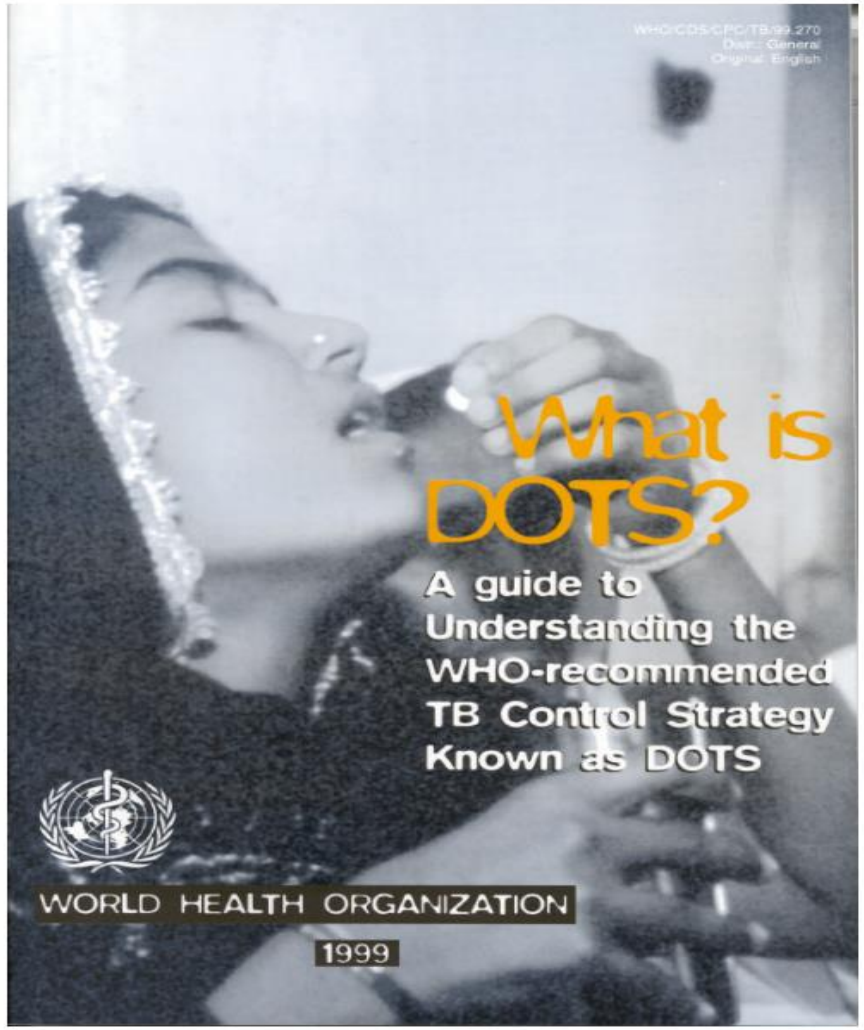
USAPI Regional TB Training 2024

Jake Nasa MD
Ebeye Hospital

Patient Monitoring of TB Treatment

Consists of four important areas:

1. Adherence- DOTS
2. Microbiologic/Bacteriologic monitoring
3. Drugs: side effects and adverse reactions
4. The patient's well-being



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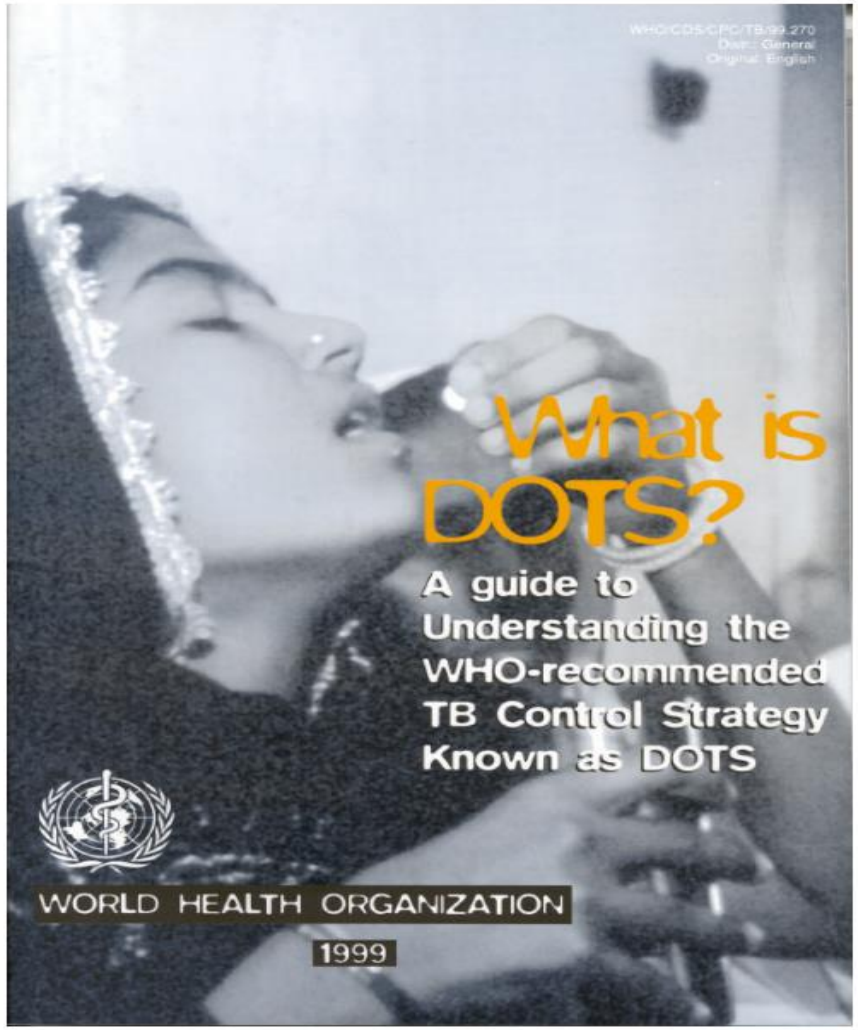


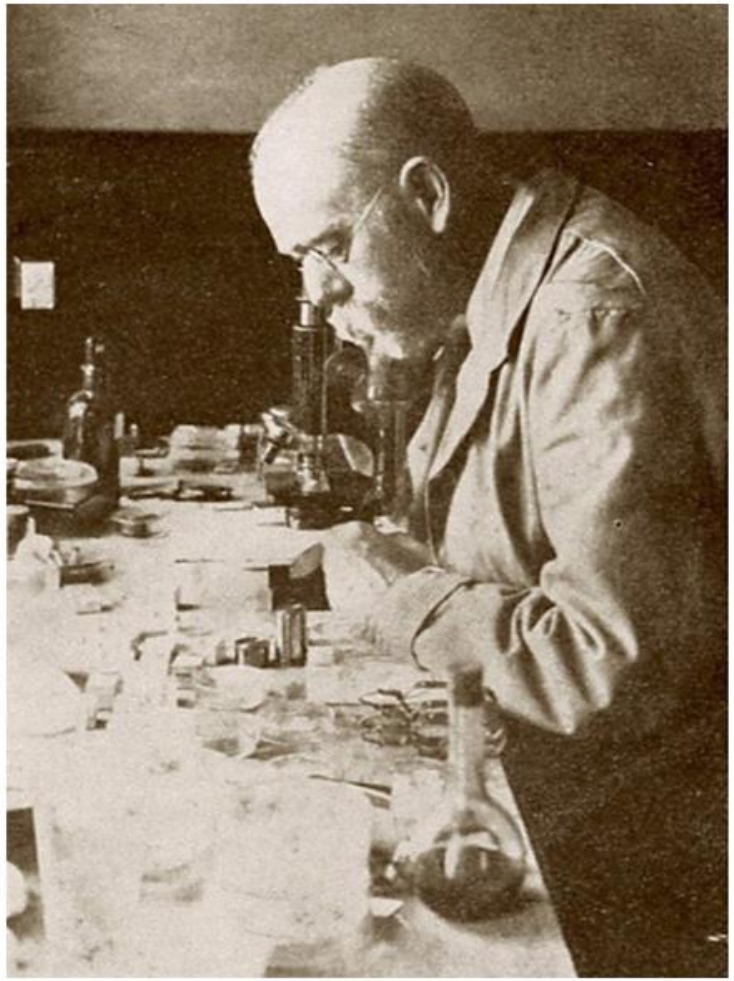
Adherence- DOTS

- The World Health Organization (WHO) emphasized the use of the word adherence instead of compliance in the late 1990's

- **Medication adherence** is defined by the World Health Organization as ***"the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider"*** Often use synonymously with compliance but they are not the same

- This shifts responsibility for successful treatment to public health programs and or the provider and not the patient

- The common method of assured adherence is supervised treatment or Directly Observed Therapy (DOT)



Robert Koch in his laboratory. He is using a microscope while surrounded by circular petri dishes

DOTS

- “Father of modern TB epidemiology "and the “Father of modern TB control“
- develop, pioneer, and demonstrate the "proof of principle" – adopted by WHO as DOTS
- "Styblo's rule", which stated that "an annual incidence of 50 sputum-smear-positive TB cases in a population of 100,000 generates an annual risk of infection of 1%" (the rule is no longer used to estimate prevalence of TB)
- responsible for instituting a systematic feedback method for analyzing outcomes of TB cases, known as the "cohort review" principle (CR)

Dr Karel Styblo
International Union Against Tuberculosis and Lung Disease (IUATLD) 1921-1998

DOT- not widely used in U.S. until 1993

Some advocate against it due to many factors including civil rights, socioeconomic status and cost

- “Moreover, there is now overwhelming conclusive evidence that at least 35% of patients will not take their medication and physicians are unable to identify which patients will and will not take their treatment. Therefore, failures and relapses are inevitable among the self-medicated.”

Sbarbaro JA (1988)

All patients should receive directly observed therapy in tuberculosis Am Rev Respir. Dis. vol. 138.

Dr. John Anthony Sbarbaro

(1936-2011)

The five pillars/principles of the WHO-recommended DOTs strategy are:

1. Political and administrative commitment
2. Case detection, primarily by microscopic examination of sputum of patients presenting to health facilities
3. Standardized short-course chemotherapy given under direct observation
4. Adequate supply of good-quality drugs
5. Systematic monitoring and accountability for every patient diagnosed

What is DOT for TB Treatment?

"Directly Observed Therapy (DOT) is the practice of observing a patient swallow his or her tuberculosis (TB) medications"

DOT means that a trained health care worker or other designated individual (Case Manager; Nurse) provides the prescribed TB drugs and watches the patient swallow every dose

When the patient is actually OBSERVED swallowing each and every dose

Reported daily all doses taken and/or missed

DOT is not:

-Given by family or friends
-Parent or guardian giving to child or adolescent
-Leaving medication at the home or bedside
-By means of pill-counts
-Allowing medical professionals to self-administer medications

National guidelines recommend DOT as part of the standard of care for TB treatment, and DOT is used by TB programs throughout the U.S. and around the world.

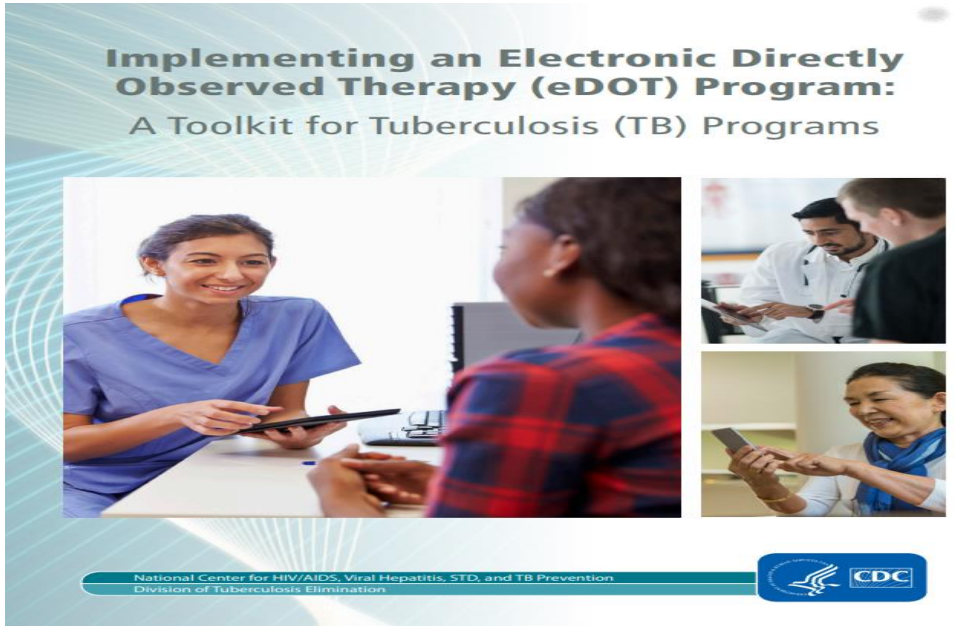
Treating Tuberculosis Using Video Directly Observed Therapy:

What is eDOT?

- eDOT is the use of electronic technologies to remotely monitor TB patients ingesting their medication, either in real-time or recorded. In addition to eDOT, this type of DOT is sometimes referred to as virtually observed therapy (VOT), mobile DOT (mDOT), remote DOT, video DOT
- (VDOT), and video-enhanced therapy (VET)

What Technologies Can be Used to Administer eDOT?

- Smartphone
- Tablet
- Computer with webcam



Benefits of eDOT

1. **vDOT can support treatment adherence and increase patient satisfaction**

- observe a patient ingesting TB medication through either live (synchronous) or recorded (asynchronous) videos
- provide patients greater flexibility and autonomy as they undergo TB treatment, which may improve patient satisfaction

2. vDOT can decrease expenses and save time for TB programs and patients

- Cost savings may include:
- Decreased time health care workers spend traveling for community-based DOT and
- Decreased vehicle maintenance and fuel costs.

