

TUBERCULOSIS REVIEW

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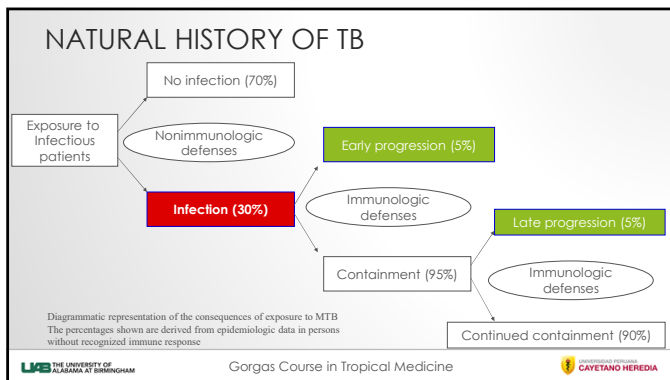
1

DISCLOSURES

- No conflicts of interest for this presentation

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2



3

TB TRANSMISSION: M TUBERCULOSIS INFECTION

- Airborne route
- Not highly infectious
 - 1 Active case ~ infect 3-10 people per year
 - Measles ~ 90% of unvaccinated contacts
- Active disease infectiousness > 1 year in high burden countries
- # hours of continues exposure to develop LTBI 8-250

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The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease

	Infection eliminated	Latent TB infection	Subclinical TB disease	Active TB disease
TSI	Negative	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Usually positive
Culture	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	Sporadically	Yes
Symptoms	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy

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5

CASE 1

- 35 yo male with 4 week history of cough, night sweats fever and weight loss
- Chest X ray as shown
- No prior history of TB
- TB contact +
- Sputum AFB 1+
- HIV neg
- Xpert MTB/Rif : MTB +/Rif R not detected

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WHAT IS YOUR TREATMENT OF CHOICE AND FOR HOW LONG?

- HRZE(2m) / HR (4m)
- HRZE (6m)
- HRZE (2m) / HR (7m)
- HRPMoxi (6 M)

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7

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REQUIREMENTS FOR ANTI -TB DRUG

- Ability to prevent emergence of resistance in the companion drug
- Early bactericidal activity
 - the fall in log₁₀ colony forming units (cfu) of *Mycobacterium tuberculosis* per ml sputum per day during the first 2 days of treatment
- Sterilizing activity
 - ability to kill either these nonreplicating bacteria or dormant bacteria under hypoxic conditions.

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WHY WE TREAT TB PATIENTS?

- To Cure the patient and reduce death or morbidity
- To reduce transmission of MTB
- To prevent the development of drug resistance

How to treat patients?

- Case Management approach (Education, counseling, field/home visits, integration of care)
- DOTS for all forms fo TB disease

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TREATMENT REGIMENS FOR DRUG SUSCEPTIBLE TB

- Forms of Tuberculosis
 - Pulmonary TB
 - Cavitary / Non cavitary
 - Culture pos/neg
 - Extrapulmonary TB
 - Bone / Joints TB
 - CNS TB (meningitis)
 - Lymph node, Pericarditis, Renal, Adrenal, laryngeal, ocular, Skin, gastrointestinal
- All forms of drug susceptible TB are treated primarily with a combination of 4 drugs: RFP / INH / PZA/ETH
- But also could use in addition: Rifapentin / Moxifloxacin

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TREATMENT REGIMENS – 6 MONTHS

Regimen	Drug ^a	Intensive Phase	Continuation Phase		Range of Total Doses	Comments ^{c,d}	Regimen Effectiveness
		Interval and Dose ^b (Minimum Duration)	Drugs	Interval and Dose ^b (Minimum Duration)			
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182-130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater ↑ Lesser
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110-94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	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 RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-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.	


Nahid, et al. CID 2016;63 (1 October)

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12

PULMONARY TB


- Newly diagnosed
 - 2HRZE/4HR ("RIPE")
- USA/CDC: Drop EMB if fully susceptible strain
- Ocular toxicity:
 - 22.5 / 1000 persons treated
 - Permanent impairment: 4.3/1000 persons
 - If EMB <=27.5/mg/kg/day
 - 19.2/1000 persons treated



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CASE 2



Patient with 4 weeks of night sweats, cough and hemoptysis, weight loss. X ray as shown and a MTB/RIF assay result show MTB + / Rif resistance not detected. What is your treatment of choice?

