# Medical & Case Management of Drug-Susceptible TB

**Ann Scarpita MPH, MSN, BSN, RN**
TB Nurse Consultant, Tuberculosis Program
Colorado Department of Public Health and Environment
Denver, CO

# Didactic Topics for Today

- Case management for drug-susceptible TB disease
- Non-stigmatizing language

# Learning Objectives

By the end of this training, participants will be able to:

1. identify the recommended regimens and first-line medications for treating drug-susceptible TB disease
2. state several criteria for when treatment for drug-susceptible TB should be extended to at least 9 months
3. describe common side effects and the associated monitoring required for individual first-line anti-TB drugs
4. describe the key components of TB case management
5. identify the baseline evaluations that should be obtained prior to starting treatment for drug-susceptible TB disease
6. monitor and document clinical findings to evaluate for response to TB treatment
7. identify stigmatizing language and describe alternative language

# Poll Question 1

How many patients with TB disease have you managed to date?

- None
- 1-5
- 6-10
- >10

# EXPOSED Chapter 1 : The Global Epidemic

# Case Management Definition

"Case Management is a collaborative process of assessment, planning, facilitation, care coordination, evaluation and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available resources to promote patient safety, quality of care, and cost effective outcomes."

~Case Management Society of America

# Poll Question 2

When a person with TB is reported to the public health department, who is ultimately responsible for ensuring that the patient is evaluated and, if necessary, completes TB treatment?

- The treating physician
- The public health department case manager
- The outreach worker who delivers the medications
- The patient
- I don’t know yet

# Case Management Definition

The Nurse Case Manager (NCM) is accountable to the patient and is responsible for leading the following activities:

- Setting goals
- Providing education, medication, and medical monitoring
- Coordinating care
- Documenting interventions
- Ensure completion of treatment
- Leading the Contact Investigation
- Evaluate and document clinical response to treatment

# Goals of TB Treatment

- Individual patient
  - Prevent the health consequences of untreated TB
  - Avoid severe or intolerable adverse effects of TB treatment
- Public health goals
  - Stop transmission of TB to contacts and the community
  - Prevent the development of acquired drug-resistance by Mycobacterium tuberculosis

# Poll Question 3

If all medications are taken on schedule, generally how long is the initial phase of treatment for drug-susceptible pulmonary TB?

- 1 month
- 2 months
- 3 months
- 4 months
- I don’t know yet

# General Principles Pan-Susceptible

- Initial Phase (initial 2 months of treatment)
  - Prevents drug resistance until drug susceptibility testing (DST) is known and increases ability to shorten treatment
- Continuation Phase (subsequent 4-7 months of treatment)


- Duration of therapy (or number of doses needed) is dependent on:
  - Drugs used
  - Extent of disease
  - Response to treatment
  - Co-morbidities (e.g. HIV, immune-compromise)

# Treatment for Drug-Susceptible TB

**Initial Phase (2-complete months)**

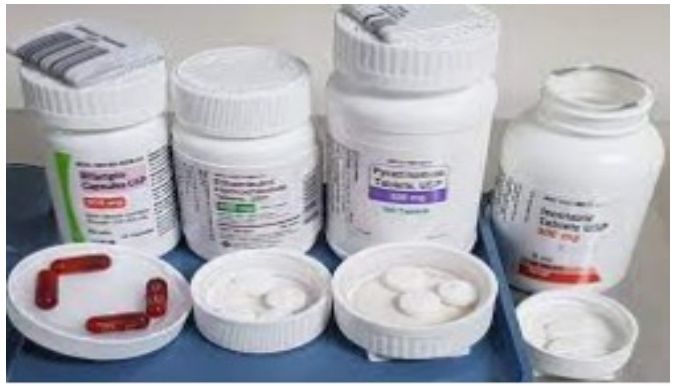
- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol
  - EMB can be dropped once confirmed susceptible
- Vitamin B6 50mg

**Continuation Phase (4-7 months)**

- Rifampin
- Isoniazid
- Vitamin B6 50mg

# Medications (Pan-Susceptible)

- Rifampin (RIF, “R”), 10 mg/kg/d
- Isoniazid (INH, “H”), 5 mg/kg/d
- Pyrazinamide (PZA, “Z”), 25 mg/kg/d
- Ethambutol (EMB, “E”), 15-25 mg/kg/d




https://www.currytbcenter.ucsf.edu/products/view/rifamycin-drugdrug-interactions-a-guide-for-primary-care-providers-treating-latent-tuberculosis