3.vDOT can help TB programs conduct quality assurance activities

-Supervisory staff can participate in monitoring during live video sessions as part of quality assurance activities. Also, staff can rewatch recorded video sessions as needed to verify a patient ingested the TB medication

Preparing a patient to use vDOT

vDOT can begin at the start of outpatient treatment or shortly after

Preparing a TB patient to use vDOT, TB program staff should assess if the TB patient or the patient's caregiver has:

•Knowledge of the prescribed medication regimen and potential side effects

•Awareness of how to respond to and report side effects

•Capacity to take (or administer) medications

•Regular access to a video-enabled phone, tablet, or computer and the internet

•Plans to change their phone or internet service provider while on vDOT

•A device and current cellphone data plan that supports the vDOT software application

•Concerns about paying monthly phone or internet costs related to vDOT

Addressing potential challenges

- TB programs implementing vDOT might experience challenges while using vDOT software

Technical challenges may include:

- Software-specific malfunctions
- Internet connection issues
- Patient's audio or video not working
- Poor quality recordings
- Inadequate memory on the device
- unable to remember how to use the software application, no phone service

Challenges taking the medication

- establish procedures to confirm that the patient ingests the prescribed medicine
- Some patients might hide pills in their mouth and spit them out later, hide medicine in clothing, or vomit the pills. If a patient does not adhere to treatment, treatment difficulties can arise

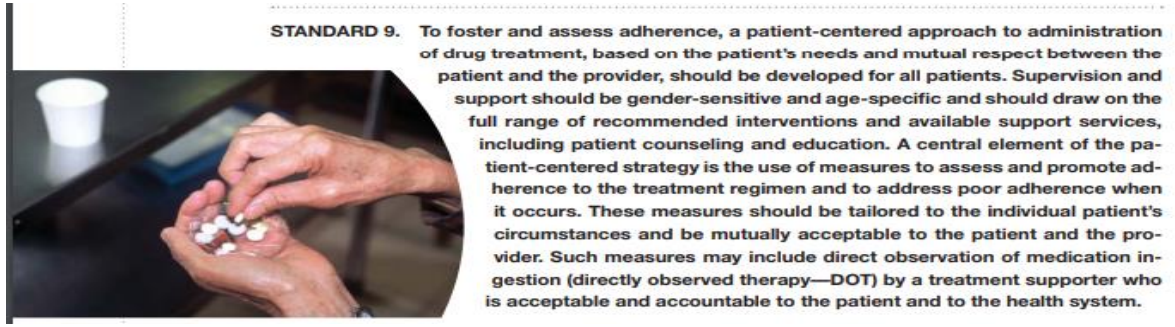
Signs that a patient might not have ingested their medication completely include:

- A patient stopping videos immediately after putting pills in their mouth
- A patient spending time out of camera view or being partially visible on screen, or
- A patient covering their mouth while ingesting medications

Potential solutions include:

- Watching the patient continuously until he or she swallows the medicine and
- Asking the patient to show inside their mouth while moving their tongue from side-to-side

Adherence Strategy



- **Inadequate treatment leads to treatment failure, relapse, continued transmission and drug resistance**.
- The provider is responsible, and the patient must be included in any strategy
- Good patient education and agreement should be included
- Incentives and enablers should be used to enhance adherence
- Legal actions (following due process, from least to most restriction) can sometimes be necessary to ensure public safety

Patient Monitoring of TB Treatment

Consists of four important areas:

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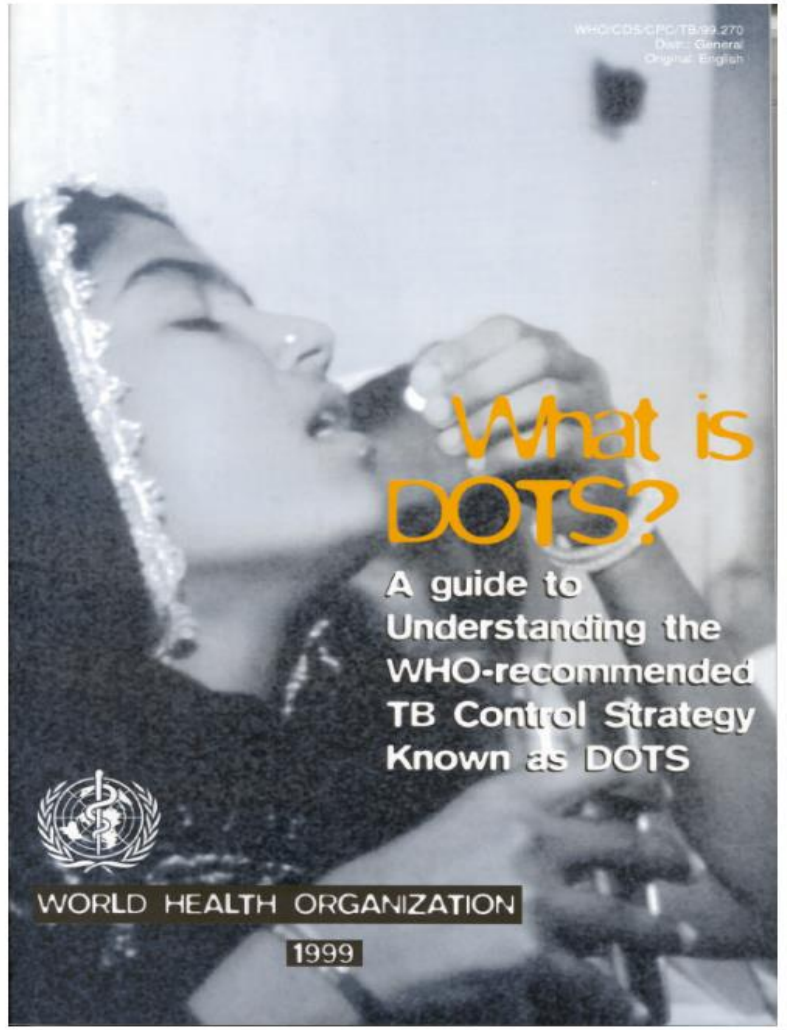
2. **Microbiologic/Bacteriologic monitoring**
3. Drugs: side effects and adverse reactions
4. The patient's well-being



Microbiologic/Bacteriologic Monitoring

To assess treatment response in patients with:
PTB: bacteriological tests are essential.
EPTB: evaluation is based on clinical evolution. However, bacteriological tests are required if patients also develop PTB.

A. Baseline tests

Baseline tests are those performed on specimens collected just prior to treatment initiation which include:

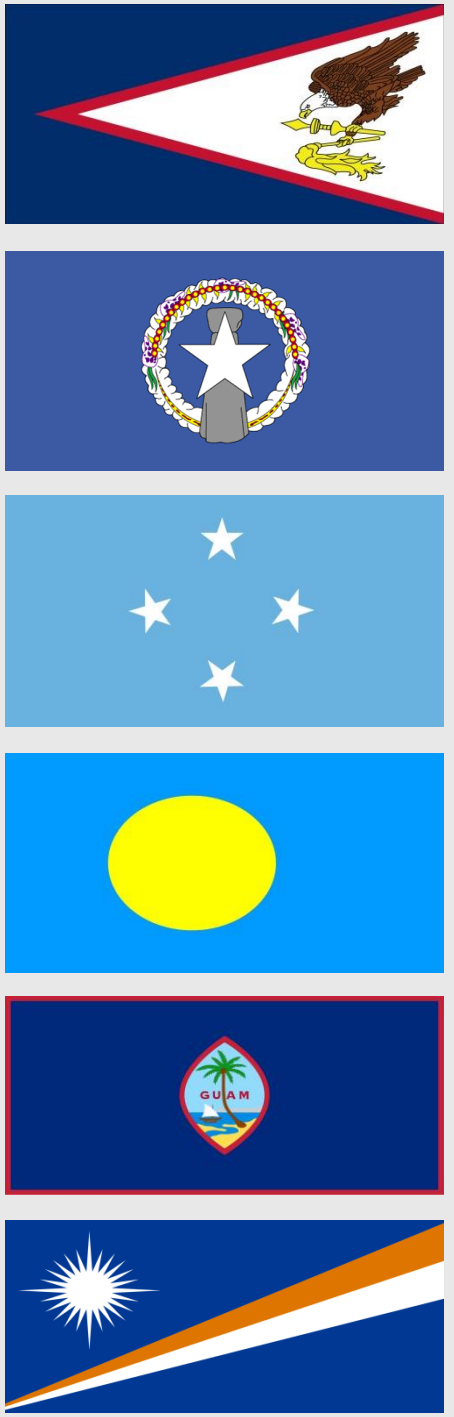
1. Rapid molecular tests (RMTs) for detection of M. tuberculosis and rifampicin & isoniazid resistance (MTB Rif assay-Genxpert)
2. Smear microscopy to monitor treatment progress
3. Culture and phenotypic DST (pDST) when indicated

B. Follow-up tests

1. Smear microscopy
2. Microscopy should be performed every 2 months until treatment completion

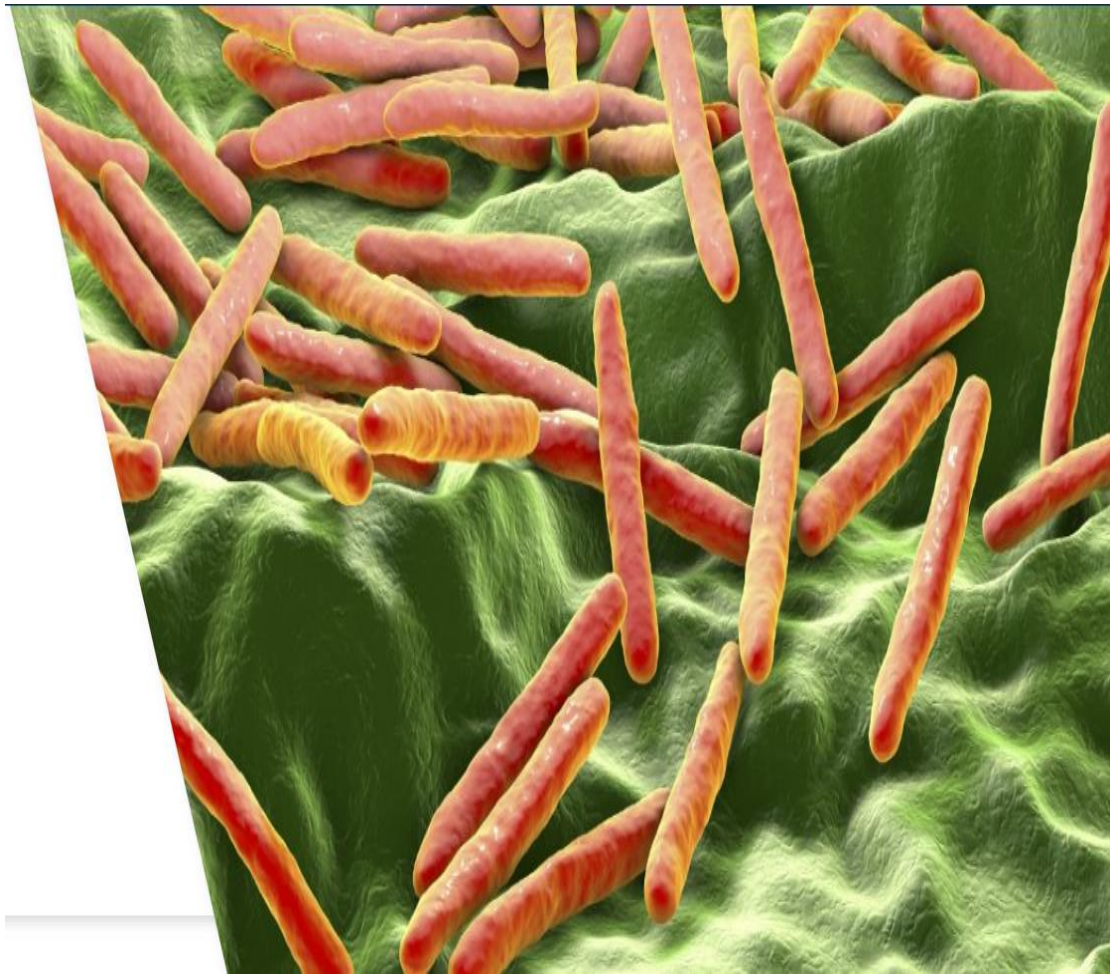
If treatment is effective, microscopy at Month 2, 4 and 6 should be negative