- RIPE x 6 months (2x4)
- RIPE x 9 months (2 x 7)
- RIPEMox x 9 months
- Refer to State Health Department or Call ID

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TREATMENT REGIMENS – 9 TO 12 MONTHS

- Intensive phase same 2 months
- Continuation phase extend to 7 - 10 months

Indications

- CNS TB, Bone and joint (12 months)
- Pulmonary cavitary disease (Not WHO)
- Patient with persistent culture positive after 2 months* (Not WHO)

* After any form of resistant disease is ruled out

Cavitary disease

- 2HRZE/4HR(WHO)

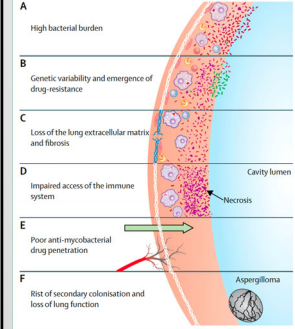
Expert opinion:

- Extension of total length of therapy to 9 months
- Extend intensive phase to 3 months

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TB CAVITARY DISEASE



- Active replication
- Population $10^7 - 10^9$
- Favors induce resistant mutants
- Necrosis and fibrosis make it difficult to macrophages to enter this area to help in disease control
- Vascular necrosis in the cavity = poor drug penetration → high bacterial burden → selection for drug resistant mutants

Urbanowski, et al. Lancet Infect Dis 2020;20: e117-28

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4 – MONTH TREATMENT REGIMEN

Four Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

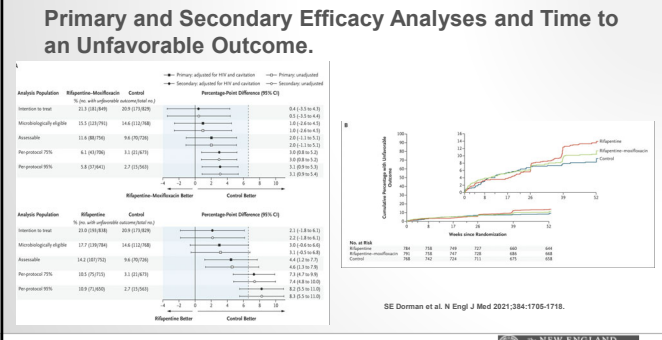
- Recommended for
 - People who are 12 years and older / Weight > 40 Kg /
 - People with HIV with CD4 counts at or above 100 cells/ microliter (µL), who are receiving or planning to start efavirenz as part of their antiretroviral therapy (ART) regimen in the absence of any other known drug-drug interactions between antituberculosis and antiretroviral medications
 - People who have no contraindications to this regimen
 - People with a negative sputum culture who are consider to have paucibacillary disease
- Drug Regimen:
 - Rifapentine / INH / PZA/ETH
 - Rifapentine / INH /PZA/ Moxifloxacin
 - Control (RIPE)

SE Dorman et al. N Engl J Med 2021;384:1705-1718.

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Primary and Secondary Efficacy Analyses and Time to an Unfavorable Outcome.



The forest plot shows percentage-point differences (95% CI) for primary and secondary outcomes. The Kaplan-Meier plot shows cumulative percentage of unfavorable outcomes over 100 weeks of randomization.

SE Dorman et al. N Engl J Med 2021;384:1705-1718.

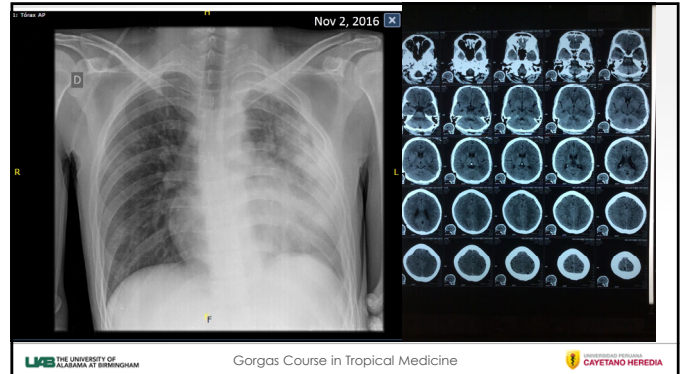
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18

