Challenges in the diagnosis of DR TB in HIV-infected patients

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Deterioration on TB treatment

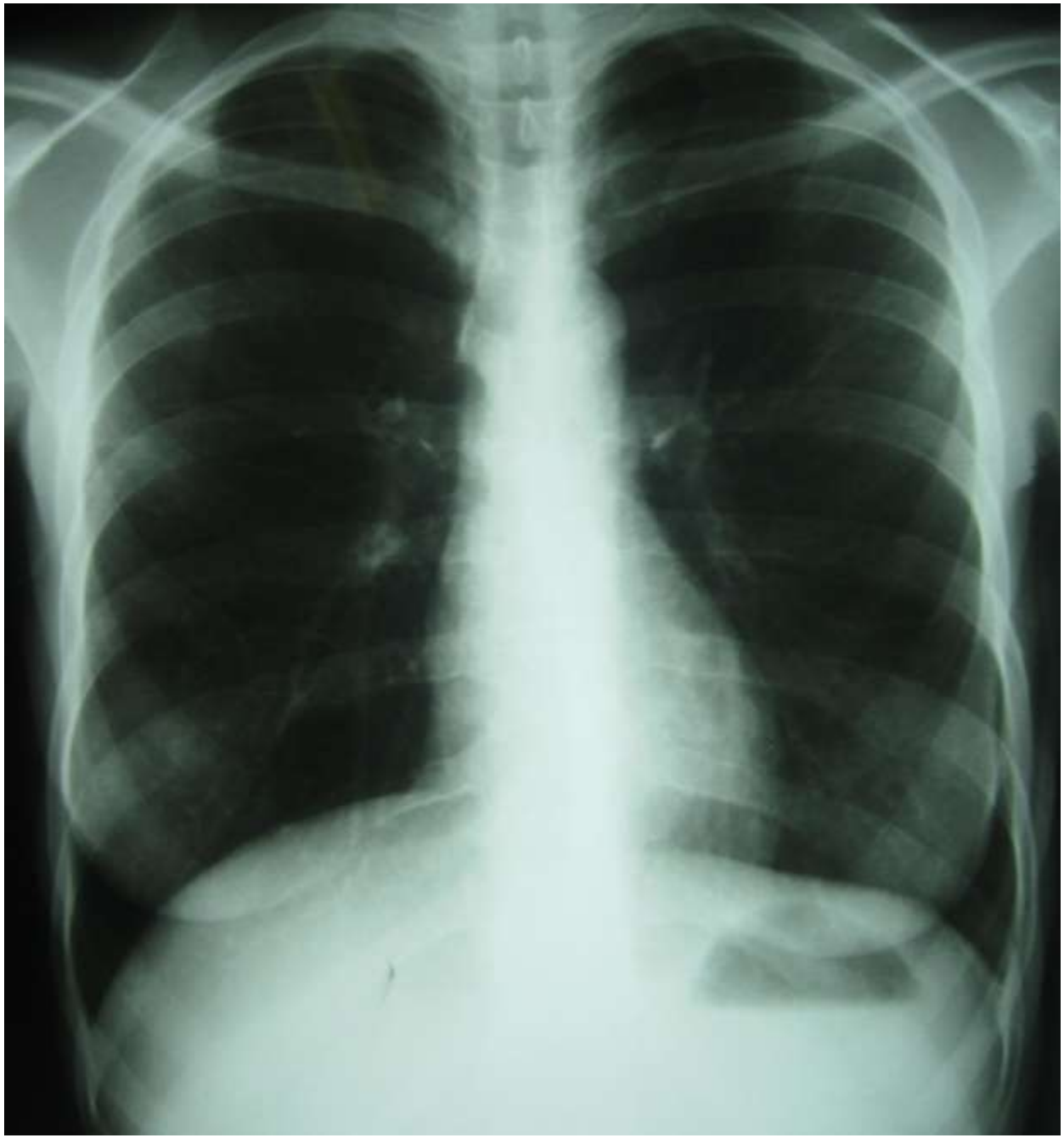
3 cases

CASE 1

- 27 year old HIV+ woman
- CD4 = 74
- Diagnosed with TB at TB clinic in Sep 2011
- Regimen 1 TB treatment on 4 Sep 2011
- ART (TDF, 3TC, EFZ) on 14 Sep 2011

- Referred in Jan 2012 to our hospital for admission
  - Weakness, lethargy, weight loss (later determined to be 19kg), night sweats, dizziness
  - Nausea, vomiting and diarrhoea for one month
  - No cough

- Significant findings
  - Pale and wasted on examination
  - Hb = 6.1 (MCV 106) WCC 10.6 Plt 516
  - Creat = 147
  - LFTs normal



Management

- Investigated for anaemia:
  - no evidence of haemolysis
  - no evidence of nutritional cause
  - parvovirus B19 PCR negative
- No stool obtained
- Sputa sent for TB microscopy and culture
- VL = LDL and CD4 = 52

- Transfused 2 units
- TDF switched to D4T (renal impairment)
- Nutritional support
- Discharged for outpatient follow-up at our hospital
  - Was seen once but then did not return.

