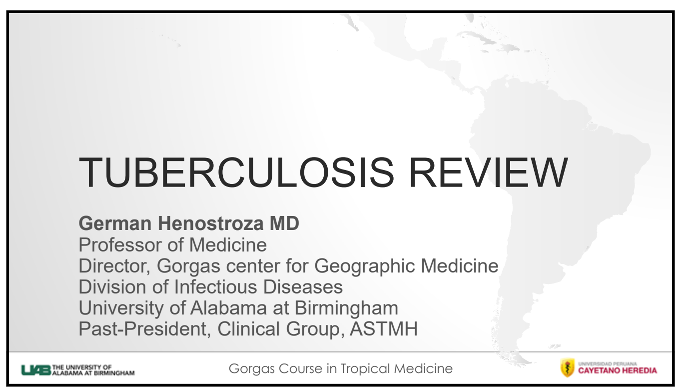
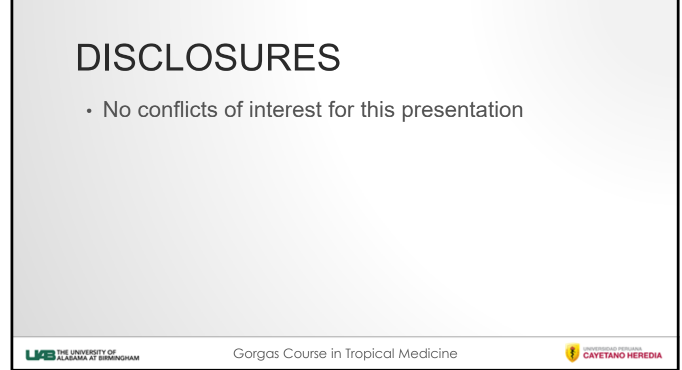
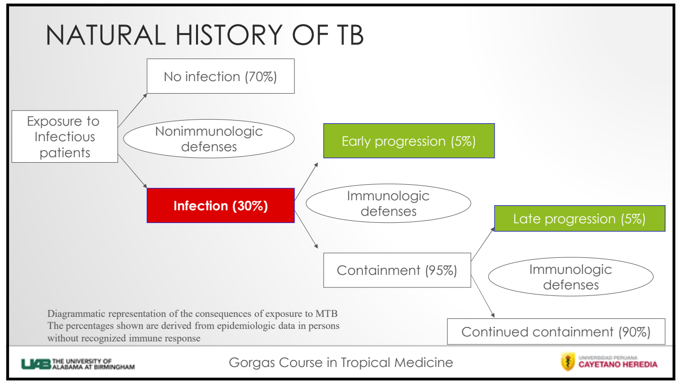