CASE 3

- HPI: 23 yo M with history of isolation and an obsessive-compulsive disorder, admitted with a 1-month history of headache, malaise and fatigue. Lives in peripheral area of Lima, Peru.
- Symptoms persisted until 1-week prior presentation, when headache increased in intensity and associated with nausea, vomiting and loss of appetite. No blurry vision. Mother reports patient looks unwell and he couldn't walk for which brought him to the ED.
- Unclear history of fever and sweating. Loss of appetite and weight loss during the last year due to an obsession related to stop eating carbs. Denies etoh, tobacco, illicit drug use
- PE: Temp 38.2 BP/RR/HR normal
- Lungs : decrease breath sounds in left lung
- Cv : no murmurs, S1, S2
- Abd: Soft , BS+ , no S/L enlargement
- Ext: No edema
- Neuro: O x 0, reactive to pain stimuli . Neck stiffness, Kernig sign pos+
- Labs: Rapid HIV test Negative

19



20

What is the most likely diagnosis?

- Cryptococcus meningitis*
- Sepsis due to *Streptococcus pneumoniae*
- TB meningitis
- Lung CA (NSCLC) with brain mets
- None of the above

21

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22

LABORATORY/EXAMS

- Bronchoalveolar lavage (BAL) cultures: AFB negative, Gram/ fungal stains negative, cultures negative
- | LP | Nov 1 |
|---------|-----------------|
| Color | Cloudy |
| WBC | 80 (90% lymphs) |
| RBC | 0 |
| Glucose | 64 |
| Prots | 264 |
- Initiated on RIPE, but obtain additional CSF for Xpert.

23

What is the most likely diagnosis?

- Cryptococcus meningitis*
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- TB meningitis
- Lung CA (NSCLC) with brain mets
- None of the above

24

What is the most likely diagnosis?

- a) *Cryptococcus meningitis*
- b) Sepsis due to *Streptococcus pneumoniae*
- c) **TB meningitis**
- d) Lung CA (NSCLC) with brain mets
- e) None of the above

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25

Diagnosis

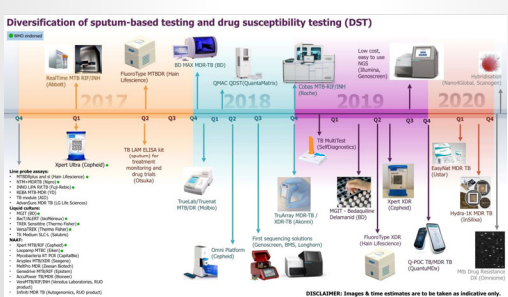
- Nov 8:
- AFB CSF (+)
- Xpert MTB/Rif assay : MTB + / Rif –
- Initial cost/test USD 17
- Recent reduction USD 7.97



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26

Diversification of sputum-based testing and drug susceptibility testing (DST)



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27

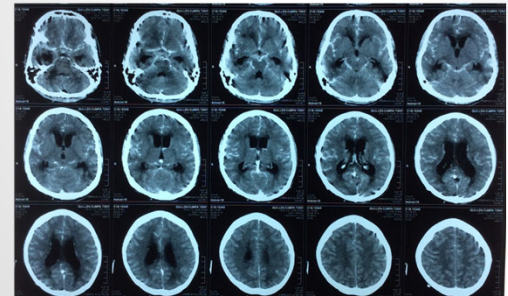
TB MENINGITIS

- Treatment
- 4 drug therapy for 12 months, intensive phase of 2 months
- Unless DR TB is suspected, adjuvant corticosteroid treatment (dexamethasone) recommended
- In TB meningitis, ***ethambutol should not be replaced by any antibiotic.***
- Do not use Amikacin as first line agent it is always a second line
- Quinolones (Moxi), has been also proposed, WHO does not recommend as 1st line agent, nor CDC. And not enough clinical information to recommend yet in meningitis.
- IF HIV infected, ARV should not be started until end of intensive phase (CDC recommendation)
- In contrary WHO as soon as possible and within 2 weeks if CD4 less than 50 (for all forms of TB), but "caution is advise" in TBM and possibly delay.

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ONE MONTH AFTER TREATMENT INITIATION



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29

2 MONTHS LATER..... WHAT IS GOING ON?



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WHAT IS YOUR DIAGNOSIS?