SPUTUM

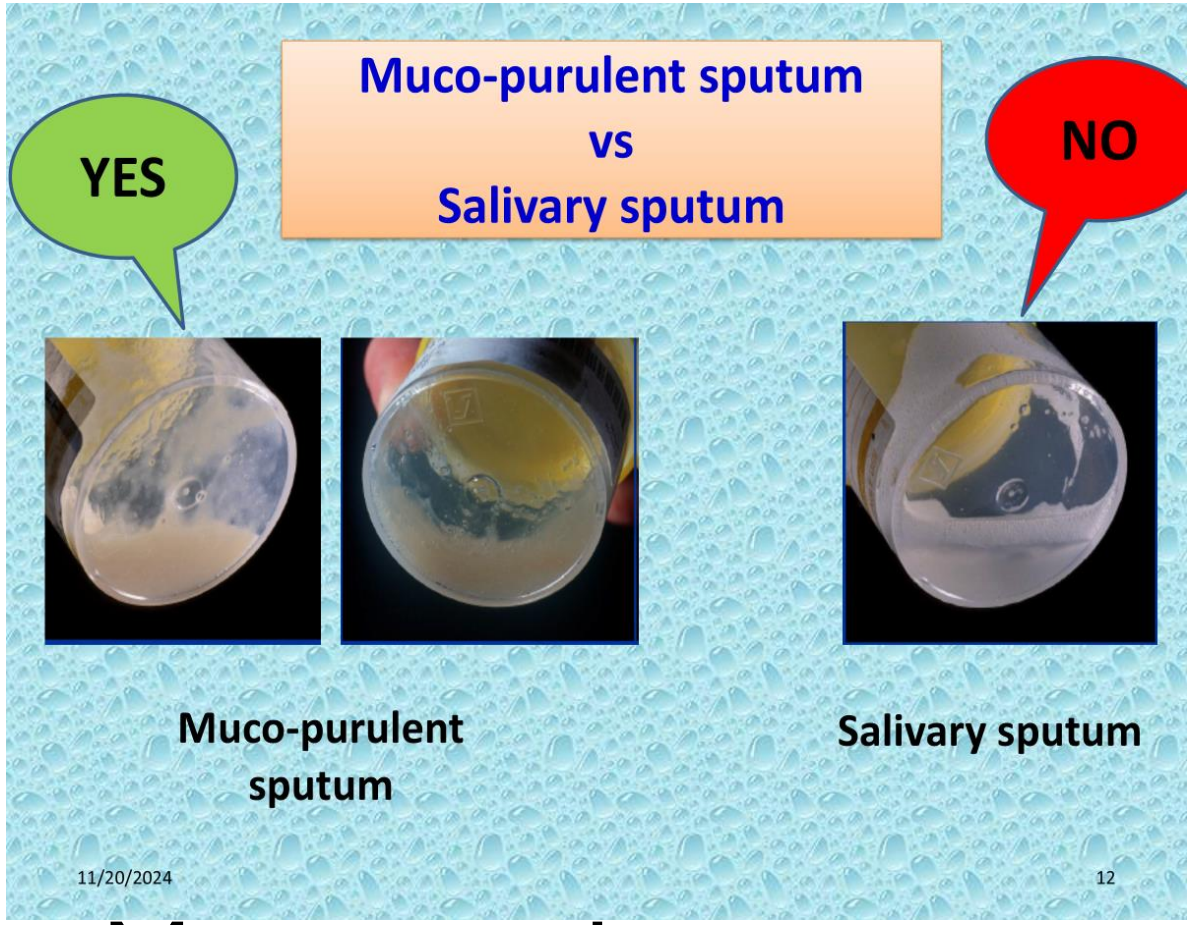


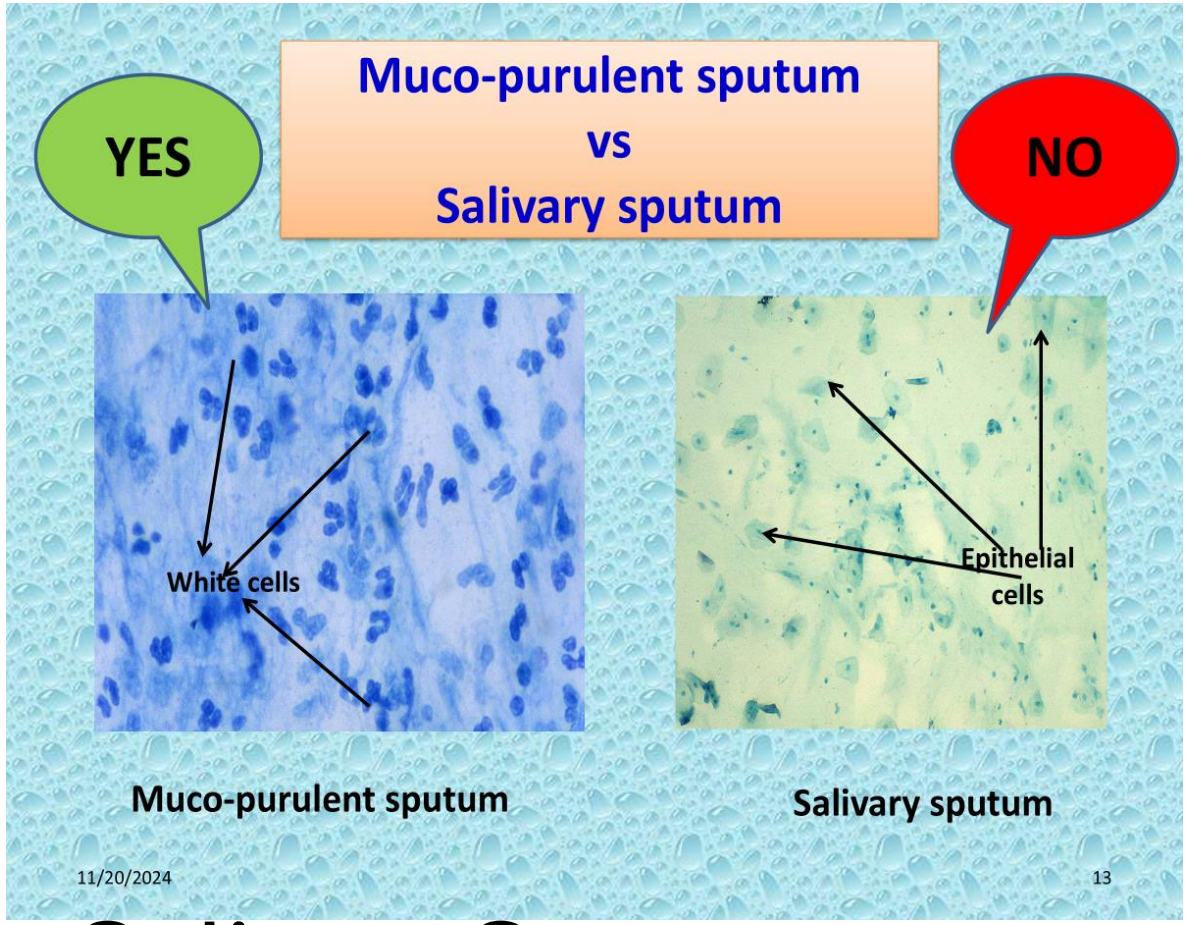
What is it about Sputum?

- Sputum contains the bacteria which cause Tuberculosis (TB).
- Important indicator of infectiousness.
- Provides information on how treatment is going.
- The collection and monitoring of sputa is a critical aspect of TB case management.



Collection of Sputum





Mucopurulent sputum vs Salivary Sputum

How to Get a Good Specimen

- Use “huff cough” to avoid sore throat, triggering vomiting.
- Get first morning specimen, when lung secretions have pooled overnight.
- Use nebulization if necessary to increase fluid in the airway and ease clearance of sputum (remember to label the sputum as “induced” if you do administer a nebulization treatment).

Microbiologic/Bacteriologic Monitoring

Main issues for collection of quality sputum in the USAPI

1. High saliva content
2. Inadequate volume (< 3mL)
3. Over 10 days storage of sputum specimens before shipping to DLS
4. Contaminated sputum from betel nut chewers
5. Incomplete TB lab requisition forms
6. Delivery of leaking sputum specimens to the laboratory
7. Mislabeled specimens
8. Collection of sputum in inappropriate specimen containers
9. Collection of sputum in non-sterile containers
10. Un-refrigerated sputum specimen after collection
11. Non-submission of 3 specimens for diagnostic/suspected TB patients

Microbiologic/Bacteriologic Monitoring

Impact of these issues on TB testing & results

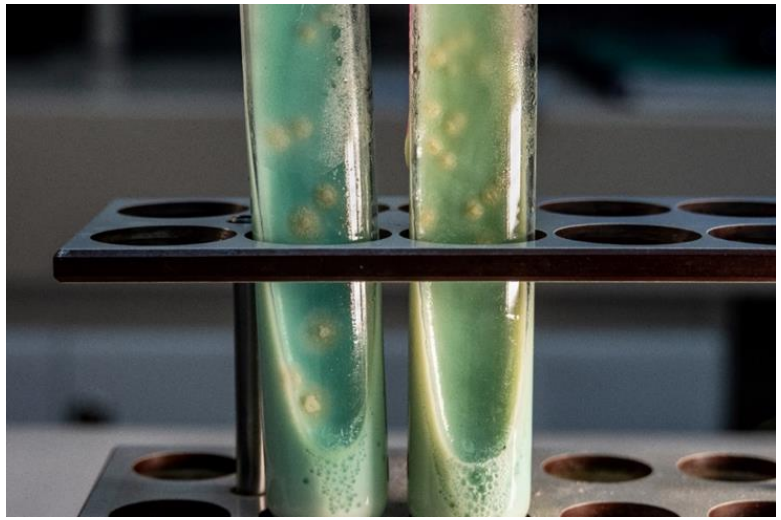
1. High saliva content	Low chances of detecting the AFBs
2. Inadequate volume (< 5mL)	Volume inadequate to do several other tests at DLS
3. Over 10 days storage of sputum specimens before shipping to DLS	Contaminants overgrowth increases, AFB growth viability decreases
4. Contaminated sputum from betel nut chewers	Contaminants overgrowth increases, AFB growth viability decreases
5. Incompletely filled TB lab requisition forms	Specimen will be rejected and not processed

Microbiologic/Bacteriologic Monitoring

Impact of these issues on TB testing & results

6. Delivery of leaking sputum specimens to the laboratory	Specimen will be rejected
7. Mislabeled specimens	Specimen will be rejected
8. Collection of sputum in inappropriate specimen containers	Transfer of sputum may leave some sputum in the old container, exposure to contaminants increased
9. Collection of sputum in non-sterile containers	
10. Un-refrigerated sputum specimen after collection	Other bacterial contaminants may overgrow AFB growth
11. Submission of 1-2 specimen	Low chances of recovery of Mtb

Sputum Culture



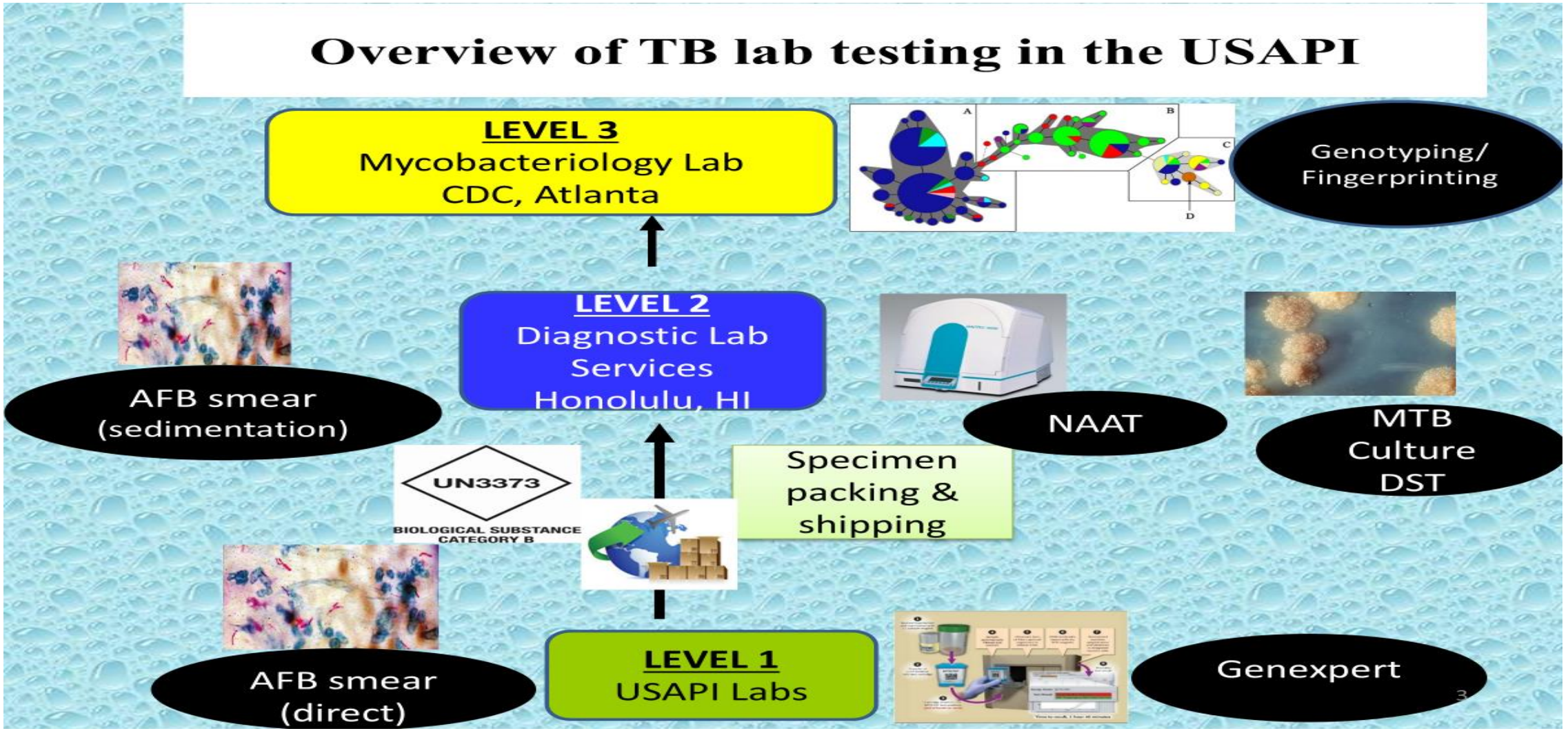
Determines Treatment Success

- Culture is when AFB grow in solid or liquid media.
- It can take eight weeks or longer for a positive sputum culture.
- Culture-conversion is when AFB no longer grow in liquid or solid media (measured from the date of collection).
- Negative smears can still contain AFB that are “dead bugs”.