# Regimens for Drug-susceptible TB

| Regimen | INTENSIVE PHASE | | CONTINUATION PHASE | | Range of total doses | Comments[3, 4] | Regimen effectiveness |
|---|---|---|---|---|---|---|---|
| | Drugs[1] | Interval and Dose[2] (Minimum Duration) | Drugs | Interval and Dose[2,3] (Minimum Duration) | | | |
| **1** | INH<br>RIF<br>PZA<br>EMB | 7 days/week for 56 doses (8 wks)<br>OR<br>5 days/week for 40 doses (8 wks) | INH<br>RIF | 7 days/week for 126 doses (18 weeks), OR<br>5 days/week for 90 doses (18 weeks) | 182<br>to<br>130 | This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis. | Greater |
| **2** | INH<br>RIF<br>PZA<br>EMB | 7 days/week for 56 doses (8 wks)<br>OR<br>5 days/week for 40 doses (8 wks) | INH<br>RIF | 3 times weekly for 54 doses (18 weeks) | 110<br>to<br>94 | Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve. | |
| **3** | INH<br>RIF<br>PZA<br>EMB | 3 x/week for 24 doses (8 wks) | INH<br>RIF | 3 times weekly for 54 doses (18 weeks) | 78 | Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance. | |
| **4** | INH<br>RIF<br>PZA<br>EMB | 7 days/week for 14 doses<br>THEN<br>2 x/week for 12 doses[5] | INH<br>RIF | Twice weekly for 36 doses (18 weeks) | 62 | Do not use 2x/weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior. | Lesser |

Source: Adapted from 2016 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-susceptible Tuberculosis, Table 2

# For presumed DS-PTB, continuation phase generally extended when…

| Cavitary disease on chest X-ray | Sputum Culture Positive after 2-months treatment | Co-Morbidity or extensive PTB disease | PZA Received for 8-full weeks | Continuation Phase: Extend to 7 months |
|---|---|---|---|---|
| No | No | No | No | Yes |
| Yes | Yes | No | Yes | Yes |
| Yes | No | Yes | Yes | Yes |
| No | Yes | Yes | Yes | Yes |

- Initial phase excluded or had insufficient duration of PZA

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| Yes | Yes | No | Yes | Yes |
| Yes | No | Yes | Yes | Yes |
| No | Yes | Yes | Yes | Yes |

- Initial phase excluded or had insufficient duration of PZA
- Cavitary disease and sputum culture (+) at 2M[1] (~ 20% relapse with 6M course)

1 Jo KW, Yoo JW, Hong Y, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. *Respir Med* 2014; 108:654–9.

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|---|---|---|---|---|
| No | No | No | No | Yes |
| Yes | No | No | Yes | Yes |
| Yes | No | Yes | Yes | Yes |
| No | Yes | Yes | Yes | Yes |

OR

+

- Initial phase excluded or had insufficient duration of PZA
- Cavitary disease and sputum culture (+) at 2M[1] (~ 20% relapse with 6M course)
- If cavitary or sputum positive extend if:
  - Lower than 10% ideal body weight (BMI of <18)
  - Active smoker
  - Diabetes, HIV infection, or any other immunosuppressing condition
  - Extensive disease on chest radiograph

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  - Lower than 10% ideal body weight (BMI of <18)
  - Active smoker
  - Diabetes, HIV infection, or any other immunosuppressing condition
  - Extensive disease on chest radiograph
- Silicotuberculosis[2] (longer duration decreased relapses from 22% to 7%)

1 Jo KW, Yoo JW, Hong Y, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. *Respir Med* 2014; 108:654–9.
2 Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council A controlled clinical comparison of 6 and 8 months of anti-tuberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. *Am Rev Respir Dis.* 1991;143:262–267.