- a) Toxoplasmosis
- b) Lymphoma
- c) Poor Management
- d) Drug resistant TB
- e) Paradoxical Reaction

31

WHAT IS YOUR DIAGNOSIS?

- a) Toxoplasmosis
- b) Lymphoma
- c) Poor Management
- d) Drug resistant TB
- e) **Paradoxical Reaction**

32

TB MENINGITIS TREATMENT COMPLICATIONS

- Hyponatremia (~45%):
 - Cerebral salt wasting ~50% Volume contraction,
 - SIADH ~ 10% normovolemic
- Tuberculomas
 - Seizures, weakness, hydrocephalus/mass effect, high ICP
 - Paradoxical reaction
- Vasculitis /Stroke ~ up to 57% of patients
 - Potential role of ASA to prevent ischemic stroke

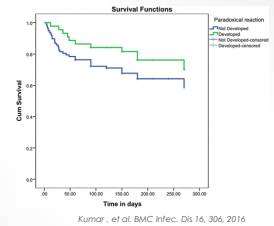
33

TB PARADOXICAL REACTION

- Clinical or radiological worsening of pre-existing tuberculosis in a patient after they have start on specific treatment

Pathogenesis

- Immunopathological damage as a consequence of an exaggerated and dysregulated host's inflammatory response
- Excessive antigen load resulting from mycobacteria lysis after treatment initiation
- Neutrophilic transformation of CSF after initiating anti-TB therapy



Kumar, et al. BMC Infect. Dis 16, 306, 2016

34

TB PARADOXICAL REACTION

Treatment

- Steroid
 - Prolong Dexamethasone course of therapy
 - Pulses
- Immune modulators
 - TNF - α inhibitors
 - Thalidomide
 - Doxycycline
 - Ibuprofen

35

CASE 4

- 34 year old female new HIV with CD4 6, VL 150K, Pulmonary TB smear +. ATT intensive phase completed. Cont. phase with INH + ETH. Start ART with EFV/TDF/FTC.
- 2 weeks after patient came to clinic complaining of this rash.
- ROS: Diarrhea on/off, afebrile, no pruritus. Relatives said that she "has not been the same".



36

What is your next course of action?

- Stop all drugs and restart one by one
- Continue therapy and only stop if rash is more than 30% BSA
- Add prednisone and Benadryl if itching
- Add vitamin supplement to the diet

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37

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38

PELLAGRA

- A disease caused by low levels of niacin or tryptophan (vitamin B-3)
- Characterized by dementia, diarrhea, and dermatitis (photodermatitis), also known as "the three Ds".
- If left untreated, pellagra can be fatal ... "4th D" ~ Death
- Other causes: eating disorders, Etoh, Hartnup Dz,
- Drugs 6-mercaptopurine, 5-fluorouracil, Isoniazid, chlofampenicol, azathioprine, phenobarbital and ethionamide
- Treatment: Niacin supplementation and change diet

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39

PELLAGRA: INH INDUCED

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40

TB AND HIV

- Same diagnostic tools, but LAMP test not favorable due to poor sensitivity in smear neg
- TB Treatment same as HIV neg
- ARV:
 - DTG based best
 - EFV
 - Raltegravir
 - Lopinavir/ritonavir
- LTBI screening:
 - Remember in HIV infected, RLS, if 4 symptom rule neg then ok to start LTBI therapy
- HIV regimens for naive patients (remember what to switch to if failing regimens)

Foundation	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adult and adolescents	DTG + 3TC or DTG + 3TC + DDP	DTG + 3TC + EFV or AZT + 3TC + EFV	DTG + 3TC or DTG + 3TC + DDP + 3TC + EFV or AZT + 3TC + EFV or AZT + 3TC + DDP + 3TC + EFV
Children	AZT + 3TC + DDP	AZT + 3TC + LPV or AZT + 3TC + ZDV	AZT + 3TC + EFV or AZT + 3TC + DDP + 3TC + EFV
Neonates	AZT or AZT + 3TC + DDP	AZT + 3TC + ZDV	AZT + 3TC + LPV