Sputum TB results

Date	Microscopy	Culture	DST
4 Aug 2011	Neg	MTB	-
23 Aug	Pos 1+	-	-
23 Aug 2011	Neg	MTB	-
13 Oct	Neg	-	-
13 Oct	Neg	-	-
13 Jan 2011	Scanty +	MTB	Rif sens INH sens
20 Jan 2011	Neg	Neg	-
20 Jan 2011	Scanty +	Contaminated	-

Re-admitted April 2011

- Intentional organophosphate poisoning
- Stabilised in high care

- Noted to be wasted and ill
- Abdominal pain and tenderness noted (especially RIF)
- Swollen right leg
- Hb = 4.9 (MCV 98) WCC 14.3 Plt 238
- Creat = 108
- CRP = 125
- CXR = Subtle nodular infiltrate in left lower zone

- What next?

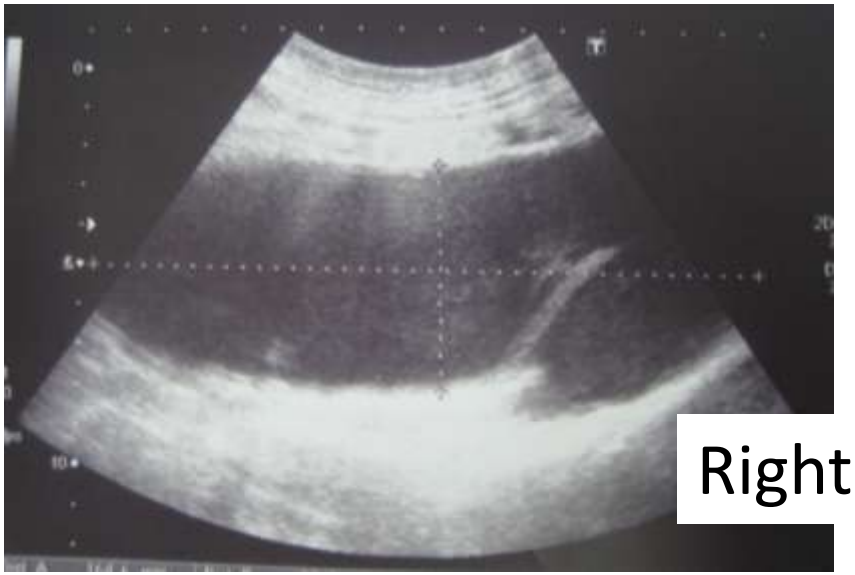
What next?

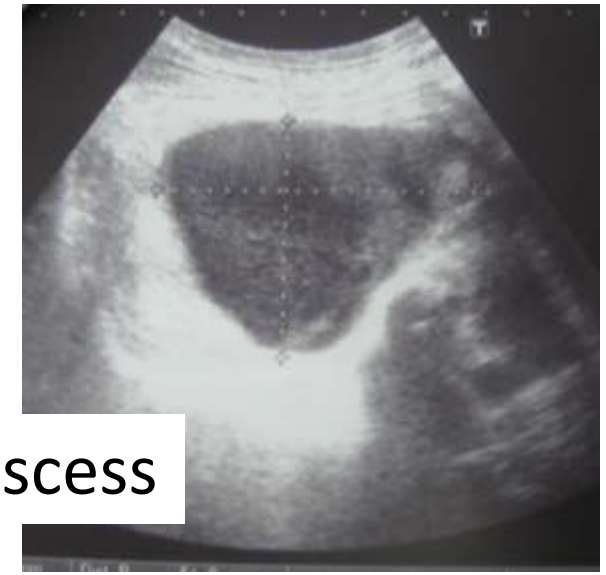
- Assessed adherence
  - ART: Possible inadequate adherence noted on pill count. Viral load in Jan LDL, but viral load in Apr was 1100 copies/ml.
  - TB: Self-reported good adherence, and TB card reviewed in Jan showed this. Phoned TB clinic and they could not provide information.
- Review of sputum TB results & further sputa sent
- Abdominal USS
- Serum CLAT = negative