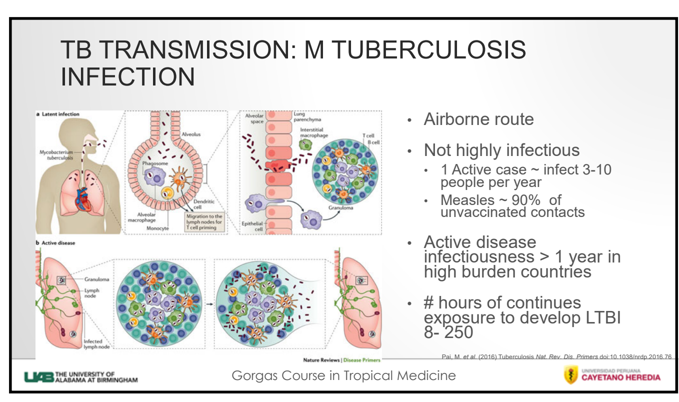
1



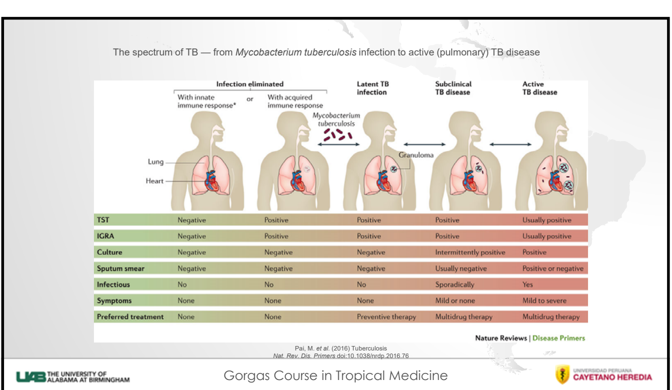
2



3

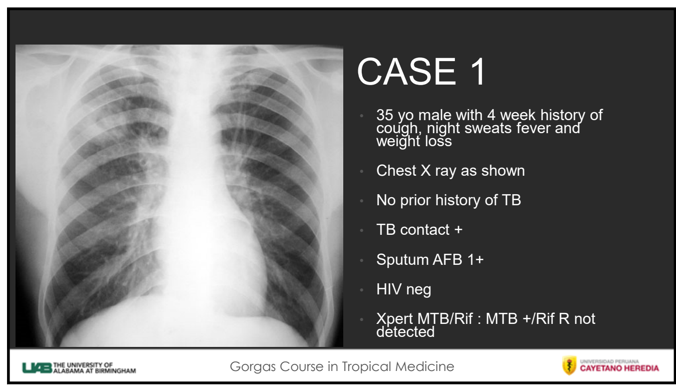


4



	With innate immune response*	With acquired immune response	Latent TB infection	Subclinical TB disease	Active TB disease
TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

5



6

WHAT IS YOUR TREATMENT OF CHOICE AND FOR HOW LONG?

a) HRZE(2m) / HR (4m)

b) HRZE (6m)

c) HRZE (2m) / HR (7m)

d) HRPMoxi (6 M)

7

WHAT IS YOUR TREATMENT OF CHOICE AND FOR HOW LONG?

a) HRZE (6m)

b) HRZE (2m) / HR (7m)

c) HRZE(2m) / HR (4m)

d) HRPMoxi (6 M)

8

REQUIREMENTS FOR ANTI -TB DRUG

- Ability to prevent emergence of resistance in the companion drug
- Early bactericidal activity
  - **the fall in log(10) 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,**

9

WHY WE TREAT TB PATIENTS?

1. To Cure the patient and reduce death or morbidity
2. To reduce transmission of MTB
3. 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

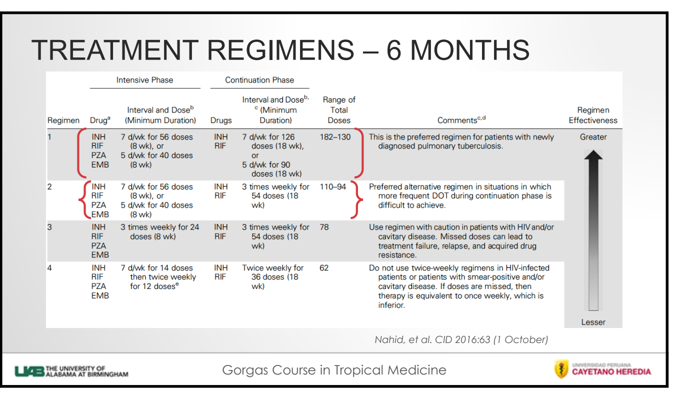
10

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

11

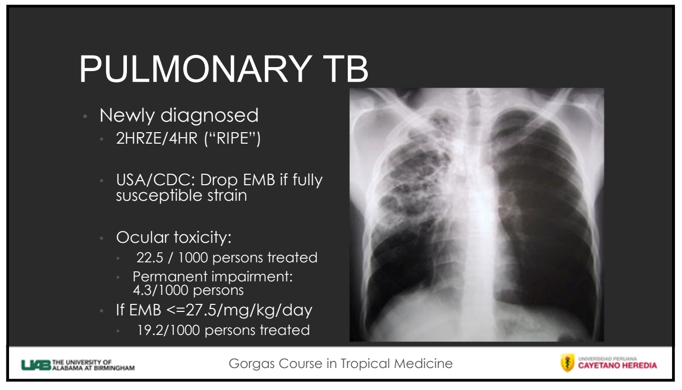
TREATMENT REGIMENS – 6 MONTHS



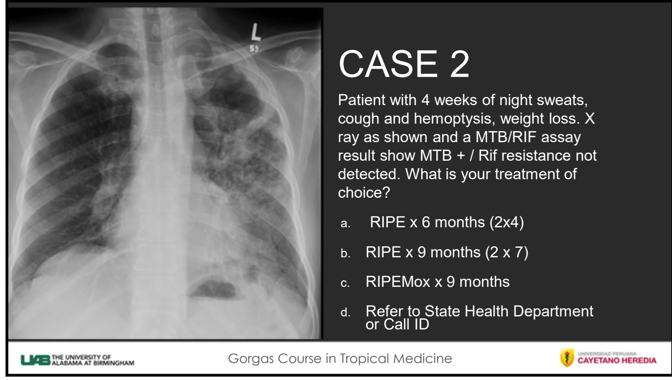
	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (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
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[e]	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.	Lesser