# NEW 4 MONTH REGIMEN: HPMZ

ORIGINAL ARTICLE

## Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Dorman et al NEJM 2021

# Slow Local Adoption

- Logistical concerns:
  - Up front molecular DST for MFX not available
  - Rifapentine shortage
  - ECGs
  - Cost
- Efficacy concerns
- Tolerability concerns (Baggio & Ananda-Rajah, 2021)
  - QT prolongation and cardiac arrhythmia
  - Tendon rupture, muscle pain, long term pain
  - Retinal detachment
  - Nausea, vomiting, diarrhea and taste disturbance (20% of patients)
  - Risk of c.diff
  - Hyperglycemia and hypoglycemia

# Management of Treatment Interruptions[a]

| Time Point of Interruption | Details of interruption | Approach |
|---|---|---|
| **During intensive phase** | Lapse is <14 days in duration | Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months) |
| | Lapse is ≥ 14 days in duration | Restart treatment from the beginning |
| **During continuation phase** | Received ≥ 80% of doses and sputum was acid-fast bacilli (AFB) smear negative on initial testing | Further therapy may not be necessary |
| | Received ≥ 80% of doses and sputum was AFB smear positive on initial testing | Continue therapy until all doses are completed |
| | Received <80% of doses and accumulative lapse is <3 months in duration | Continue therapy until all doses are completed (full course), unless consecutive lapse is > 2 months. If treatment cannot be completed within recommended timeframe for regimen, restart therapy from the beginning (i.e., restart intensive phase, to be followed by continuation phase)[b] |
| | Received <80% of doses and lapse is ≥ 3 months in duration | Restart therapy from the beginning, new intensive and continuation phases (i.e., restart intensive phase, to be followed by continuation phase) |

a According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear, culture, and drug susceptibility testing.
b The recommended time frame for regimen, in TB control programs in the U.S. and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months.

*Source: Adapted from 2016 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-susceptible Tuberculosis, Table 6, New York example*

# Completion of Therapy

Completion of treatment **is** primarily defined by the number of ingested doses within a specified time frame.

Completion is **not** determined **only** by the number of doses but also the time frame.

Examples:

- 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
- 6-month daily regimen (5 days/wk) = at least 130 doses
- Daily dosing is 7 days per week. Complete either 26 weeks or 39 weeks
  - 5 out of 7 days (5/7) can be considered “daily” treatment