Abdominal ultrasound

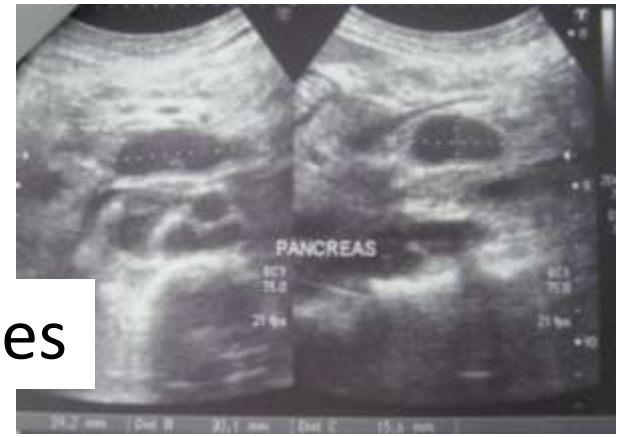
- Hypoechoic area inferior to pancreas, likely necrotic LN (4 x 3 x 2 cm)
- Right psoas abscess extending from kidney to femoral head (17 x 8 x 6 cm)
- Splenic microabscesses
- Free fluid in pouch of Douglas
- DVT in right common and superficial femoral veins

Abdominal USS





Right psoas abscess



Necrotic lymph nodes

Next step?

USS guided aspirate of psoas abscess: requested Xpert on pus

- Psoas abscess aspirate (19 April)
  - Smear 3+ AFB
  - Xpert: MTB with Rif resistance
  - Culture: MTB
  - DST on culture: Rif resistance, but susceptible to INH, Oflox, Ethio and Amikacin

- Sputum
  - 13 Apr: Smear negative, cultured MTB, also Rif monoresistance
  - 26 Apr: Smear and culture negative
  - 26 Apr: Smear and culture negative

Follow-up

- Referred for inpatient MDR TB treatment plus INH

- Two recent sputum cultures negative and discharged for outpatient treatment

Questions and issues

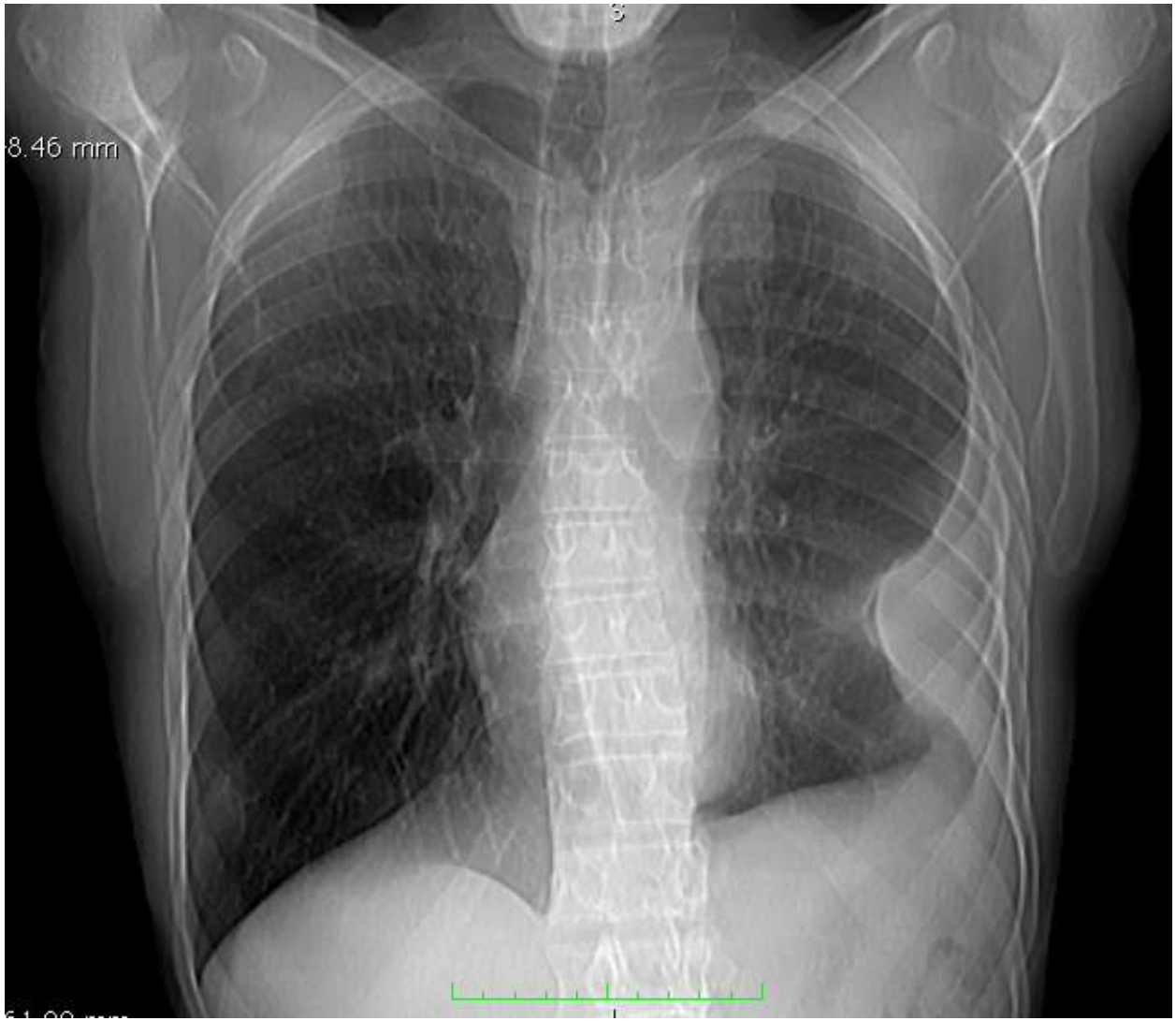
- Should she have been started on empiric MDR TB treatment earlier?
- Complicated by her not re-attending for follow-up
- Adherence difficult to assess at referral hospital
  - How does clinician at this level differentiate poor adherence from possible drug resistance?
- Was this initially mixed infection or was rifampicin resistance selected due to inadequate adherence?
- Psychological issues poorly assessed and addressed
  - Seen by Social Worker and “social isolation” reported
  - No formal assessment for depression or consideration of treatment