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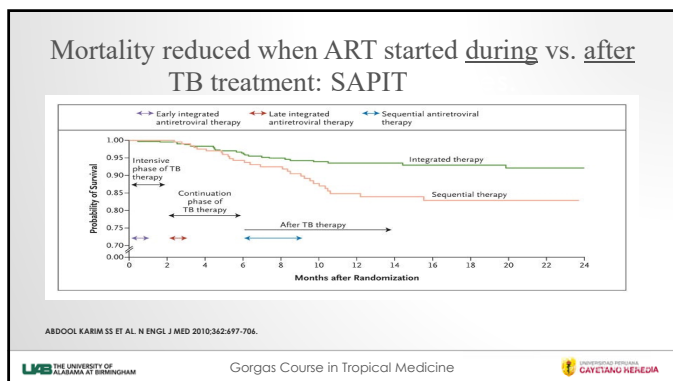
41

Key characteristics of trials of timing of ART during TB treatment

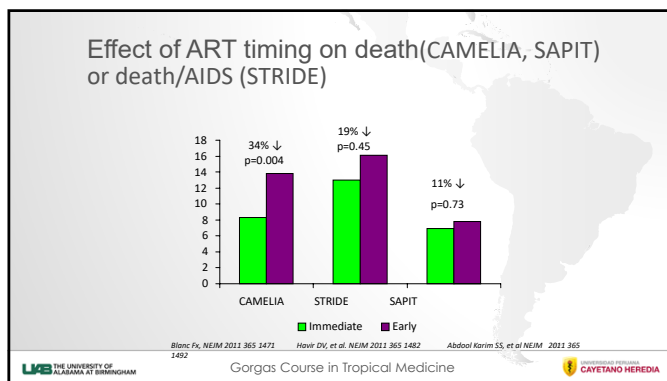
Study	Setting	Key enrollment criteria	Median CD4 (IQR)	Primary endpoint
CAMELIA	Cambodia	Smear +, CD4 < 200	25 (10 - 56)	Death
STRIDE	Multi-national	Clinical TB, CD4 < 250	77 (36 - 145)	AIDS or death
SAPIT	South Africa	Smear +, CD4 < 500	150 (77 - 254)	AIDS or death

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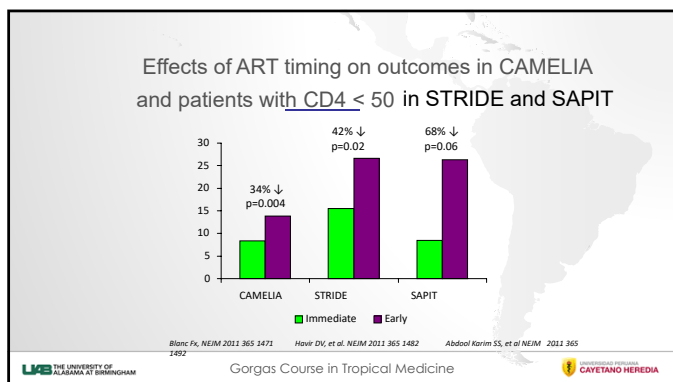
42



43



44



45

- ### Are there any risks for starting ART at 2 weeks ?
- Immune Reconstitution (no mortality)
 - ART response (no difference)
 - Drug toxicity (no difference)
 - TB response (no difference)

46

- ### TAKE HOME POINTS
- Delaying ART until end of TB tx = increases mortality
 - Critical that ART is started within 2 weeks among TB/HIV with advanced immune suppression (CD4 <50) and by 8 weeks in others
 - WHO recommendation: All TB patients co-infected with HIV should be offered ART irrespective of CD4 cell count no later than 8 weeks and by 2 weeks for CD4 <50
 - Immediate ART is significantly associated with more severe adverse events. Thus, it might be a consideration to delay ART for 4–8 weeks after TB treatment is initiated in such situations.

47

- ### CASE 5
- A 24 yo male patient from the Philippines living in the USA for the last 5 years complained of cough for 3 weeks, and has a positive Auramine stain on a sputum sample:
- no recognized risk factors for MDR-XDR
 - Xpert MTB/RIF results: high bacterial load, positive mutations (*rpoB*)
 - Xpert MTB/XDR results: resistance to H, susceptibility to Eto, FQ, AG
 - DST is pending
- ### What would you recommend him?

48

WHAT WOULD YOU RECOMMEND?

1. Wait for the phenotypic results (DST)
2. Perform a Genotype MTBDR plus test (LiPa)
3. Repeat the Xpert MTB/XDR (NAAT)
4. Perform a Cobas MTB/RIF-INH (NAAT)
5. Start MDR-TB treatment

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49

WHAT WOULD YOU RECOMMEND?