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

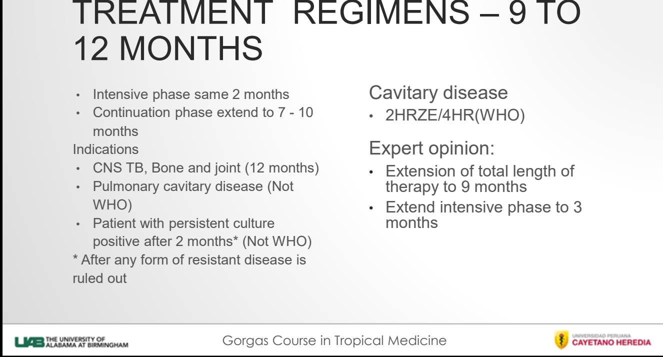
12



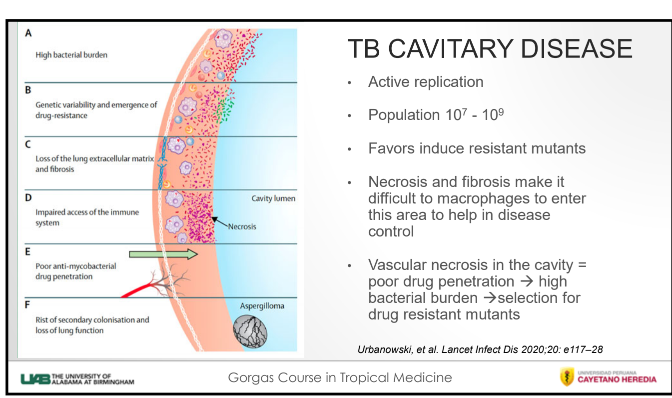
13



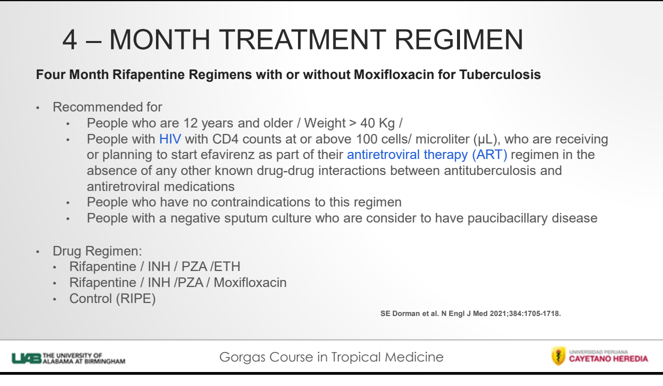
14



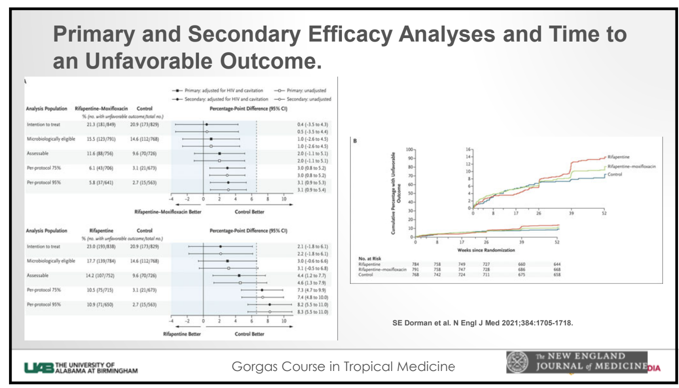
15



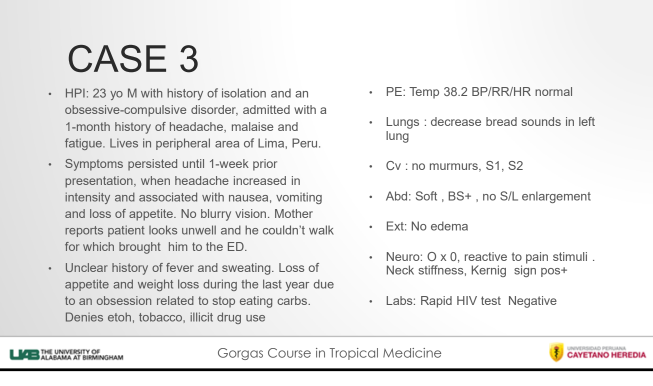
16



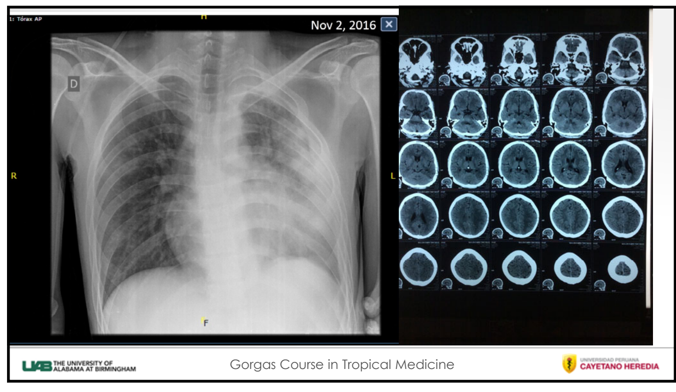
17



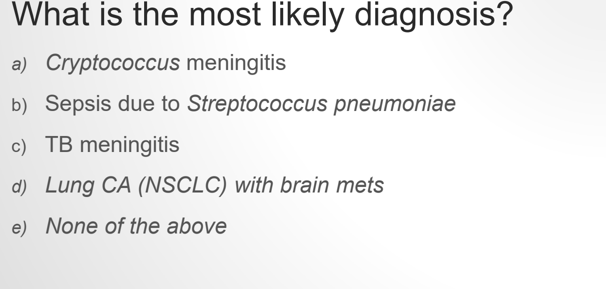
18



19



20



Gorgas Course in Tropical Medicine

21

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*

Gorgas Course in Tropical Medicine

22

LABORATORY/EXAMS

- Bronchioalveolar 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.

Gorgas Course in Tropical Medicine

23

What is the most likely diagnosis?