CASE 2

- 39 year old HIV+ man
- On second-line ART, CD4 = 143
- Previous TBM in 2005
- Diagnosed with disseminated TB in Aug 2011
  - Abdominal USS: lymphadenopathy
  - Left pleural effusion: ADA 99, but TB culture negative

- Symptoms including leg weakness improved
- CRP remained elevated and anemia

- TB culture of pleural fluid again negative
- Rifampicin levels in therapeutic range
- 2 x sputum cultures negative
- Presented in May 2012 still on RHZE with progressive leg weakness and sensory loss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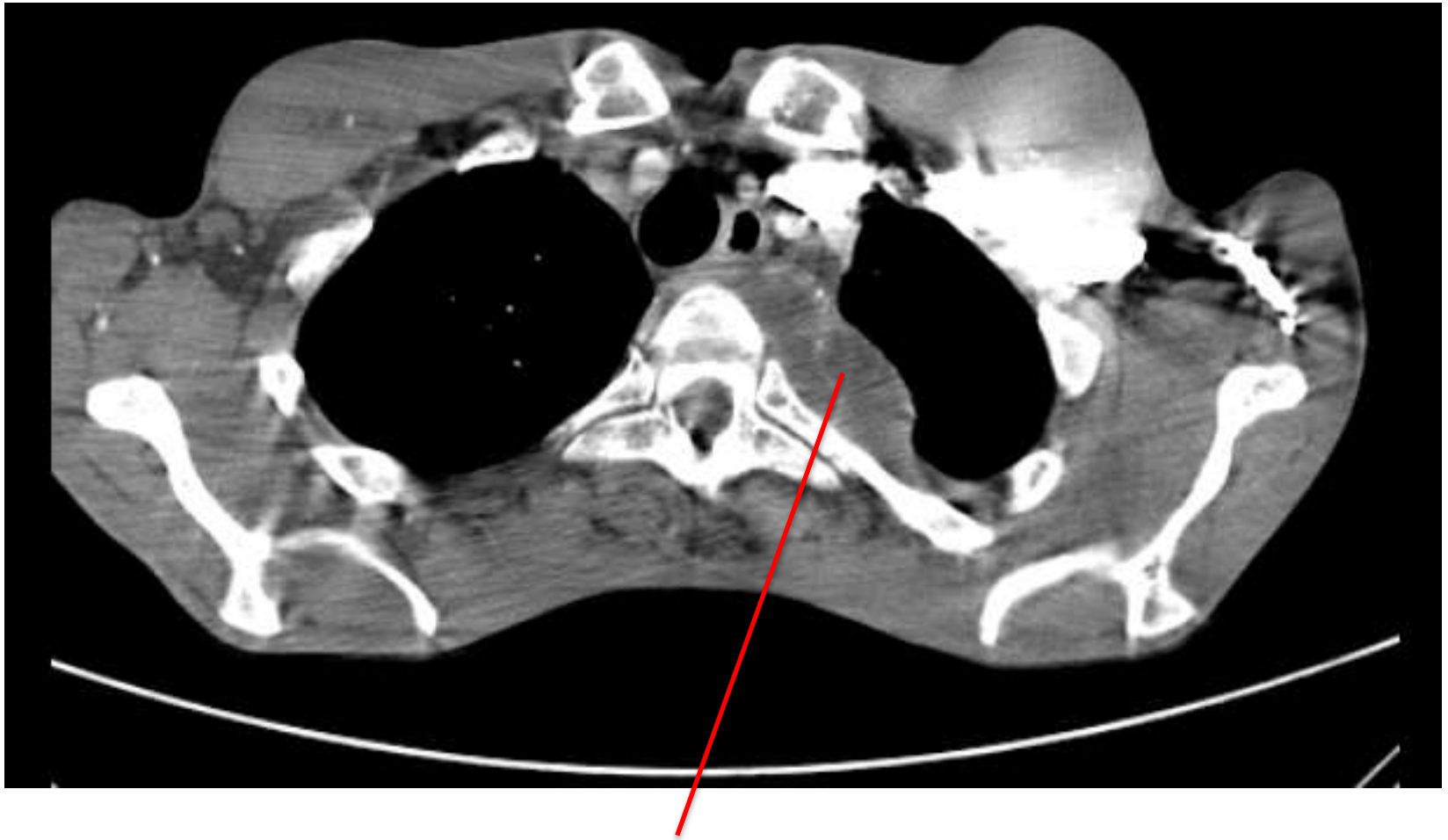