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5. **Start MDR-TB treatment**

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50

WHICH DRUG REGIMEN WOULD YOU RECOMMEND ?

- a. 9 months of daily ZEMfxL
- b. BPaL – 6 months
- c. BPaLM – 6 months
- d. Individualized longer regimen – 18 months
- e. BPaZE – 9 months

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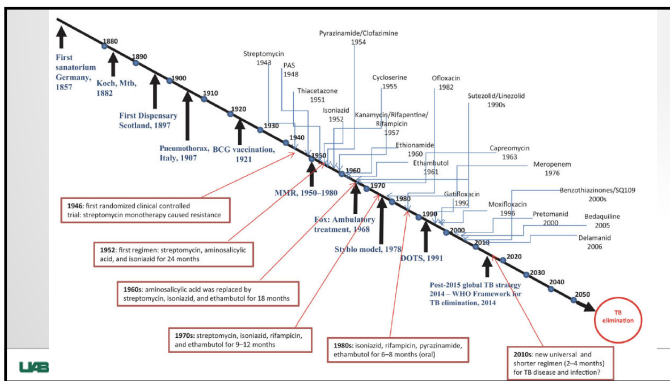
51

WHICH DRUG REGIMEN WOULD YOU RECOMMEND ?

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52



53

DRUG RESISTANT TB DEFINITIONS

- **Mono-resistance:** One single drug
- **Poly-resistance:** Multiple drugs but not MDR/RR-TB
- **MDR/RR- TB:** multidrug-resistant or rifampin-resistant tuberculosis
 - **Multidrug-Resistant (MDR-TB):** At least resistant to INH and Rif
 - **Rifampin resistant (RR-TB):** Rifampin resistant tuberculosis. Consider equivalent as MDR ~90%.
- **Pre-XDR :** TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfill the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone^a
- **Extensively Drug Resistant (XDR-TB):** MDR/RR-TB plus resistance to any fluoroquinolone^a and at least one additional Group A drug^b
 - ^a Levofloxacin and moxifloxacin
 - ^b Bedaquiline, Linezolid

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54

BPAL REGIMEN

- **Approved by FDA in 2019** for treatment of XDR, pre-XDR and non-responsive/intolerant to MDR treatment
- Only for those with **pulmonary disease**
- **HIV-infected with CD4>50 cells/uL** receiving ARVs (check drug-interactions)
- **Not approved** for pregnant-children; peripheral neuropathy grade 3-4; QTcF>500 ms; LFT > 5 ULN; Hb < 8 mg/dl; potassium below normal

55

BPAL REGIMEN

- **B** 400mg once-daily for 2 wk followed by 200mg x3/wk for 24 weeks; **Pa** 200mg once daily
- **L** 1200mg/d; dose adjustment 600mg/d or 300mg/d or interruption
- all taken with food
- 26 weeks or 39 weeks if delayed response
- check for toxicity (see detailed instructions at the CDC)

56

TB-PRACTECAL REGIMEN-MDR EARLY RELEASE OF RESULTS

- last evaluations in December 2022
- multi-centre, open label, randomized, controlled, II-III
- **B** 400mg once daily (2wk), 200 mg x3/wk (22w); **Pa** 200mg once daily (24wk); **L** 600mg/d (16wk), 300mg/d or 600mg x3/wk per 8 wk; **Mfx** 400mg/d (24wk) [**BPaLM regimen**]
- **89% cured vs. 51% standard of care (stopped by DSMB)**
- WHO made a preliminary update of guidelines

<https://www.msf.org/drug-resistant-tuberculosis-trial-results-updated-treatment-guidelines>

57

BPaL/ BPaLM INDICATIONS

- People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
- People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB. 11
- Adults and adolescents aged 14 years and older.
- All people regardless of HIV status.
- Patients with less than 1-month previous exposure to Bedaquiline, Linezolid, pretomanid or Delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
- Pretomanid 200 daily x 26 weeks
- BDQ 400 QD x 2 weeks, then 200mg 3/week x 24 weeks
- Linezolid 1200 QD x 26 week (600 Mg)
- Moxifloxacin 400 mg QD x 26 weeks
- Adverse effects
 - Myelosuppression and peripheral and optic neuropathy (LNZ)
 - Hepatotoxicity, lactic acidosis, QT prolongation (>500), and pancreatitis

58

CASE 6

- 58 yo male presenting with 8 month history of back pain numbness in both lower extremities , fever , night sweats and weight loss.
- TB contact –
- Works in the market carrying 50 kg potato bags
- Eats “queso fresco” with corn in the market



59

CASE 3



60

WHAT IS YOUR DIAGNOSIS?