# Completion of Therapy

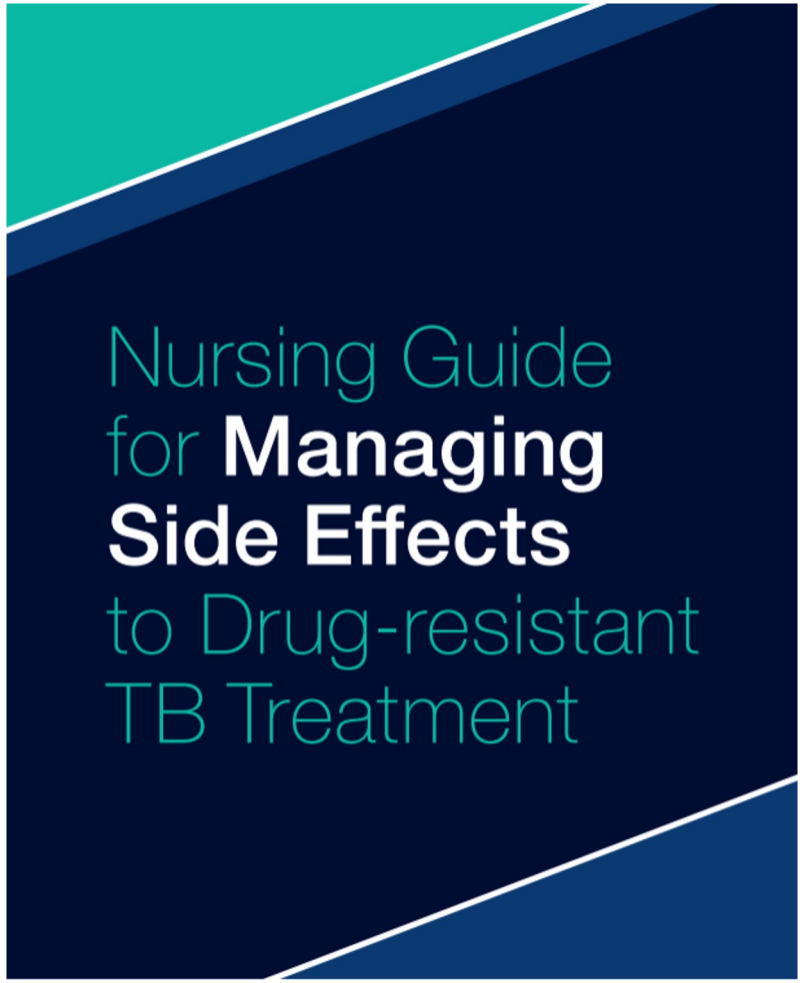
Specified doses must be administered

| Phase | Treatment Length | Completion Criteria |
|---|---|---|
| **Initial Phase** | 2 months | Within 3 months |
| | | Cannot miss more than 2 weeks in initial phase or start over. |
| **Continuation Phase** | 4 months | Within 6 months |
| | 7 months | Within 9 months |

Consider therapy interrupted if target doses not met within specified time period

# Adverse Reactions

# Adverse Reactions

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CURRY INTERNATIONAL TUBERCULOSIS CENTER

UCSF
University of California San Francisco

Stop TB Partnership
TB REACH

CDPHE

# Adverse Reactions: First-Line Drugs

| Drug / daily dose | Hepatotoxicity | Specific adverse | Additional |
|---|---|---|---|
| Rifampin, 10mg/kg (max: 600 mg) | + | Rash, pruritus, hypersensitivity<br>GI upset<br>Thrombocytopenia<br>Hemolytic anemia | Speeds metabolism of many drugs (consider drug-drug interactions) |
| INH, 5 mg/kg (max: 300 mg) | ++ | Peripheral neuropathy<br>Drug-induced lupus<br>CNS symptoms<br>Optic neuritis | Co-administer with B6 |
| PZA, 25 mg/kg | ++ | Gout<br>Hyperuricemia<br>Arthralgias<br>Photosensitivity | Dose adjustment to TIW in CrCl<30<br>Dose after hemodialysis |
| EMB, 15-25 mg/kg | | Retrobulbar neuritis (dose-related, exacerbated by chronic kidney disease) | Use higher dose only during initial months.<br>Dose adjustment to TIW in CrCl<30<br>Dose after hemodialysis |

# Adverse Reactions:
# Second-Line Drugs (commonly used)

| Drug / daily dose | Hepatotoxicity | Specific adverse | Additional |
|---|---|---|---|
| Rifabutin, 5 mg/kg (max: 300 mg) | + | Anterior uveitis<br>Leukopenia<br>Thrombocytopenia<br>Arthralgias | <20% of rifampin-resistant strains will have in vitro susceptibility to RFB |
| Moxifloxacin, 400mg | Rare | QTc prolongation<br>Tendon rupture<br>GI upset<br>C diff risk | |
| Levofloxacin, 750mg (typically) | | QTc prolongation<br>Tendon rupture<br>GI upset<br>C diff risk | Dose adjustment to TIW in CrCl<30 |

# Drug Interactions

- Relatively few drug interactions substantially change concentrations of anti-tuberculosis drugs
- Anti-tuberculosis drugs sometimes change concentrations of other drugs:
  - Rifamycins can decrease serum concentrations of many drugs, (e.g., most of the HIV-1 protease inhibitors, hormonal birth control), to sub-therapeutic levels
  - Isoniazid increases concentrations of some drugs (e.g., phenytoin) to toxic levels

# Treatment Failure

- Defined as positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured
- Single new drug should **NEVER** be added to a failing regimen; it may lead to acquired resistance to the added drug
- Add at least three new drugs to the existing regimen being cognizant of the possibility of drug resistance
- Encourage ongoing consultation through State TB Program