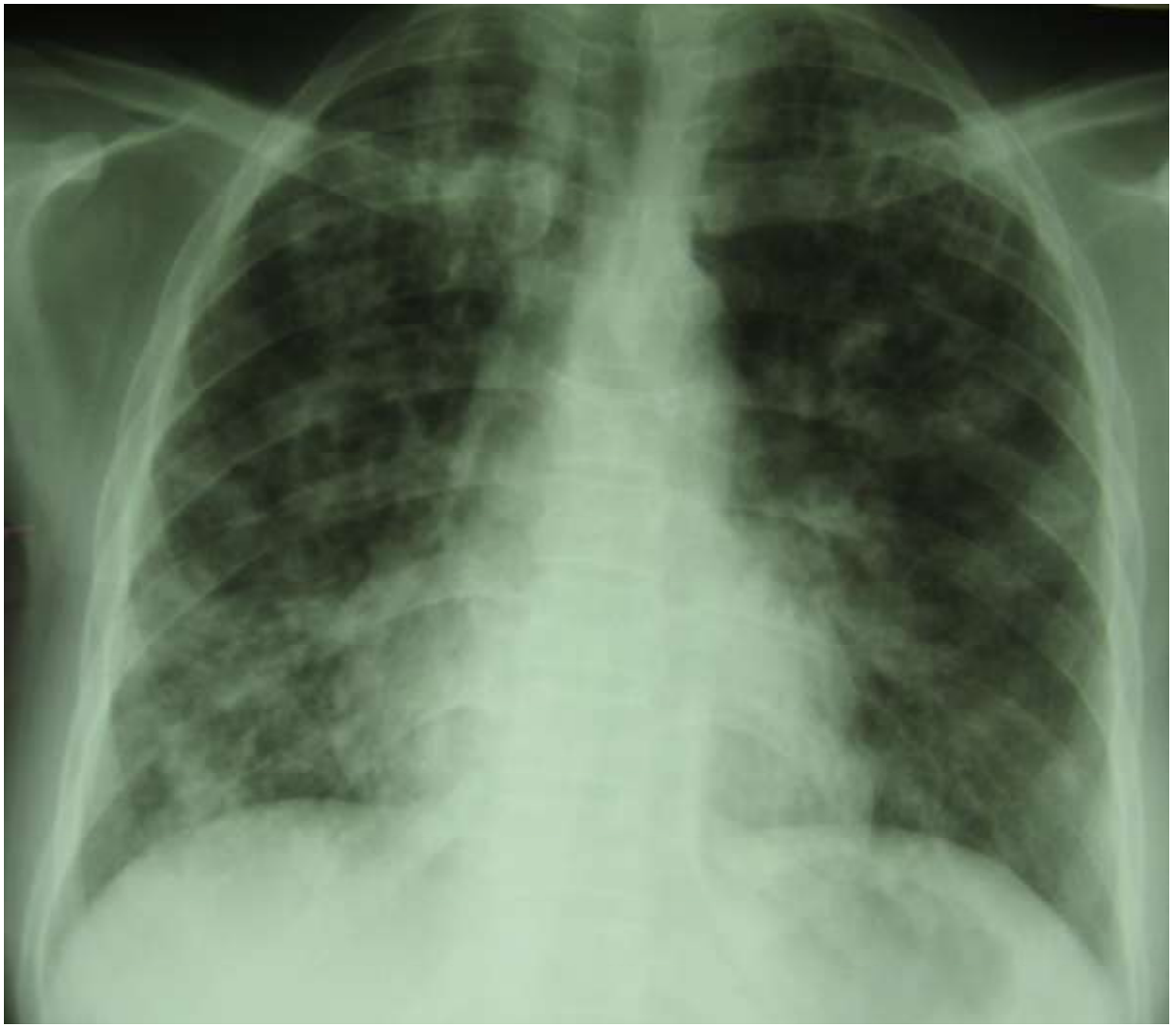
Pus aspirate sent for Xpert:
MTB with rifampicin resistance
(Confirmed MDR on culture)