- Spinal cord abscess - MRSA
- Brucellosis
- Tuberculosis
- Paracoccidioidomycosis
- Spinal tumor/malignancy

61

WHAT IS YOUR DIAGNOSIS?

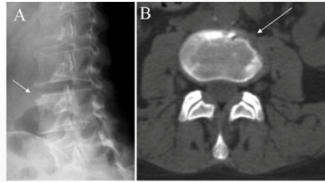
- Spinal cord abscess - MRSA
- Brucellosis
- Tuberculosis**
- Paracoccidioidomycosis
- Spinal tumor/malignancy

62

POTT'S DISEASE

Radiological characteristic

- Lytic destruction of anterior portion of vertebral body
- Increased anterior wedging
- Collapse of vertebral body
- Reactive sclerosis on a progressive lytic process
- Enlarged psoas shadow with or without calcification



63

STEROIDS AND ACTIVE TB

TB meningitis: *NEJM* 2004;351:1741-51

- reduction in mortality evaluated at 9m; 32% vs 41%, $p=0.01$
- no effect in preventing sequelae,
- no statistical effect in HIV+ve
- dose and duration depend on severity (6-8 weeks)

- prednisone 60mg/d for 4 weeks, then 30mg/d for 4 weeks, 15mg/d for 2 weeks, and 5mg/d for 1 week (11 weeks)
- IMPI study- no benefit of prednisolone for death, CT req pericardio-cent. or constr pericarditis
- HIV-67%, only 24% on ART

- Mortality reduction in HIV- and Reduction of constriction in HIV+ (Cochrane review 2017)

TB pericarditis (??):

- in patients with effusive-constrictive: *Lancet* 1987;2:1418-22
 - lower mortality; 4% vs 11%, $p<0.05$, more rapid resolution of symptoms
 - less need for pericardiectomy; 21% vs 30%, $p<0.05$
 - no reduction of constrictive pericarditis
- in patients with effusive pericarditis: *Lancet* 1988;2:759-64.
 - reduced the need for repeated pericardiocentesis; 9% vs 23%, $p<0.05$
 - lower mortality; 3% vs 14%, $p<0.05$
 - no effect on preventing constriction

- Pott's disease with cord compression if acute
 - Need to r/o MDR TB
- TB Paradoxical Response, miliary TB

64

CASE 7



- 55 year old man presents with a evolving lesion for almost 40 years. Not painful, non pruritic elevated serpiginous verrucous plaque
- Treated multiple times with abx and steroids
- Truck driver, amazon jungle, TB contact neg
- Came to the IMT AVH , Lima Peru during the Gorgas course

65



What is the most likely diagnosis?

- Psoriasis
- Chromoblastomycosis
- Leprosy
- Lupus vulgaris
- Squamous Cell Carcinoma

66

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67

LUPUS VULGARIS

- Plaque, atrophic at the center, with a warty elevated border
- Granulomas are tuberculoid, small, attached to the dermis
- Underlying fibrosis may be present
- Deeper in the dermis one can see tuberculoid granulomas
- Treatment full course of TB therapy
- Rapid response to treatment ~ 5 weeks



Courtesy Dr Bravo: Gorgas Trop derm




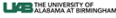


68

GORGAS COURSES

- GORGAS DIPLOMA, 9-sem (DTMH), Peru
- GORGAS Advanced, 2-sem, Peru
- GORGAS Trop Derm, 1 sem, Peru y Rep Dom
- Gorgas Tropical Parasitology, 1 sem
- Gorgas Med Student, 4 sem
- Gorgas Snakes, spiders and scorpions, 1 sem
- Gorgas Travel Medicine, 1 sem


- 1500 health care workers trained
 - Physician, nurses, PhD
 - All corners of the world except antarctica





69

Learn Tropical Medicine in the Tropics!



Thank you

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70