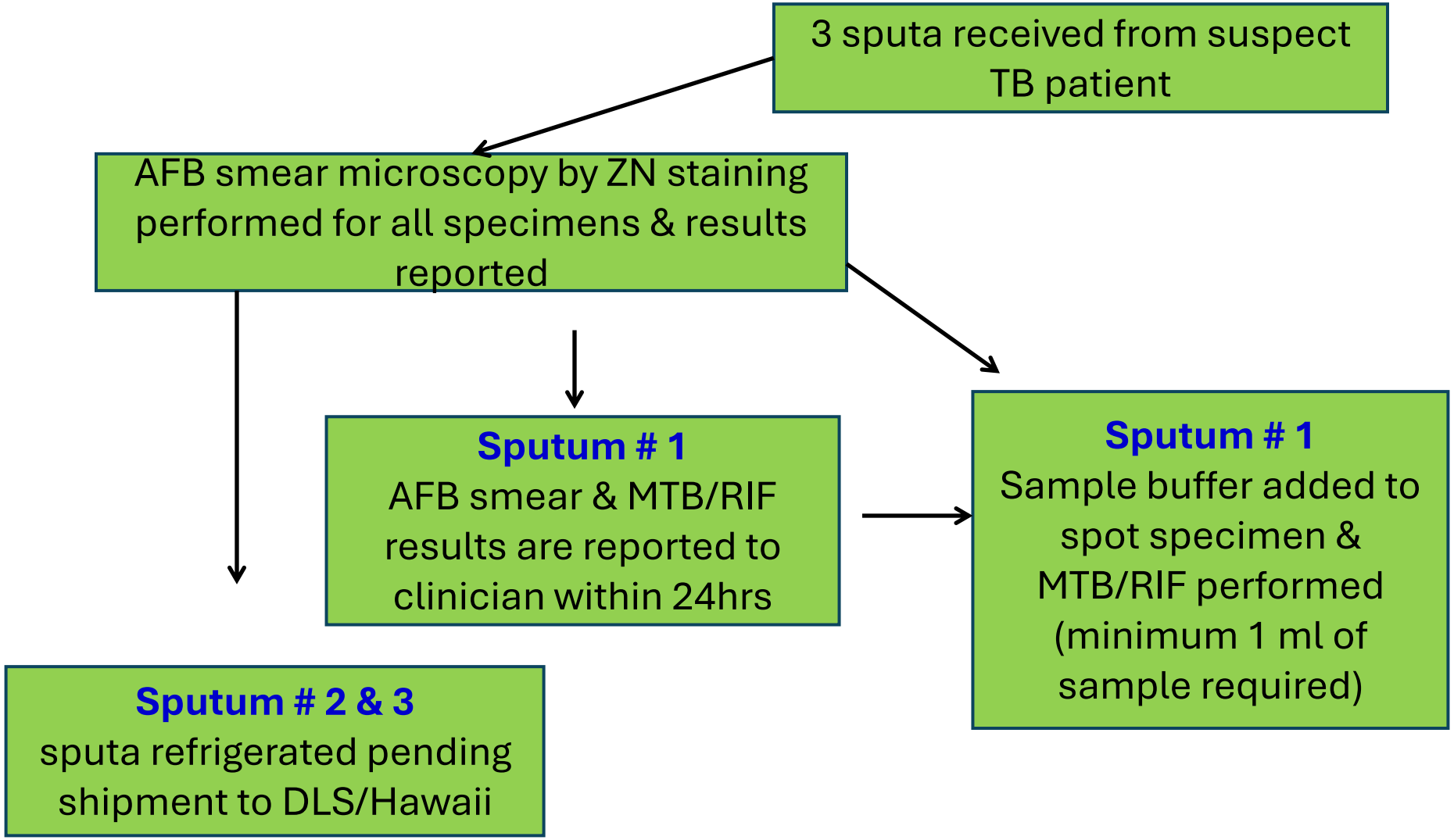
Treatment Failure

- **Continuously or recurrent sputum culture-positive after four months of treatment.**
- Evaluate carefully if persistently positive cultures after three months.
- Reasons include diabetes, malabsorption, nonadherence, unrecognized drug resistance

Microbiologic/Bacteriologic Monitoring



Laboratory Testing Algorithm Suspect TB Patients



Note: Only specimen # 1 is tested by GenXpert and others are referred to DLS.

Lab Request Form for TB Smear Microscopy and Xpert MTB/RIF Form (version Nov 2018)

Laboratory Request Form for TB Smear Microscopy and Xpert MTB/RIF Assay

Date Requested _____

Please complete one (1) form for each specimen submitted.

Patient Information

Name _____ Medical Record No _____

Age _____ Date of Birth _____ Sex: M☐ F☐

Complete address _____ Phone No.1 _____

_____ Phone No.2 _____

Patient's Emergency Contact Information

Name of Contact _____

Complete address _____ Phone No.1 _____

_____ Phone No.2 _____

General Treatment Information

Health Unit _____ Patient's TB No _____

Reason for Examination Diagnosis☐ Follow-up: Weekly☐ Monthly☐ _____ (indicate month)

TB Suspicion (diagnosis only) High ☐ Low ☐

Doctor _____

Specimen Collection Details

Date of Collection _____ Time of Collection _____

Specimen Type Sputum☐ Gastric Lavage☐ Other☐ (specify)_____

Number in series (circle the number) Specimen [1] [2] [3]

Collected by _____

RESULTS (to be completed by laboratory)

Lab Serial No._____ Date Received _____

LIS No.		Spec Type[1]	Date of Collection	Date of Exam	Volume of Specimen	Visual Appearance[2]	AFB Smear Result[3]	Xpert MTB/RIF Result
	1							MTB : [ ] DETECTED [ ] NOT DETECTED RIF –R: [ ] DETECTED [ ] NOT DETECTED [ ] INDETERMINATE
	2							
	3							

1 S = Sputum O = Other

2 M = Mucoid B = Blood-stained S = Salivary P=Purulent MP=Mucopurulent

3 Grading system for AFB smear result

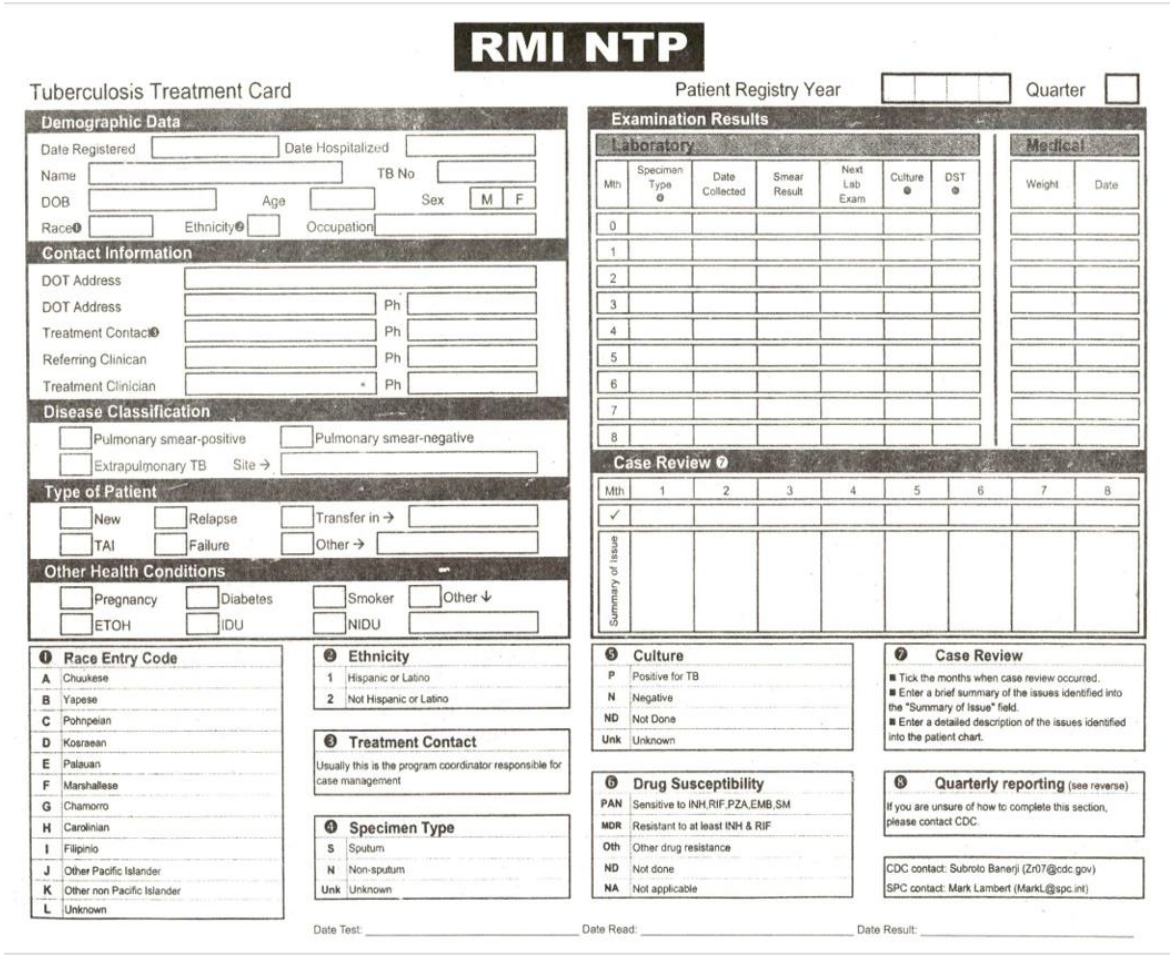
Neg	No AFB seen in at least 100 fields	Actual AFB #	1 – 9 AFB per 100 fields
1+	10 – 99 AFB per 100 fields	2+	1 – 10 AFB per field in at least 50 fields
3+	>10 AFB in at least 20 fields		

Comments _____

Date _____ Examined by (Signature) _____

Rev.11.2018/AUL/RLC/ltn

TB Treatment Card



RMI NTP

Tuberculosis Treatment Card

Patient Registry Year ____ Quarter ____

Demographic Data

Date Registered ____ Date Hospitalized ____

Name ____ TB No ____

DOB ____ Age ____ Sex M F

Race ❶ ____ Ethnicity ❷ ____ Occupation ____

Contact Information

DOT Address ____

DOT Address ____ Ph ____

Treatment Contact ❸ ____ Ph ____

Referring Clinician ____ Ph ____

Treatment Clinician ____ Ph ____

Disease Classification

☐ Pulmonary smear-positive ☐ Pulmonary smear-negative

☐ Extrapulmonary TB Site → ____

Type of Patient

☐ New ☐ Relapse ☐ Transfer in → ____

☐ TAI ☐ Failure ☐ Other → ____

Other Health Conditions

☐ Pregnancy ☐ Diabetes ☐ Smoker ☐ Other ↓

☐ ETOH ☐ IDU ☐ NIDU ____

Examination Results

Laboratory

Mth	Specimen Type ❹	Date Collected	Smear Result	Next Lab Exam	Culture ❺	DST ❻
0						
1						
2						
3						
4						
5						
6						
7						
8						

Medical

Weight	Date

Case Review ❼

Mth	1	2	3	4	5	6	7	8
✓								
Summary of issue								

❶ Race Entry Code

A	Chuukese
B	Yapese
C	Pohnpeian
D	Kosraean
E	Palauan
F	Marshallese
G	Chamorro
H	Carolinian
I	Filipinio
J	Other Pacific Islander
K	Other non Pacific Islander
L	Unknown

❷ Ethnicity

1	Hispanic or Latino
2	Not Hispanic or Latino

❸ Treatment Contact

Usually this is the program coordinator responsible for case management

❹ Specimen Type

S	Sputum
N	Non-sputum
Unk	Unknown

❺ Culture

P	Positive for TB
N	Negative
ND	Not Done
Unk	Unknown

❻ Drug Susceptibility

PAN	Sensitive to INH,RIF,PZA,EMB,SM
MDR	Resistant to at least INH & RIF
Oth	Other drug resistance
ND	Not done
NA	Not applicable

❼ Case Review

- Tick the months when case review occurred.
- Enter a brief summary of the issues identified into the "Summary of Issue" field.
- Enter a detailed description of the issues identified into the patient chart.

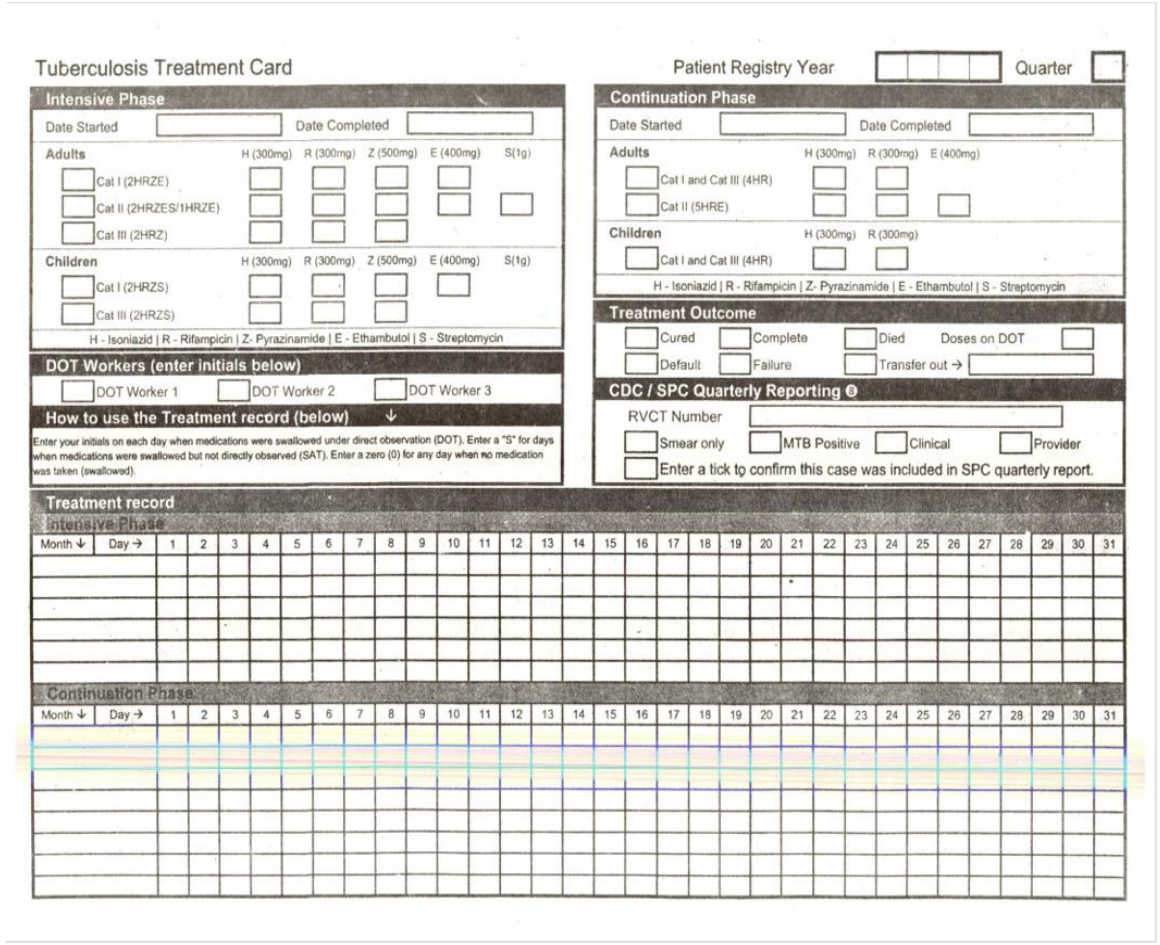
❽ Quarterly reporting (see reverse)

If you are unsure of how to complete this section, please contact CDC.