CASE 3

(Pre-Xpert era)

- 27 year old HIV-infected woman admitted with the following history
  - Completed TB treatment 2 weeks ago
  - TB symptoms (cough and constitutional)

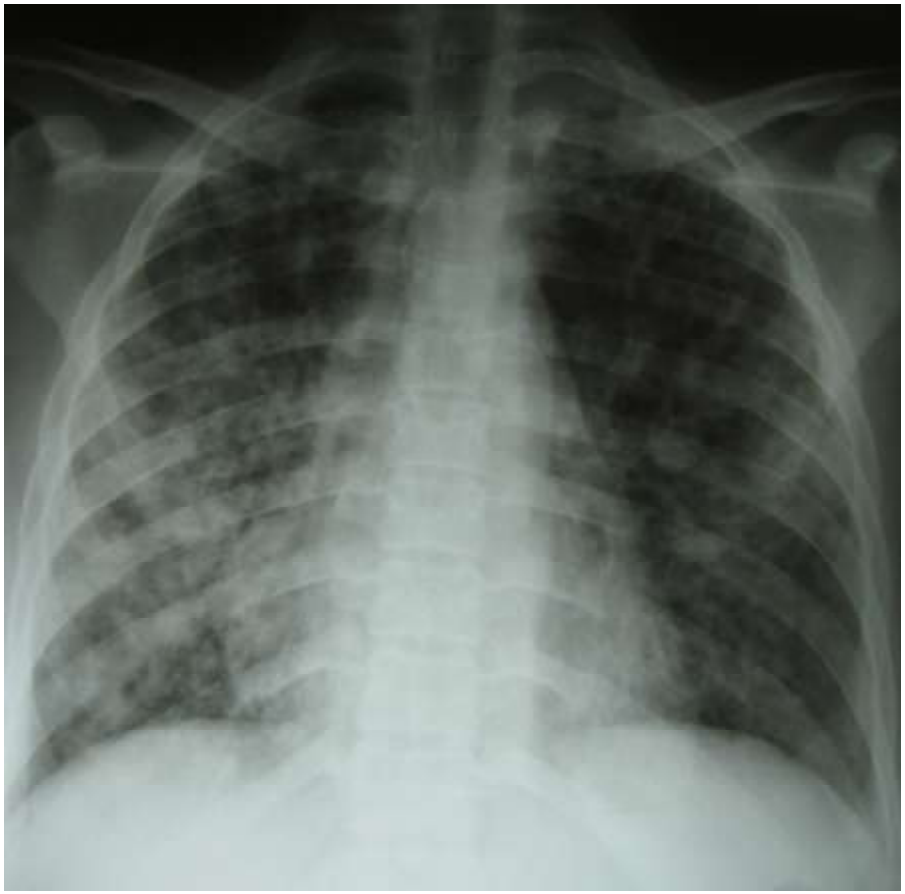
- CD4 = 27



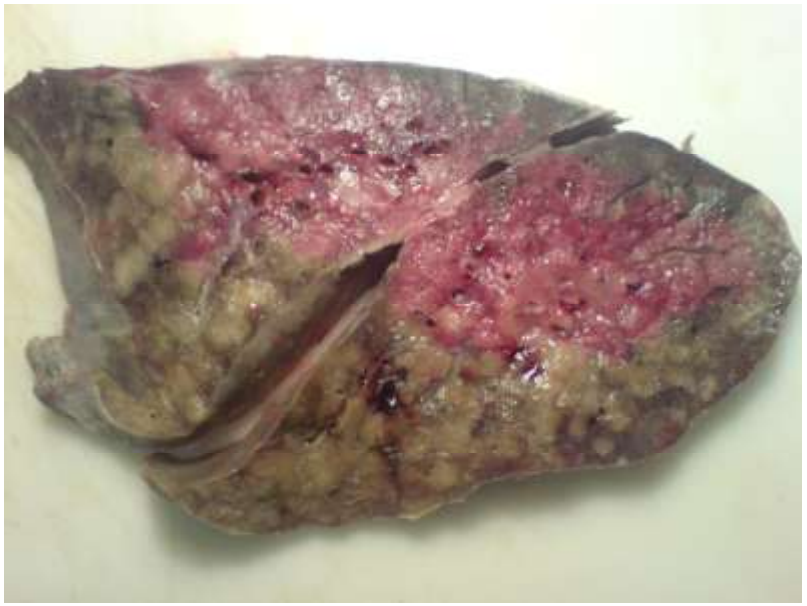
In the ward

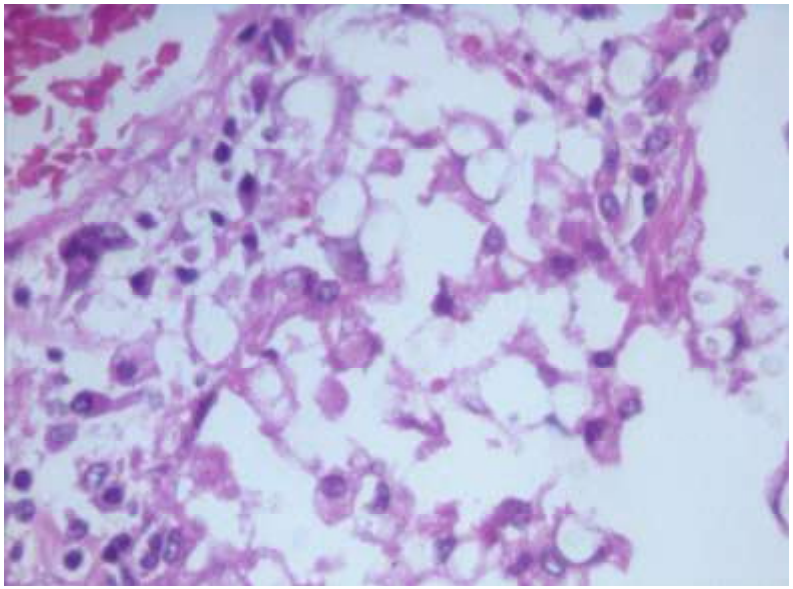
- Co-amoxiclav x 1 week
- Sent 2 sputa for TB MC&S
- Smears negative
- No improvement after a few days
- Started Regimen 2 TB treatment
- Referred the patient to the clinic

- What do you think of this management?