a) *Cryptococcus* meningitis

b) Sepsis due to *Streptococcus pneumoniae*

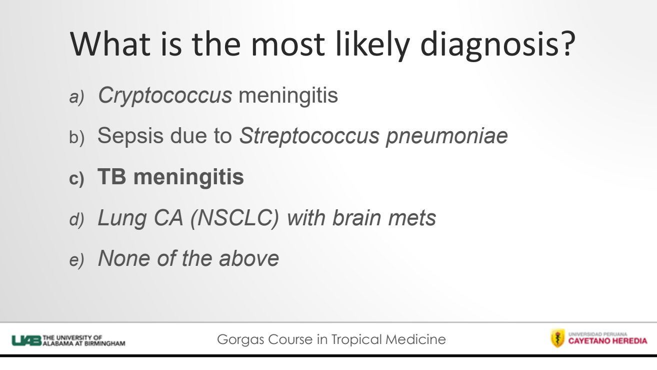
c) TB meningitis

d) *Lung CA (NSCLC) with brain mets*

e) *None of the above*

Gorgas Course in Tropical Medicine

24

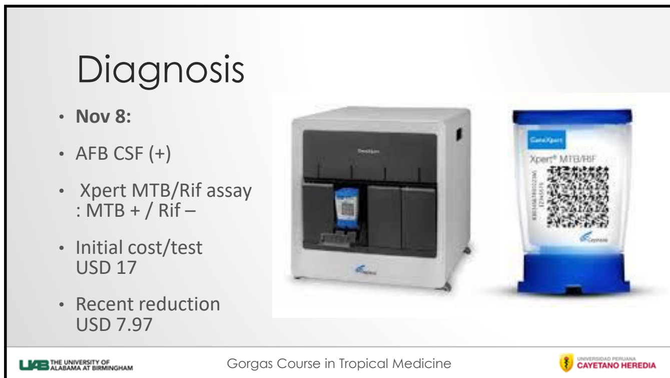


Gorgas Course in Tropical Medicine

25

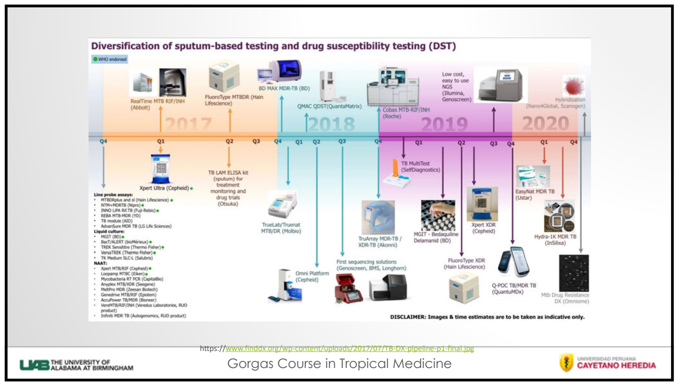
Diagnosis

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



Gorgas Course in Tropical Medicine

26



https://www.finddx.org/wp-content/uploads/2017/07/TB-DX-pipeline-p1-final.jpg

Gorgas Course in Tropical Medicine

27

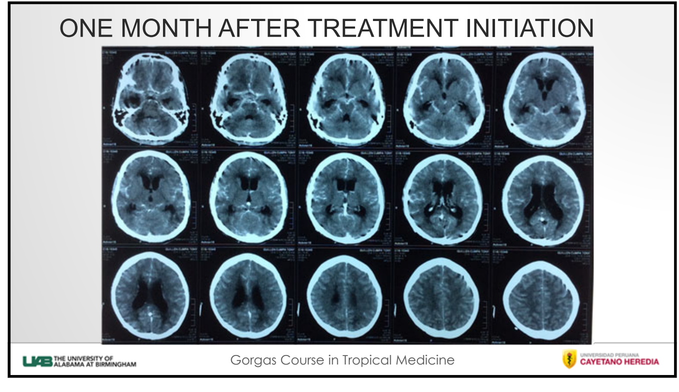
TB MENINGITIS

- 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 .

Gorgas Course in Tropical Medicine

28

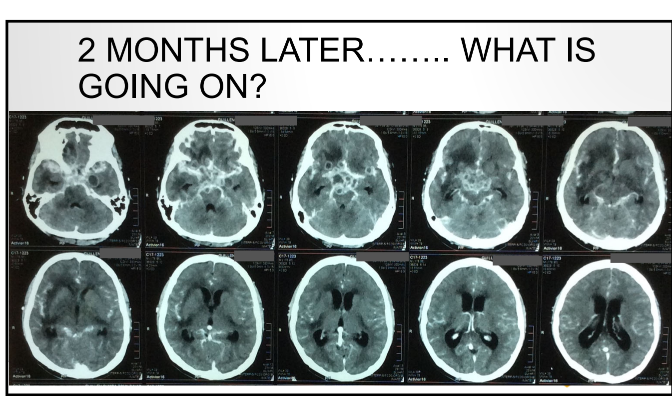
ONE MONTH AFTER TREATMENT INITIATION



Gorgas Course in Tropical Medicine

29