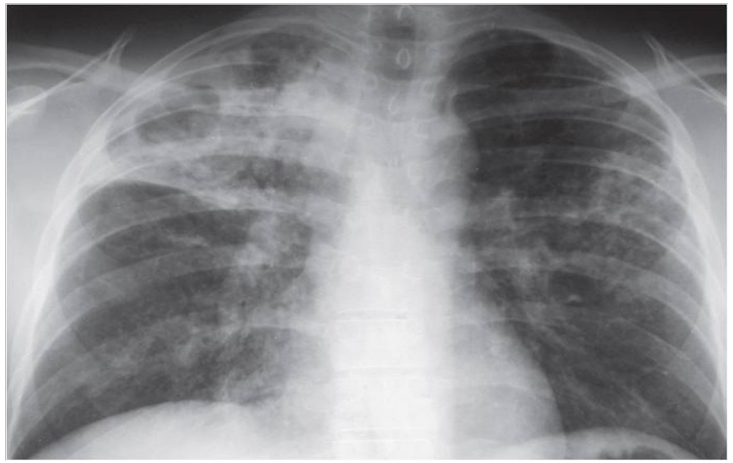
# Treatment Failure

- Red flags-
  - Delayed culture conversion (i.e. > 60 days); may need to use smears as surrogate while awaiting cultures
  - Worsening imaging at 2 months
  - Worsening or persistent symptoms at 2 months
- At risk – large burden of disease, cavitary, diabetic
- Recommendations-
  - Determine if development of resistance has occurred (repeat DST, molecular testing) and if regimen needs to be expanded
  - Assess if malabsorption present
  - Assess adherence
  - Check drug levels (TDM)

# Relapse

- A patient's cultures become and remain negative while receiving anti-tuberculosis drugs, but at some point after completion of therapy:
  - Patient develops culture-positive TB disease again

    OR
  - Patient experiences clinical or radiographic deterioration consistent with active TB disease



# Relapse

**Most relapses occur within the first 12 months after completion of therapy.**

- Patients who had cavitation on initial CXR and a positive culture at completion of 2 months of therapy are at an increased risk of relapse with standard 6-month regimens.
- Other factors that make relapse more likely:
  - Cavitary disease or sputum positive
  - Extensive Disease
  - Lower than 10% ideal body weight
  - Active smoker
  - Diabetes, HIV infection, or any other immunosuppressing condition
  - Extensive disease on chest radiograph
- Patients with relapse are at an increased risk for acquired drug resistance, especially if the therapy was not directly observed

# Respond in the Chat:

What are the steps of TB case management?

# Steps of Case Management

- Steps in TB case management:
  - Establish rapport/Provide education
  - Stop transmission/Start medications
  - Home assessment/Contact investigation

# Key Components

- Assess current status of the client
  - Medical/Physical
  - Psychological
  - Financial
  - Social
  - Cultural
- Holistic care

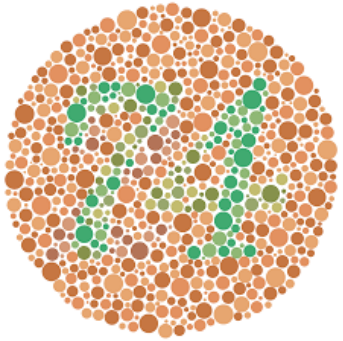

Case Management
Public Benefits
Medical Needs
Immigration Relief
Legal Center Support
Law Enforcement Advocacy (federal, state, local)
Mental Health Needs
Permanent Housing/Rental Assistance
ood/ Clothing/ Transportation
Individual Counseling
Education/ Job training/ Job placement
Interpretation/ Translation
Substance abuse referral
Children's Services
Family Reunification Planning

# Key Components of TB Case Management

- Initial Review:
- Review and discuss any problems or concerns
  - Is more clinical information needed?
  - Is the patient infectious? Is isolation needed?
  - Are there any other medical/social problems that need to be addressed?
  - Is the treatment regimen appropriate based on ATS/CDC Guidelines?
  - Is an interpreter needed?
  - Is the home safe for the patient and inhabitants?
  - Are there outreach workers who will be seeing the patient?

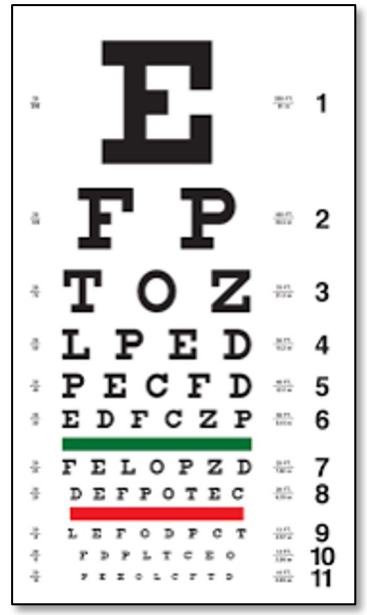
# Monitoring

# Baseline Evaluation



History and Physical

- Medication review
- Weight and Height (BMI)
- Imaging (CXR for pulmonary, may be other imaging for extra-pulmonary)
- CBC and CMP
- HIV screening
- Hepatitis B/C screening
  - For IVDU, foreign-born Asia/Africa
- Visual acuity, red-green color discrimination
  - Ishihara and Snellen