CDC contact: Subroto Banerji (Zr07@cdc.gov)

SPC contact: Mark Lambert (MarkL@spc.int)

Date Test: ____ Date Read: ____ Date Result: ____



Tuberculosis Treatment Card

Patient Registry Year ____ Quarter ____

Intensive Phase

Date Started ____ Date Completed ____

Adults	H (300mg)	R (300mg)	Z (500mg)	E (400mg)	S(1g)
☐ Cat I (2HRZE)					
☐ Cat II (2HRZES/1HRZE)					
☐ Cat III (2HRZ)					

Children	H (300mg)	R (300mg)	Z (500mg)	E (400mg)	S(1g)
☐ Cat I (2HRZS)					
☐ Cat III (2HRZS)					

H - Isoniazid | R - Rifampicin | Z- Pyrazinamide | E - Ethambutol | S - Streptomycin

Continuation Phase

Date Started ____ Date Completed ____

Adults	H (300mg)	R (300mg)	E (400mg)
☐ Cat I and Cat III (4HR)			
☐ Cat II (5HRE)			

Children	H (300mg)	R (300mg)
☐ Cat I and Cat III (4HR)		

H - Isoniazid | R - Rifampicin | Z- Pyrazinamide | E - Ethambutol | S - Streptomycin

DOT Workers (enter initials below)

☐ DOT Worker 1 ☐ DOT Worker 2 ☐ DOT Worker 3

How to use the Treatment record (below) ↓

Enter your initials on each day when medications were swallowed under direct observation (DOT). Enter a "S" for days when medications were swallowed but not directly observed (SAT). Enter a zero (0) for any day when no medication was taken (swallowed).

Treatment Outcome

☐ Cured ☐ Complete ☐ Died Doses on DOT ____

☐ Default ☐ Failure ☐ Transfer out → ____

CDC / SPC Quarterly Reporting ❽

RVCT Number ____

☐ Smear only ☐ MTB Positive ☐ Clinical ☐ Provider

☐ Enter a tick to confirm this case was included in SPC quarterly report.

Treatment record

Intensive Phase

Month ↓ / Day →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Continuation Phase

Month ↓ / Day →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Other Patient Monitoring Assessment

I. Clinical Visits

A. Baseline assessment

Assessment includes:

-Symptoms of TB and their severity (cough, fever, night sweats, weight loss, shortness of breath, ability to perform daily activities); vital signs and weight

-Comorbidities and other risk factors for adverse effects requiring monitoring adaptation.

-Psychological assessment

B. Follow-up visits

Each follow-up visit, assessment includes:

- Clinical progress, vital signs and weight. Dosages should be adjusted to the weight if necessary.
- Occurrence of adverse effects, Adherence to treatment , Psychological assessment.
- **Frequency of visits depends on the patient's clinical condition and evolution**:

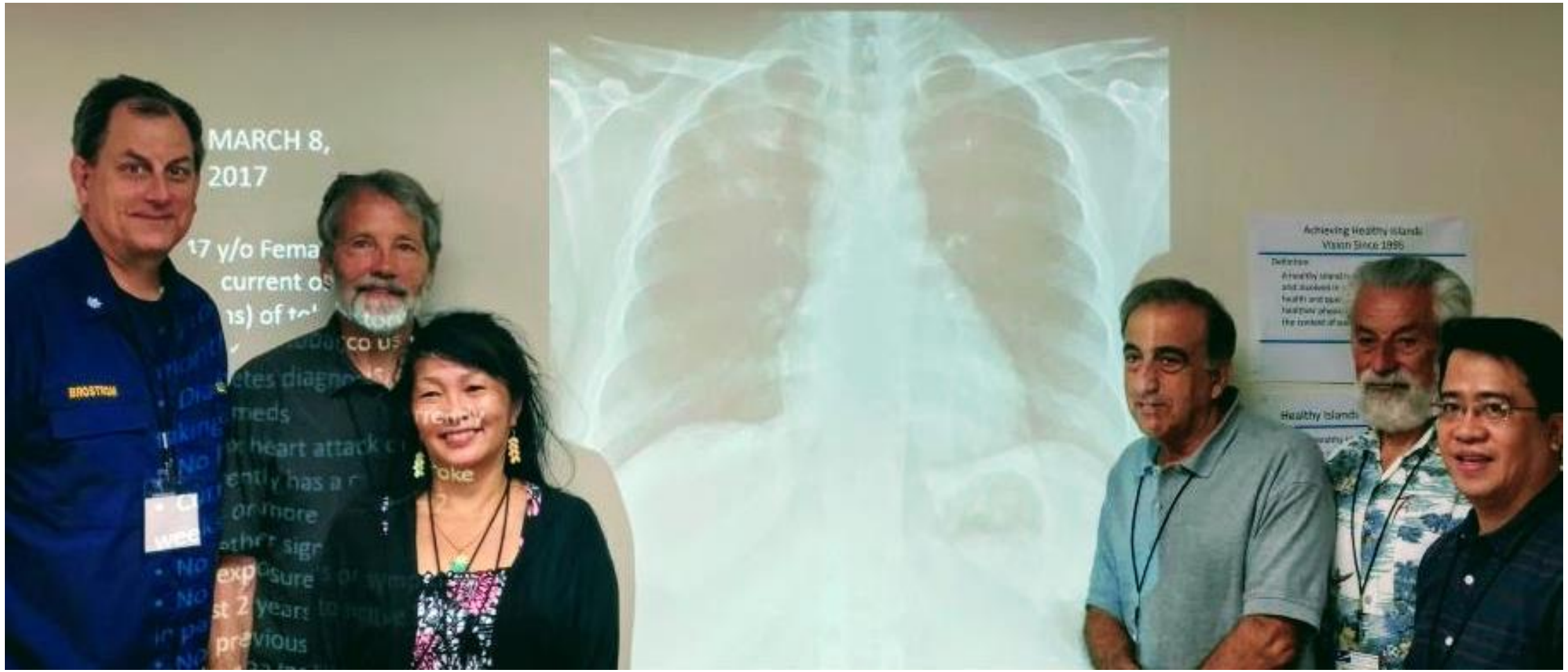
1. A visit every other week for the first month, then once a month if there is no particular problem.
2. Additional visits may be required in case of comorbidities, severe or multiple adverse effects, pregnancy, etc.
3. **Visits should coincide with bacteriological examinations and other investigations when possible**.
4. The clinician should take into account any information and concerns regarding treatment tolerance and adherence reported by the patient or the team responsible for the patient's follow-up and support.

Other Patient Monitoring Assessment

II. Biological Test-Baseline and during treatment Blood test
III. Radiography

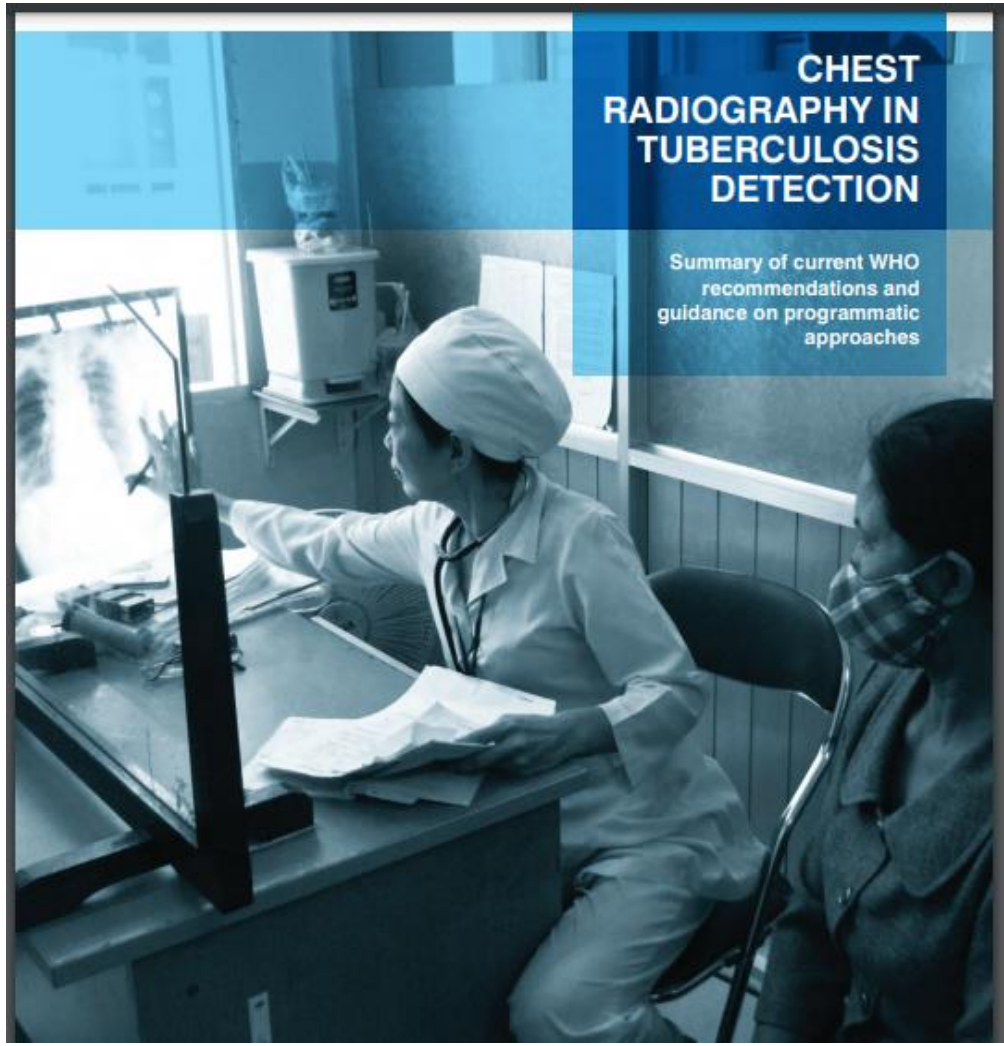
Full blood count- CBC	HIV-infected patients on rifabutin or zidovudine (AZT), at baseline, then once a month for the first 2 months, then if indicated.
Liver function tests- Complete Metabolic Panel (ALT,AST)	Patients with pre-existing hepatic disease, at baseline, then once a month.
Serum Creatinine- BUN	Patients with renal insufficiency at baseline, then if indicated.
HbA1C and/or blood glucose level (FBS, RBS)	All patients, at baseline, to detect diabetes. If diabetes is detected, monitor according to standard protocols.
HIV, hepatitis B and C	For patients with undocumented HIV, hepatitis B and C status; HIV test every 6 months in high HIV prevalence areas. Tests can be repeated in case of recent exposure.
CD4 count and viral load	HIV-infected patients: at baseline, then every 6 months.

Radiologic Examination and Monitoring:



Radiologic Examination and Monitoring:

- Good for Diagnosis (not as good for extensive treatment monitoring) for Pulmonary TB
- Recommended to have follow-up radiograph at 2 months into treatment (not a bad idea to assess treatment progress) and at the end of treatment
- **Not necessarily the indicator of treatment success because it can take a long time for the lungs to heal and look more normal**
- Used post-treatment for MDR-TB (6-months, 12-months, 24-months)
- Don’t panic if it looks worse at the beginning (happens due to immune reconstitution) but worry if it is worse at the end of treatment



Radiologic Examination and Monitoring:

- There is no comprehensive WHO guidance on using CXR in triaging individuals with respiratory symptoms
- In the absence of such guidance **where it is available and feasible in the outpatient primary care setting, CXR can be used as an effective triage test for those seeking care for respiratory complaints**.
- CXR is a sensitive tool for identifying TB, meaning that it **identifies most people with a high likelihood of having the disease,** while correctly ruling out TB in most persons when the X-ray is read to look for any abnormality consistent with TB
- CXR can help identify other pulmonary conditions, such as lung cancer and occupational lung diseases like silicosis, as well as other intrathoracic diseases that require further diagnostic evaluation

Radiologic Examination and Monitoring:

- CXR is a useful general triage test for pulmonary conditions because it helps identify which type of further diagnostic evaluation patients require to correctly diagnose the cause of their illness.
- A normal CXR helps rule out a number of pulmonary conditions and prompts diagnostic evaluation for conditions consistent with no radiological findings, while an abnormal CXR prompts evaluation for conditions consistent with radiographic changes, including but not limited to bacteriological evaluation for TB
- **In any case,when used as a triage test, CXR should be followed by further diagnostic evaluation to establish a diagnosis**