2 MONTHS LATER…….. WHAT IS GOING ON?



30

WHAT IS YOUR DIAGNOSIS?

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

Gorgas Course in Tropical Medicine

31

WHAT IS YOUR DIAGNOSIS?

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

Gorgas Course in Tropical Medicine

32

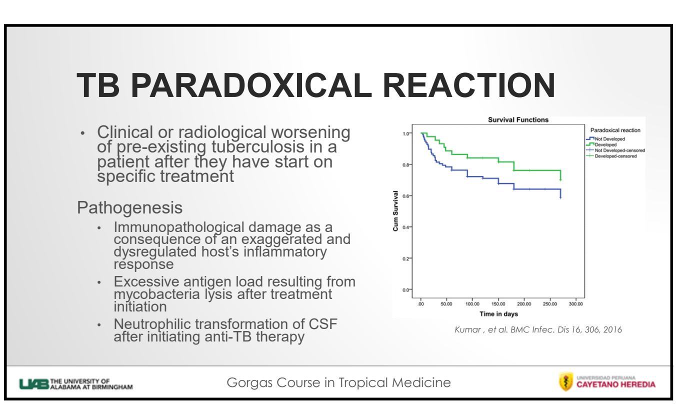
TB MENINGITIS TREATMENT COMPLICATIONS

- 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

Gorgas Course in Tropical Medicine

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 Infec. Dis 16, 306, 2016

Gorgas Course in Tropical Medicine

34

TB PARADOXICAL REACTION

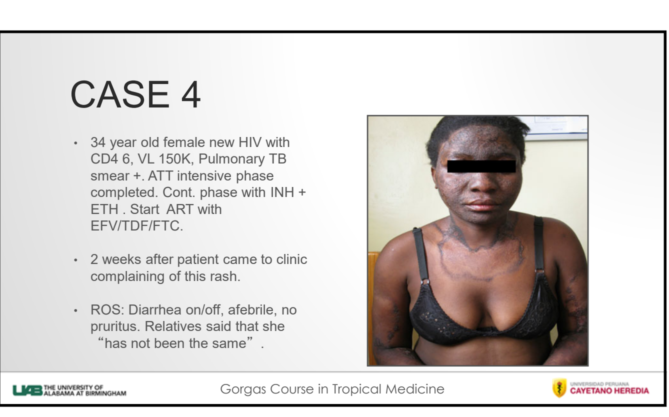
Treatment
- Steroid
  - Prolong Dexamethasone course of therapy
  - Pulses
- Immune modulators
  - TNF -α inhibitors
  - Thalidomide
  - Doxycicline
  - Iburophen

Gorgas Course in Tropical Medicine

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".