Presented 3 weeks later with seizures, headaches and confusion
CRYPTOCOCCAL MENINGITIS diagnosed on CSF
Patient died after 2 days on Amphotericin-B





Pulmonary cryptococcosis

- Autopsy series on mines where 24% were HIV+
  - 589/8421 (7%) had pulmonary cryptococcosis
  - 52% undiagnosed, many misdiagnosed as PTB

- CM cases at GF Jooste - 15% diagnosed with SNTB in 3 months prior to admission

- Serum cryptococcal antigen is positive in 7% of patients entering ART programme in Guguletu

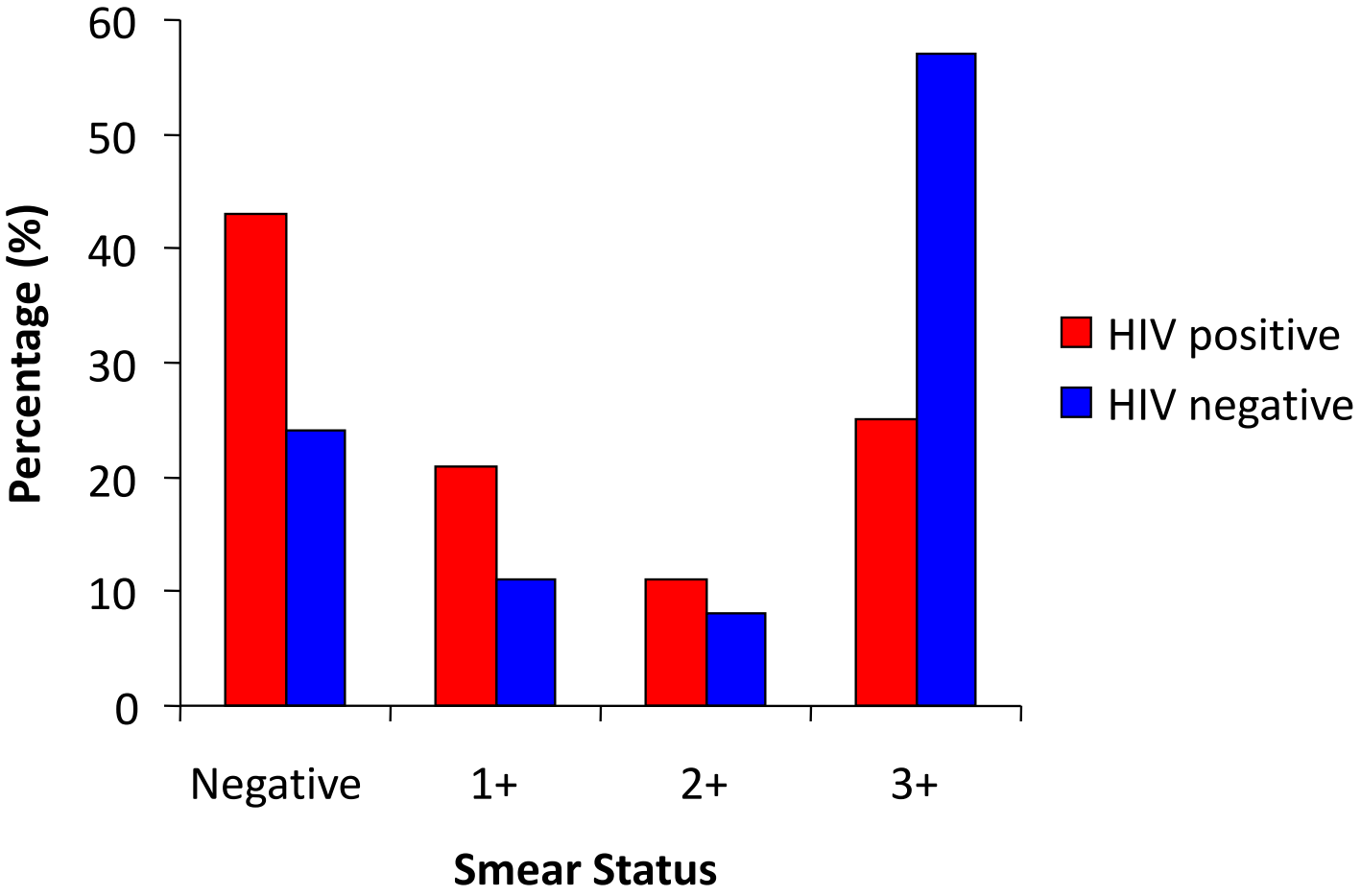
Wong, IJTLD 2007
Jarvis, unpublished
Jarvis, Clin Infect Dis 2009