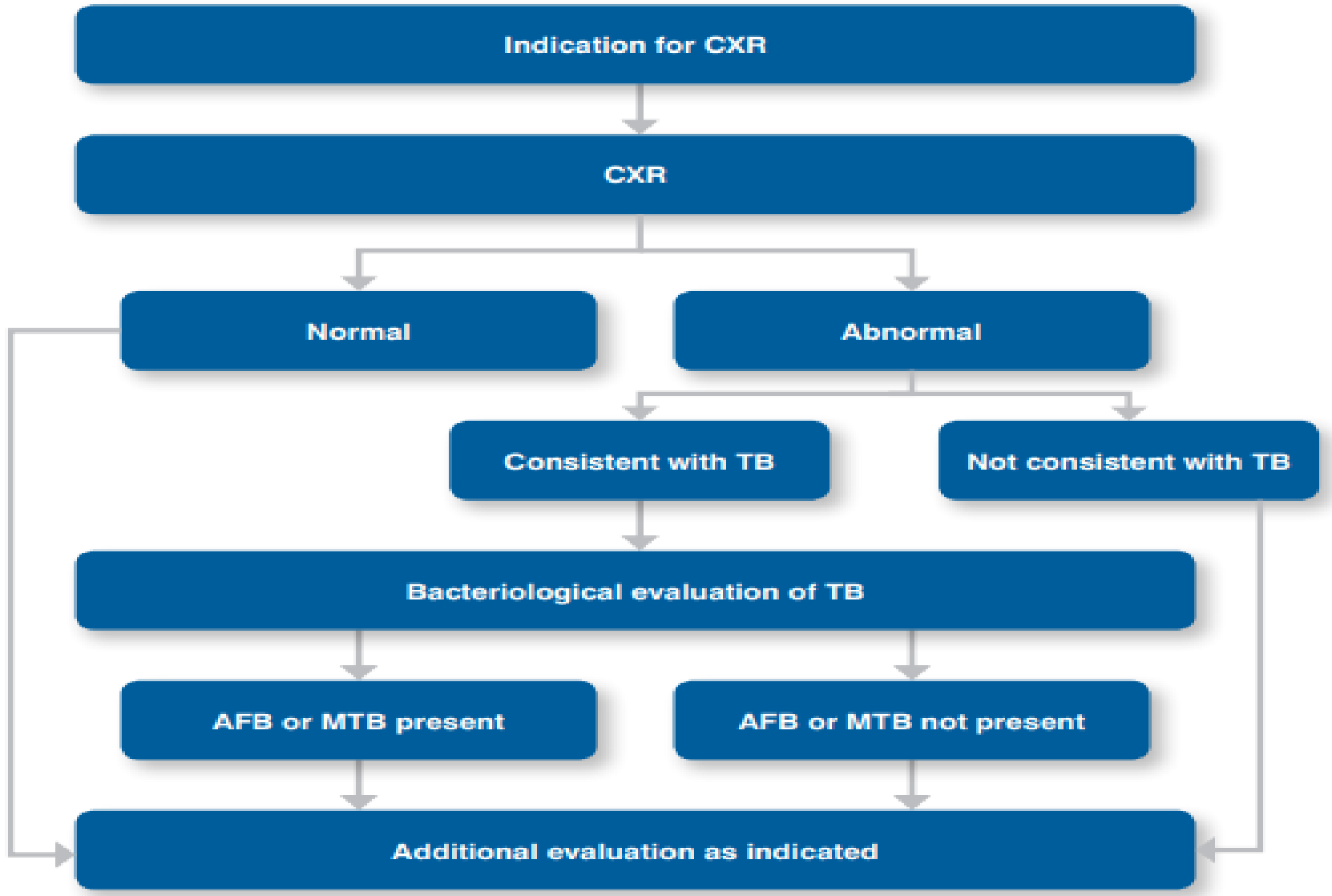
Radiologic Examination and Monitoring:

- Generating differential diagnoses for conditions other than TB may be the primary objective of ordering a CXR. Regardless of the reason for obtaining a CXR, **it is important that any CXR abnormality consistent with TB be further evaluated with a bacteriological test**
- CXR may have higher specificity for pulmonary TB than assessing symptoms alone, depending on how the X-ray is read. Therefore, triaging using **CXR can help reduce the number of persons who undergo bacteriological TB testing without decreasing the detection of true TB cases**. CXR also improves the positive predictive value of subsequent bacteriological tests by increasing the pre-test probability of TB

Radiologic Examination and Monitoring:

- CXR triaging also increases the positive predictive value of Xpert MTB/RIF testing. The specificity of the Xpert MTB/RIF assay for detecting TB is high (99%, with liquid culture as reference standard)
- introducing CXR before a bacteriological test can increase the total number of clinically diagnosed cases and, thus, also the total number of false-positive cases, depending on what further evaluation and treatment decisions are made for patients with abnormal CXR and negative bacteriological tests.

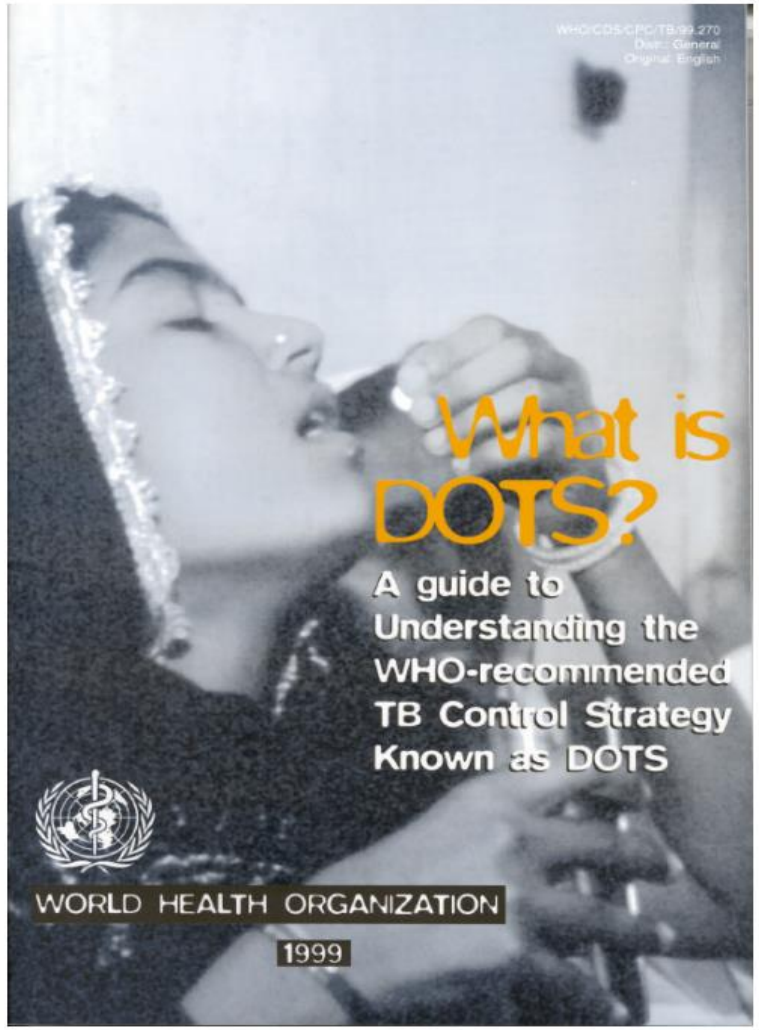
FIG. 1. Using chest radiography as a triage tool



Patient Monitoring of TB Treatment

Consists of four important areas:

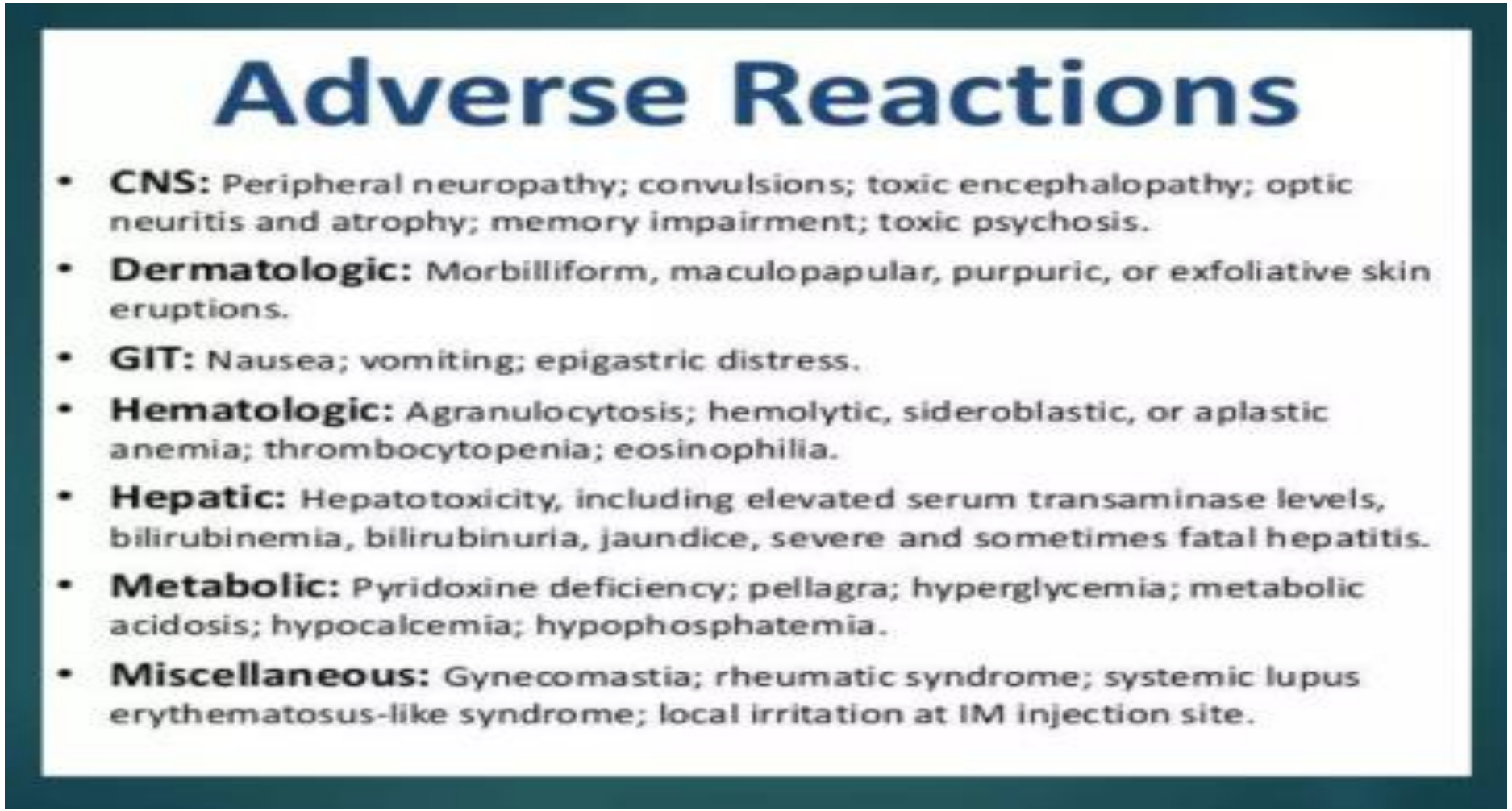
1. Adherence- DOTS
2. Microbiologic/Bacteriologic monitoring
3. **Drugs: Side Effects and Adverse Reactions**
4. The patient's well-being



First-Line TB Medications Isoniazid (INH)

- Metabolized in the liver (acetylation process under genetic control).
- Excreted in urine.
- Unwanted effects often are dose related.
- Daily dosing: 5mg/kg, max 300mg.
- Intermittent dosing: 15mg/kg, max 900mg
- Adverse reactions include:
- **Hepatotoxicity**
- **Neurologic syndromes**
- **Rheumatoid syndrome**
- Lupus syndromes
- Monoamine poisoning
- Hematologic hypersensitivity

Isoniazid (INH):



Neurologic Syndromes Caused By INH

1. Peripheral neuropathy is dose-related and increases with activity.

- Occurs less than 0.2% at normal doses.
- Increased risk with nutritional deficiency, diabetes, HIV infection, renal failure, alcoholism and in pregnant or breastfeeding women

Recommendation: Supplement with pyridoxine (vitamin B-6): 25-50mg/day

2. Central nervous system effects (autonomic dysfunction)

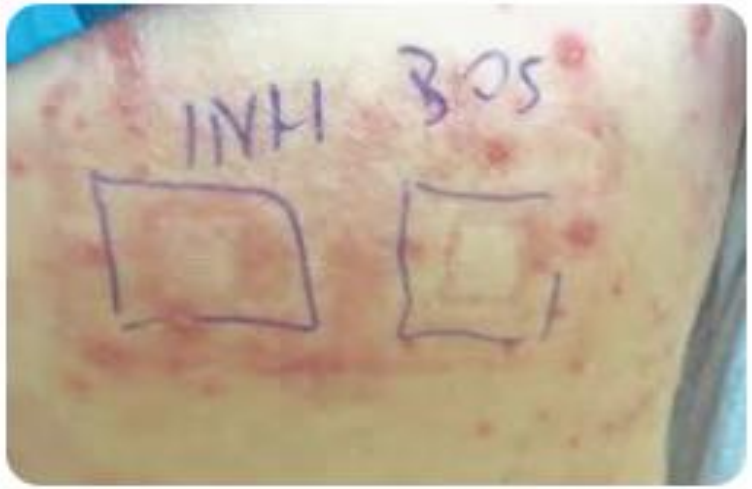
- Rare.
- Headaches, irritability, dysphoria, depression , psychosis, dysarthria (drunk-like speech), inability to concentrate, insomnia, optic neuritis (blindness), and seizures.

Recommendation: Continue treatment if symptoms are minor and tolerable.