Gorgas Course in Tropical Medicine

36

What is your next course of action?

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

37

What is your next course of action?

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

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, chloramphenicol, azathioprine, phenobarbital and ethionamide
- Treatment: Niacin supplementation and change diet

39

PELLAGRA: INH INDUCED

5 Hydroxytryptamine
Tryptophan
Kynurenin → Kynurenic Acid (Photosensitising agent)
Nicotinic Acid (Niacin)
Nicotinamide
NAD ← Competitive Inhibition by isoniazid and ? pyridoxine
NADP

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 naïve patients(remember what to switch to if failing regimens

Table 4.3 Preferred and alternative first-line ART regimens for adults, adolescents, children and neonates

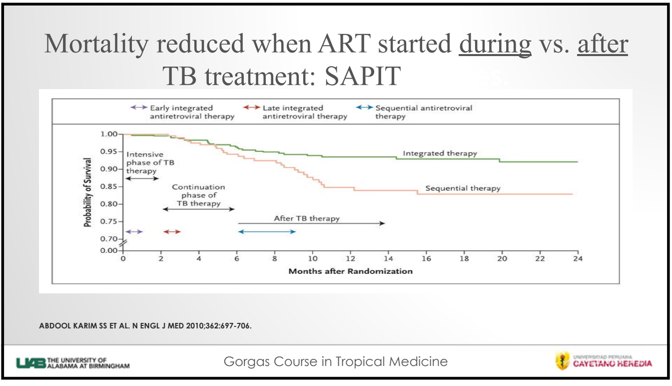
41

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

42

Mortality reduced when ART started during vs. after TB treatment: SAPIT

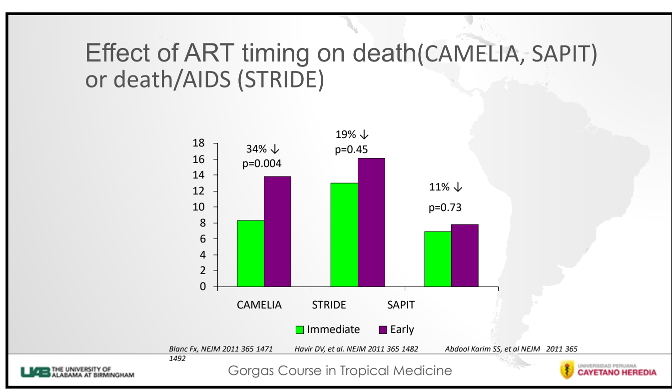


ABDOOL KARIM SS ET AL. N ENGL J MED 2010;362:697-706.

Gorgas Course in Tropical Medicine

43

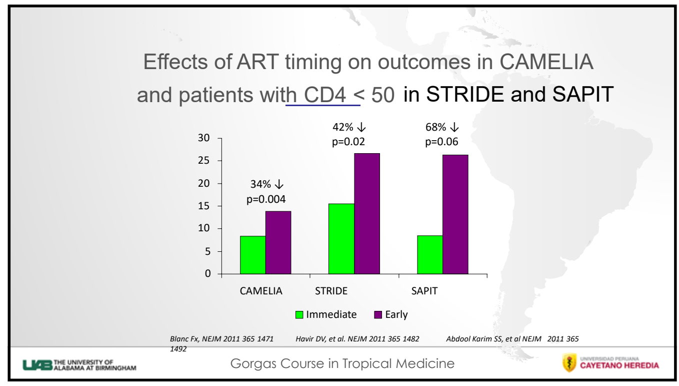
Effect of ART timing on death(CAMELIA, SAPIT) or death/AIDS (STRIDE)



Gorgas Course in Tropical Medicine

44

Effects of ART timing on outcomes in CAMELIA and patients with CD4 < 50 in STRIDE and SAPIT



Gorgas Course in Tropical Medicine

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)

Gorgas Course in Tropical Medicine

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.