# Clinical Monitoring

- Daily
  - Adherence (DOT)
  - Symptom review
- Monthly (and prn)
  - Face-to-face symptom review by RN
    - Visual acuity, color discrimination (if on EMB)
    - Weight: re-dose medications as needed
- CXR (for pulmonary TB) or other imaging
  - Depends: 2 mo, 6 mo, or end of treatment
- Sputum:
  - Every 2 weeks until culture conversion

# Laboratory Monitoring

- Routine lab monitoring is not typically recommended except for those at high-risk or symptomatic

**<u>Regardless, clinical monitoring is a MUST!</u>**

- LFTs:
  - Underlying hepatic disease
  - Pregnancy or post-partum
  - HIV
  - IVDU or ETOH abuse
  - Consider: Age >50 yo, concomitant hepatotoxic medications
- Creatinine
  - Underlying renal disease
  - PZA, EMB require renal dosing if creatinine clearance <30
- CBC
  - Underlying hematologic abnormality
  - Rifabutin (can cause leukopenia, thrombocytopenia)

# Directly Observed Therapy (DOT)

Monitoring Treatment of TB

# Directly Observed Therapy (DOT)

- Health-care worker watches patient swallow each dose
- DOT is standard of care for all patients who have TB disease
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters

# DOT/EDOT/VDOT

DOT: Direct Observed Therapy: Traditional form when a patient is watched taking their medication in person

EDOT: Electronic Direct Observed Therapy (EDOT): Patient is observed taking their medication over electronic streaming

VDOT: Video Direct Observed Therapy: Video is recorded and a nurse reviews videos to ensure patient is taking their medication

# Diligence

Through the diligence of public health employees, we can eliminate TB!

# Non-Stigmatizing Language

# Examples of Non-Stigmatizing Language

**Stigmatizing Words**

- Compliance
- Defaulter
- Suspect
- Case
- HIV-infected
- Homeless
- Contact
- Illegal

**Alternative Non-Stigmatizing Word**

# Stop the Sigma Fact Sheet

## Eliminating Stigmatizing Language

### Non-hurtful Replacement Language

**Key Terms suggested by the Stop TB Partnership**

| Use this….. | Not that….. |
|---|---|
| **Adherence / Non-adherence** | Compliance / Non-compliance |
| **Person lost to follow up** | Defaulter |
| **TB Prevention and Care** | TB Control |
| **Person to be evaluated for TB** | TB Suspect |
| **HIV-Positive** | HIV-infected |

### HNTC Survey Results

**Language suggested by participants**

| Use this….. | Not that….. |
|---|---|
| **TB Infection** | Latent TB |
| **Lack of housing; Under-housed; People experiencing homelessness** | Homeless/Homelessness |
| **Immigrant** | Alien |
| **Undocumented** | Illegal; Illegal alien |
| **Person with TB disease** | TB case |
| **Treatment failed** | Treatment failure |
| **Missed doses/Non-adherent** | Delinquent |
| **Contact Analysis; Contact Elicitation; Contact Identification** | Investigation; Investigate |
| **Exposed to TB** | TB contact |
| **Tuberculosis** | Consumption; White Plague |

Source: https://www.heartlandntbc.org/tb-stigma/

# Break

**The 20-20-20 Rule**

For every 20 minutes spent looking at a screen, a person should look at something 20 feet away for 20 seconds


CASE
STUDY

# Questions

# Algorithm: Duration of continuation-phase for a clinical case (culture negative)

High clinical suspicion for active TB = place patient on initial-phase RIPE regimen (2 mo.)

If specimen is negative at the end of the initial phase but CXR improved, give continuation-phase treatment of INH/RIF daily or thrice weekly for additional 4-7 months.

REPORT to LPHA or State TB Program initially and then again at continuation phase.

# Algorithm: Duration of continuation-phase for a Clinical Case (culture negative)

If no clinical improvement or on CXR after 2 months (8 weeks) of RIPE treatment for active TB disease

Regimen may be discontinued and individual is considered fully treated for LTBI