Stop if one of the more serious reactions occurs

Hypersensitivity Reactions Caused By INH

- Allergic reaction
- Rare < 1 %
- Symptoms:
- Fever
- Rash
- Stevens-Johnson Syndrome (extensive rash that blisters and includes mucus membranes)



- Recommendation: Stop medication – treat symptoms if severe

Hepatotoxicity Caused By INH

- **Recommendations:**

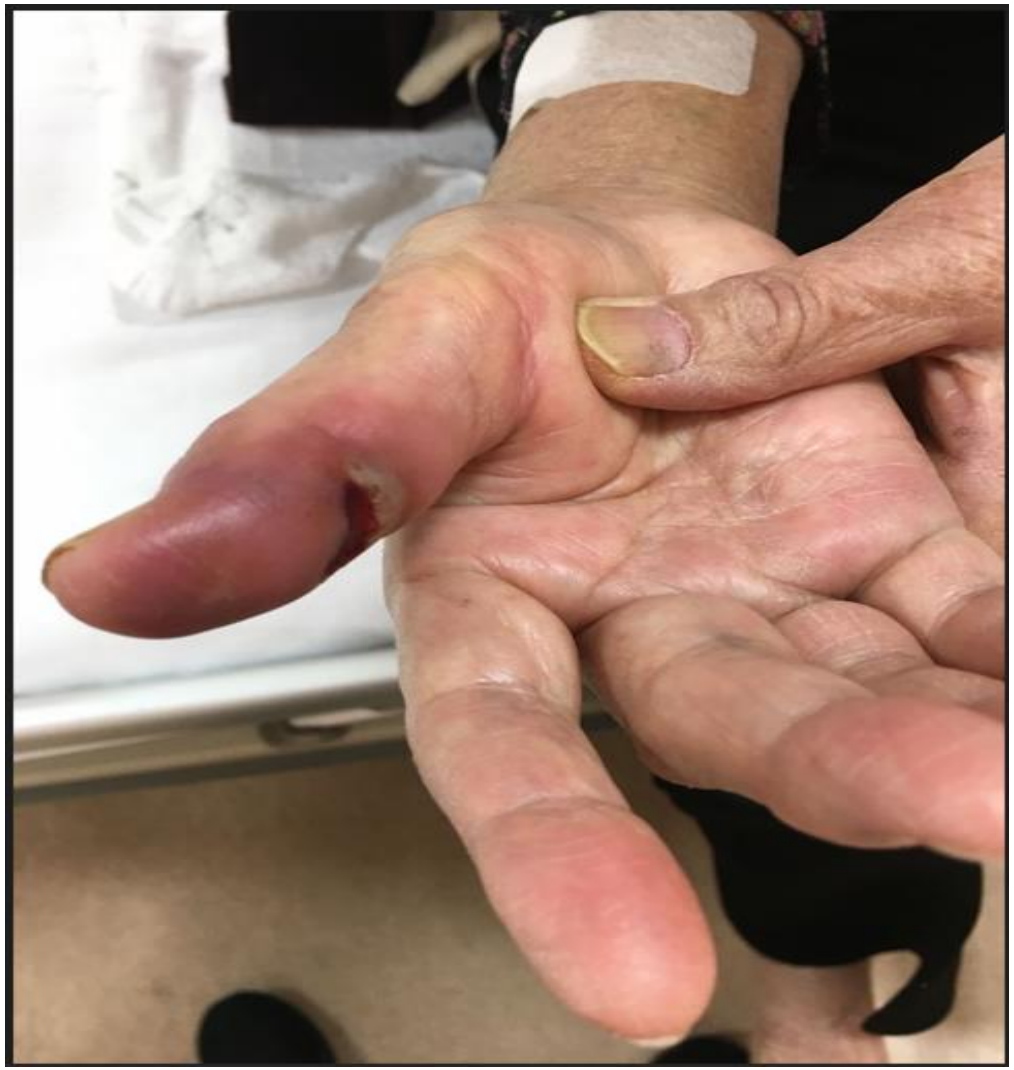
- Stop treatment if:
  - ALT 3x upper limit of normal (3xULN)
- with symptoms (+/- 123)
  - ALT 5x upper limit of normal (5xULN)
- without symptoms (+/- 205)
  - AST 3xULN with symptoms (+/- 114)
  - AST 5x ULN without symptoms (+/- 190)
  - 10-20% have asymptomatic elevations of aminotransferase (amino or aspartate) up to five times the upper limits of normal which usually returns to normal (hepatic adaptation) without stopping the medication

Hematologic Reactions Caused By INH

- Hemolytic anemia, thrombocytopenia and neutropenia
- Rare (less than 1%).
- Symptoms include: paleness, jaundice (thrombocytopenia), dark urine, weakness, dizziness, confusion, enlarged spleen (anemia), low platelets producing easy bruising, prolonged bleeding, rash, enlarged lymph nodes, fever, and increased infections (neutropenia)
- Recommendation: Stop medication –symptoms resolve rapidly (within days).

Rheumatoid Syndrome Caused By INH

- **Joint pain.**
  - Rare.
  - Includes: sudden onset of joint pain, tenderness in hands or other joints like elbows, wrists, shoulders, hip and spine.



- **Recommendations:**
  - Continue treatment if symptoms are minor and tolerable.
  - Stop if one of the more serious reactions occurs.

First-Line TB Medications Rifampin (RIF)

- **Rifampin (RIF) – Rifamycins also include rifapentine and rifabutin**
- Metabolized in the liver by cytochrome P450 3A4 (CYP3A4) enzyme system which can inhibit effectiveness of many other drugs.
- Excreted in urine.
- Unwanted effects often are dose related.
- Dosing is daily or intermittent 10mg/kg, max 600mg
- Adverse reactions include:
- Cutaneous reactions **-Gastrointestinal reactions**
- Immunologic reactions **-Hepatotoxicity**
- Hypersensitivity **-Discoloration of body fluids**

Cutaneous Reactions Caused By RIF

- Mild allergic reaction.
- 6% of patients.
- Pruritus (itching), rash, or flushing.

Recommendations:

- Continued treatment may be possible.
- Drug re-challenge over several days, use antihistamine or desensitization process (in hospital or clinic)

Gastrointestinal Reactions Caused By RIF

- Mild or severe.
- Variable incidence
- **Nausea, anorexia, abdominal pain, vomiting, and diarrhea**

Recommendations:

- Watch for underlying hepatotoxicity (check liver enzymes). Most often can continue medication with support:
- **Administration of antiemetic or antacid 30 minutes before taking medication.**
- Take medication at bedtime.
- Encourage hydration.
- Eat a light (non-fatty) snack before taking medication.

Hepatotoxicity Caused By RIF

- Transient asymptomatic hyperbilirubinemia or clinical hepatitis.
- Low occurrence (under1%, but higher if taken with INH 2.7%).
- Symptoms: nausea, jaundice, anorexia, abdominal pain, vomiting, diarrhea or symptoms of cholestasis.

- **Recommendation:**
- Check Liver enzymes including total bilirubin and alkaline phosphatase.

Discoloration of Body Fluids Caused By RIF

- Common and usually not serious
- Nearly all patients experience this
- **Orange discoloration of sputum, urine, sweat, saliva, tears**.

Recommendation:

- Warn patient that soft contact lenses, dentures, and clothing can become permanently stained.

First-Line TB Medications Pyrazinamide (PZA)

- Pyrazinamide (PZA) –synthetic derivative of nicotinamide (B-3)
- Metabolized in the liver.
- Excreted in urine but metabolites can accumulate.
- **Major source of hepatotoxicity of TB medications** (less in combination with multidrug shorter regimens).
- Daily Dosing: 25mg/kg.
- Intermittent Dosing: 35mg/kg.
- Adverse reactions include:
- Hepatotoxicity
- **Acute gouty arthritis (hyperuricemia)**
- **Dermatitis**

Hepatotoxicity Caused By PZA

- **10-20% of patients have asymptomatic elevations of aminotransferase (amino or aspartate) up to five times the upper limits of normal.**
- This usually returns to normal (hepatic adaptation) without stopping the medication.
- **PZA is the most likely cause of hepatotoxicity** when liver enzymes are above the recommended levels (7.9% five times the upper limit of normal and 5.3% symptomatic) and usually occurs at the beginning of treatment.
- With long term use of PZA, 2.6% of patients develop elevated LFTs.

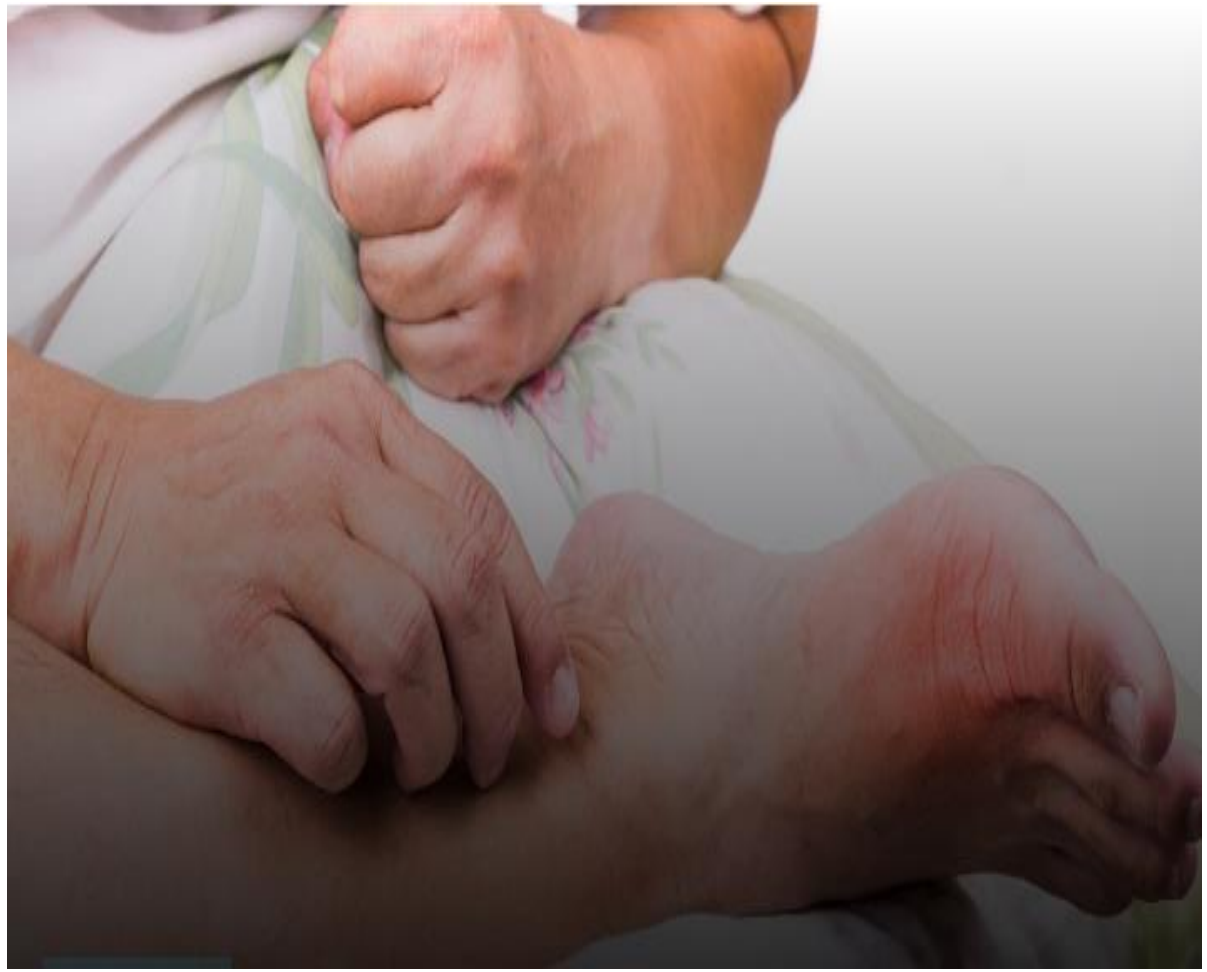
Hepatotoxicity Caused By PZA

- Symptoms: nausea, vomiting, abdominal tenderness, discomfort near ribs on right upper abdomen, jaundice, and hepatic enlargement.

Recommendation:

- Stop treatment if ALT or AST is:
- 3xULN with symptoms OR
- 5xULN without symptoms.
- **If all medication stopped, wait until LFTs decrease to below two times the upper limit of normal (2xULN) and restart a drug challenge according to recommended guidelines.**
- Look for a possible underlying cause.
- Monitor LFTs every 2-3 weeks, then every 4-8 weeks if within normal limits.

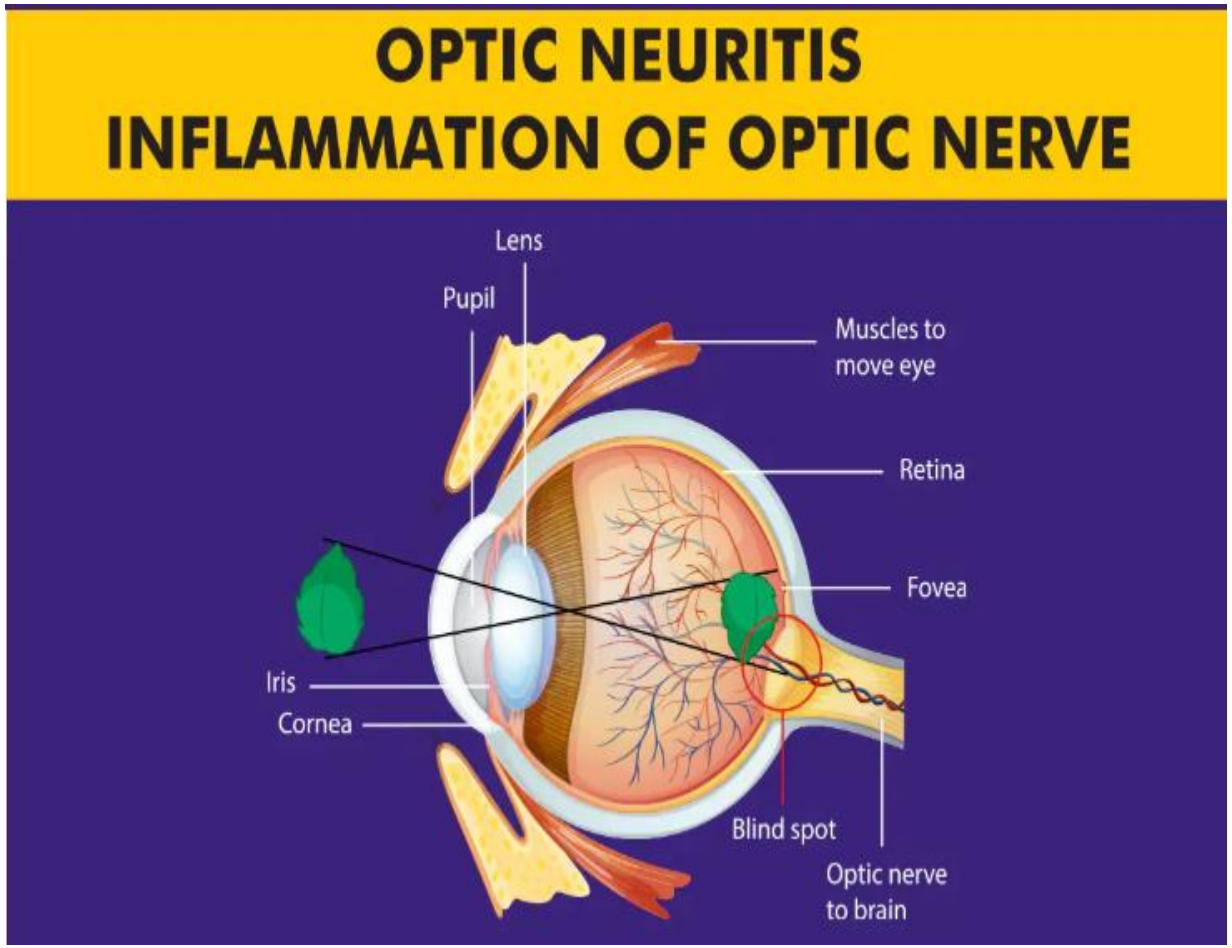
Acute Gouty Arthritis Caused By PZA (Hyperuricemia)



- **Serum uric acid concentrations elevated (hyperuricemia) to >7.0mg/dl.**
- **40% of patients have some polyarthralgia.**
- Serious acute gouty arthritis is rare unless there is pre-existing gout.
- **PZA decreases renal uric acid secretion, metabolites accumulate and increase uric acid.**
- Symptoms: pain, tenderness and/or swelling of joints.
- Affects fingers, shoulders, and knees
- **Recommendation:**
- Use anti-inflammatory medication for symptomatic relief.
- Switch to intermittent dosing (helps prevent accumulation of metabolites).