Gorgas Course in Tropical Medicine

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 (*rpo*B)
- Xpert MTB/XDR results: resistance to H, susceptibility to Eto, FQ, AG
- DST is pending

What would you recommend him?

Gorgas Course in Tropical Medicine

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

49

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**

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

51

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

52

First sanatorium Germany, 1857
Koch, Mtb, 1882
First Dispensary Scotland, 1897
Pneumothorax, Italy, 1907
BCG vaccination, 1921
MMR, 1950–1980
Fox: Ambulatory treatment, 1968
Styblo model, 1978
DOTS, 1991
Post-2015 global TB strategy 2014 – WHO Framework for TB elimination, 2014
TB elimination

1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020 2030 2040 2050

Streptomycin 1943
PAS 1948
Thiacetazone 1951
Isoniazid 1952
Pyrazinamide/Clofazimine 1954
Cycloserine 1955
Kanamycin/Rifapentine/Rifampicin 1957
Ethionamide 1960
Ethambutol 1961
Capreomycin 1963
Meropenem 1976
Ofloxacin 1982
Sutezolid/Linezolid 1990s
Gatifloxacin 1992
Moxifloxacin 1996
Pretomanid 2000
Benzothiazinones/SQ109 2000s
Bedaquiline 2005
Delamanid 2006

1946: first randomized clinical controlled trial: streptomycin monotherapy caused resistance
1952: first regimen: streptomycin, aminosalicylic acid, and isoniazid for 24 months
1960s: aminosalicylic acid was replaced by streptomycin, isoniazid, and ethambutol for 18 months
1970s: streptomycin, isoniazid, rifampicin, and ethambutol for 9–12 months
1980s: isoniazid, rifampicin, pyrazinamide, ethambutol for 6–8 months (oral)
2010s: new universal and shorter regimen (2–4 months) for TB disease and infection?

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 rifampicin-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 fulfil 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

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 or care *(stopped by DSMB*)**
- WHO made a preliminary update of guidelines

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

57

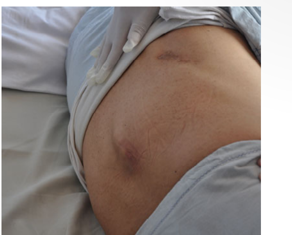
BPaL/ BPaLM INDICATIONS

- 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.
- Pretonamid 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

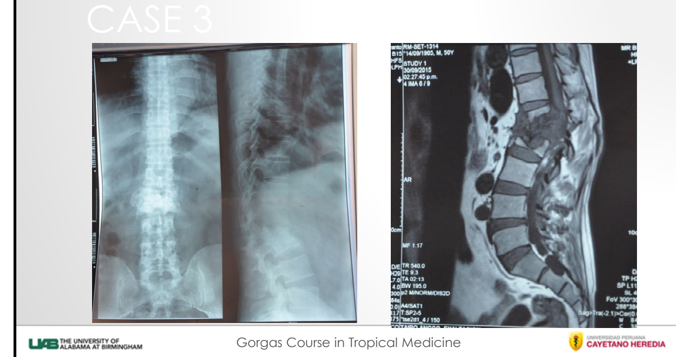
CASE 6

- 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?

a) Spinal cord abscess - MRSA
b) Brucellosis
c) Tuberculosis
d) Paracoccidioidomycosis
e) Spinal tumor/malignancy

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM — Gorgas Course in Tropical Medicine — UNIVERSIDAD PERUANA CAYETANO HEREDIA

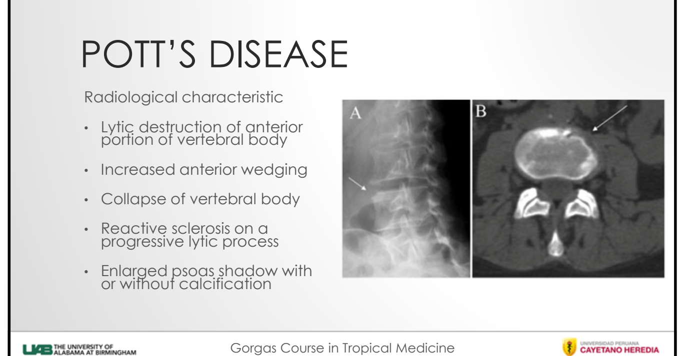
61

WHAT IS YOUR DIAGNOSIS?

a) Spinal cord abscess - MRSA
b) Brucellosis
c) Tuberculosis
d) Paracoccidioidomycosis
e) Spinal tumor/malignancy