First-Line TB Medications: Ethambutol (EMB)

- Ethambutol (EMB)
- Metabolized in the liver.
- Daily Dosing: 15-25mg/kg.
- Long-term Dosing: 15mg/kg.



Adverse reactions include:

- **Optic neuritis**
- Cutaneous reactions

Optic Neuritis Caused By EMB

- Possibly due to decreased copper levels in mitochondria or accumulation of zinc in lysosomes of retinal ganglion cells.
- Dose and duration-related severity.
- Risk is less than1% at doses of 15mg/kg/day.
- Symptoms: **blurred vision or red/green color blindness**

Recommendations:

- **Perform baseline vision testing (acuity and colorblindness)** and regular (monthly) vision testing while on EMB.
- Stop EMB if visual changes occur

Cutaneous Reactions Caused By EMB

- Allergic Reaction- rare
- Symptoms: fever, rash, and **Stevens-Johnson syndrome** (extensive rash that blisters and includes mucus membranes).
- Continued treatment may be possible.
- Drug re-challenge over several days, use antihistamine or desensitization process.
- EMB can be discontinued when drug sensitivities are known and isolate is pan-sensitive (EMB has limited role in treatment).

Second& Third-Line TB Medications

HEPATITIS	NEUROLOGICAL	RENAL	OPTHALMOLOGIC	HEMATOLOGICAL (rare)
Ethionamide	**Peripheral Neurotoxicity:**	Streptomycin	**Vision Changes:**	Linezolid
PAS	Ethionamide	Amikacin	Linezolid	Cycloserine (rare)
Levofloxin (rare)	Linezolid	Capreomycin		Capreomycine (rare)
				Levofloxacin (rare)
	Central Neurotoxicity:			Moxifloxacin (rare)
	Ethionamide			Streptomycin (rare)
	Cycloserine			PAS (rare)
	Fluroquinolones			
	Amikacin			
	Linezolid			

New Medications:

- Bedaquiline (BDQ) – QTc prolongation, nausea, rash
- Pretomanid (Pa) – peripheral neuropathy, anemia, hepatotoxicity, optic neuropathy, QT prolongation (in combined therapy)

Main adverse effects and likely responsible drugs

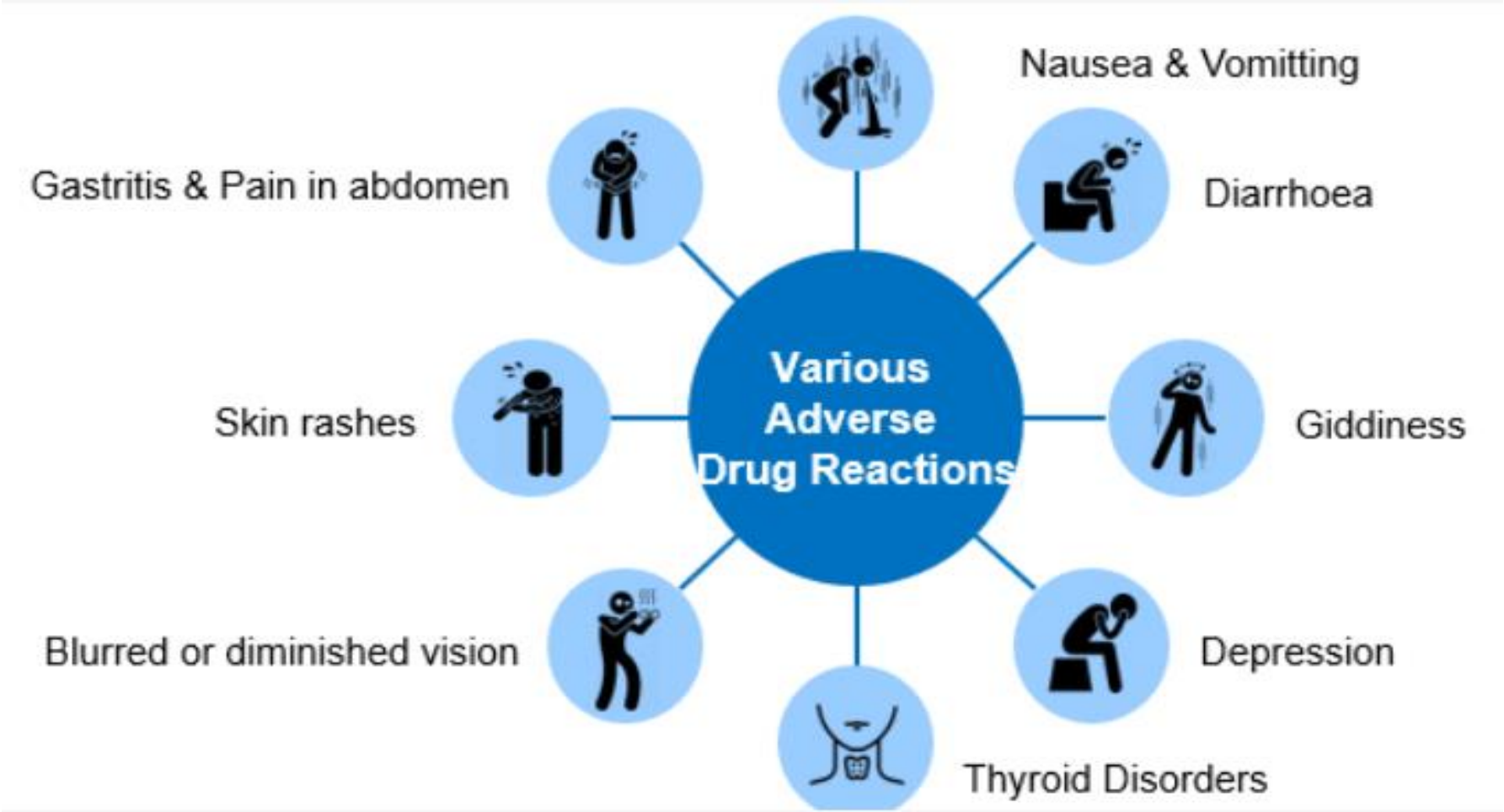
- Adverse effects: Rapid management of adverse effects is essential to increase tolerance and improve outcomes.
- In the event of minor adverse effects, drugs should not be stopped. Providing support and using ancillary medicines is all that is necessary.
- In the event of major adverse effects, the regimen may need to be adapted.

Adverse effects	Drug(s) likely responsible	Management
Minor		
Nausea, vomiting	Eto, Z	Supportive. Do not stop
Arthralgia	Z	Supportive. Do not stop
Peripheral neuropathy	H, Eto	Appendix 17
Orange/red urine, tears, etc.	R, P	Patients should be told before starting treatment that this is normal.
Major		
Skin reactions	E, Z, R, H, P, Mfx, Eto	Stopped and refer
Hepatotoxicity	Z, H, R, P, Eto	If it is thought that the liver disease is caused by the anti-TB drugs, all drugs should be stopped. If the patient is severely ill with TB and it is considered unsafe to stop TB treatment, a non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started.
Optic neuritis	E	Stopped and refer
Haematologic disorders	R, P, H, E	Stopped and refer

Symptom-Based Approach to Managing Side-effects of Anti-TB drugs

Side-effects	Drug(s) probably responsible	Management
Major		*Stop responsible drug(s) and refer to clinician urgently*
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
Minor		*Continue anti-TB drugs, check drug doses*
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily (*3*)
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration (*3*)

Adverse Drug Reactions:



Anti-TB Drugs (U.S.)

- **First-Line**
- Isoniazid (INH or H)
- Rifampin (RIF or R)
- Rifabutin (RFB)
- Rifapentine (RPT)
- Pyrazinamide (PZA or Z)
- Ethambutol (EMB or E)

Second-Line

- Amikacin (AK)
- Streptomycin (SM)
- Moxifloxacin (MOX or Mfx)
- Levofloxacin (LFX or Lfx)
- Ethionamide (ETA or Eto)
- Para-aminosalicylic acid (PAS)
- Linezolid (LZD or Lzd)
- Cycloserine (CS or Cs)

Third-Line

Bedaquiline (BDQ or Bdq), Delamanid (DLM or Dlm), Clofazimine (CZ)
Pretomanid (Pa), Imipenem, High-dose INH, High-dose RIF, Amoxicillin

Anti-Tuberculosis Medications

- With TB we have limited curative options in terms of medication and therefore we walk a fine line between side effects and adverse reactions
- Medications and monitoring must be individualized.
- **Some common side effects can be the first sign of an adverse event**
- Medication can also have different effects on people due to: age, other medical conditions, social habits, drug-drug interactions, and foods.

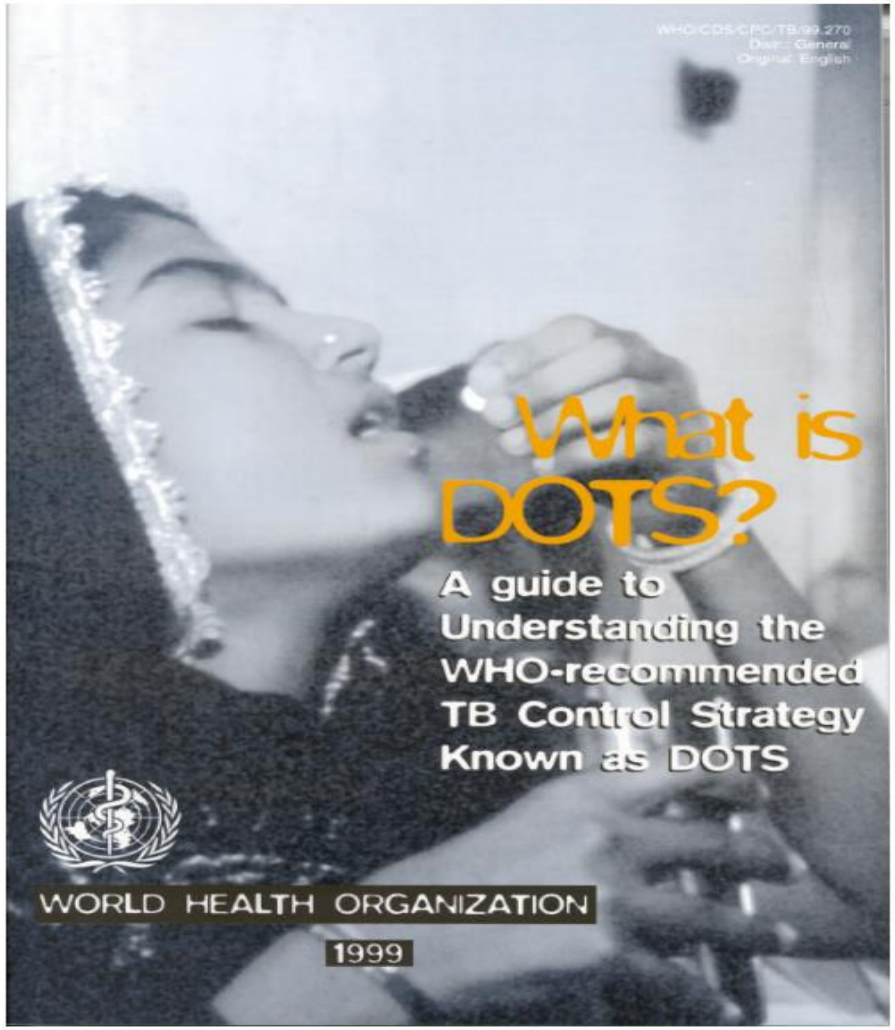
Anti-Tuberculosis Medications

- Almost all **TB medications are toxic in some way and second-line TB medications are the most toxic**
- However, **treatment of infectious TB is more important than minor side effects** or even some adverse events
- Research is being done to develop more humane, less toxic, and shorter regimens for both TB and drug-resistant TB

Patient Monitoring of TB Treatment

Consists of four important areas:

1. Adherence- DOTS
2. Microbiologic/Bacteriologic monitoring
3. Drugs: Side Effects and Adverse Reactions
4. **The patient's Well-being**



Patients Well Being

TB has a significant impact on people's lives (consider)

- Financial
- Emotional
- Socioeconomic
- Associated Stigma and cultural impact
- Functional limitations due to the disease
- Comorbidities impacted
- Age, Gender and other demographic factors

Acknowledgement: Philip Wegner, Vasiti Uluiviti, CDC, WHO and Mayo Clinic for the slide information.

KOMMOL TATA!