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM — Gorgas Course in Tropical Medicine — UNIVERSIDAD PERUANA CAYETANO HEREDIA

62



63

STEROIDS AND ACTIVE TB

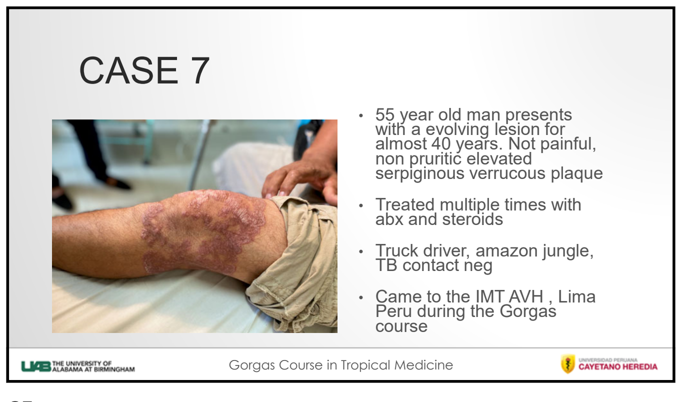
TB meningitis: ***NEJM 2004;351:1741-51***
- reduction in mortality evaluated at 9m; 32% vs 41%, p=0.01
- no effect in preventing sequelae,
- no statistical effect in HIV+ve
- dose and duration depend on severity (6-8 weeks)

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
- 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 pericardiocent. or constr pericarditis
  - HIV+ 67% , only 14% on ART
- Mortality reduction in HIV - and Reduction of constriction in HIV+ (Cochrane review 2017)

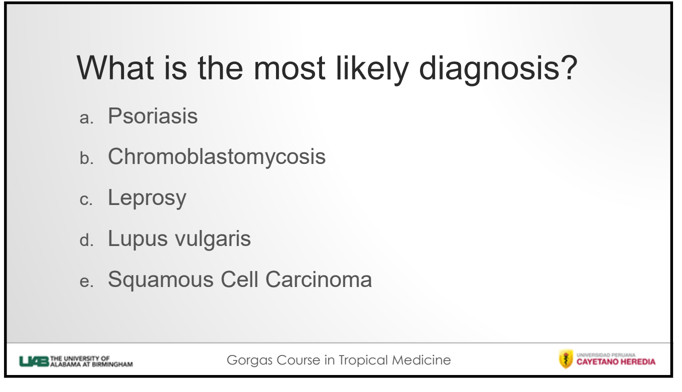
- Pott's disease with cord compression if acute
  - Need to r/o MDR TB
- TB Paradoxical Response, milliary TB

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM — Gorgas Course in Tropical Medicine — UNIVERSIDAD PERUANA CAYETANO HEREDIA

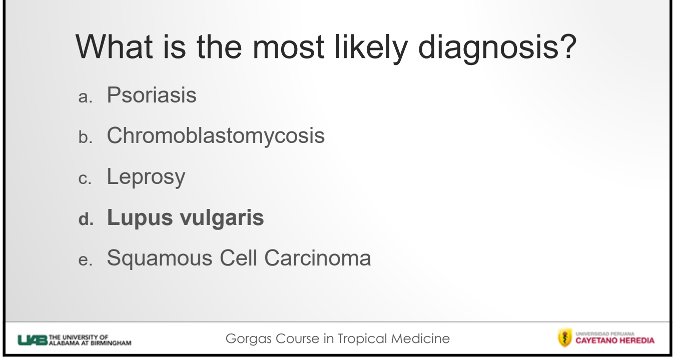
64



65

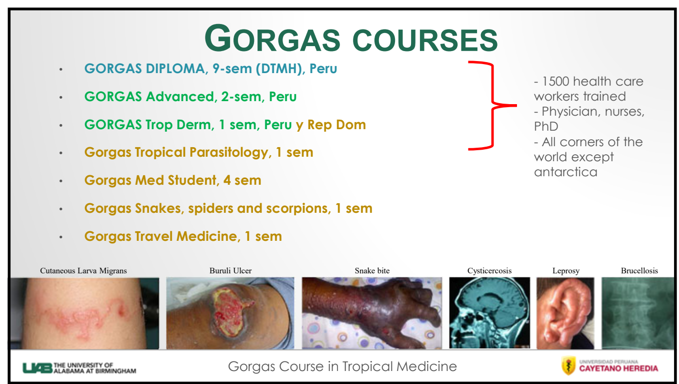


66



67

68



69

70