DISCUSSION

1. Sputum paucibacillary in advanced HIV
2. Extrapulmonary TB
3. Broader spectrum of differential diagnoses
4. Temporary improvement on first line Rx
5. When to consider empiric MDR treatment

1. Sputum paucibacillary

Sputum smear and HIV status in drug-susceptible TB



Source: Elliott AM. Tubercle Lung Dis. 1993.

Xpert sensitivity and HIV status

	HIV positive	HIV negative
Sensitivity in culture-positive samples		
Smear microscopy	86/193 (44·6%, 37·7–51·6)	234/341 (68·6%, 63·5–73·3)
MTB/RIF test	173/210 (82·4%, 76·7–86·9)	304/335 (90·7%, 87·2–93·4)
Sputum positive	84/86 (97·7%, 91·9–99·4)	204/206 (99·0%, 96·5–99·7)
Sputum negative	89/124 (71·8%, 63·3–78·9)	100/129 (77·5%, 69·6–83·9)

Boehme, Lancet 2011

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

	MDR TB	XDR TB
Total with available medical records, n	123	139
Female sex, n (%)	53 (43)	78 (56)
Age, years, median (IQR)	34 (29–43)	34 (29–42)
Tested for HIV, n (%)	94 (76)	117 (84)
HIV positive, n (% tested)	85 (90)	115 (98)
CD4 measured at TB diagnosis, n (% of HIV+)	41 (48)	36 (31)
Median (IQR)	87 (41–217)	66 (24–169)
VL measured at TB diagnosis, n (% of HIV+)	12 (14)	18 (16)
Median	160,000	135,500
(IQR)	(81,500–1,010,000)	(180–410,000)
Receiving antiretroviral therapy at time of TB diagnosis, n (% of HIV+)	13 (15)	25 (22)
Positive sputum smear, n (%)	77 (63)	84 (61)
Presence of extrapulmonary TB, n (%)	34 (28)	41 (30)
Previous TB Treatment		
Any, n (%)	92 (75)	96 (69)
Past year, n (%)	67 (55)	78 (56)
Previous hospitalization within past 2 years, n (%)	63 (51)	79 (57)
Referred for second line TB therapy: n (%)	46 (37)	35 (25)
Time to referral: median days (IQR)	69 (53–95)	66 (52–84)

Definition of abbreviations: IQR = interquartile range; MDR = multidrug-resistant; TB = tuberculosis; VL = HIV viral load; XDR = extensively drug-resistant.

Only 63% of MDR and 61% of XDR patients smear + at DR TB diagnosis

In patient deteriorating clinically, negative smear does not exclude DR TB

Gandhi, AJRCCM 2010

Sputum induction

- To obtain specimen if cough non-productive
- To improve diagnostic yield of sputum

Tuber Lung Dis. 1995 Feb;76(1):72-6.

The use of sputum induction for establishing a diagnosis in patients with suspected pulmonary tuberculosis in Malawi.

Parry CM, Kamoto O, Harries AD, Wirima JJ, Nyirenda CM, Nyangulu DS, Hart CA.

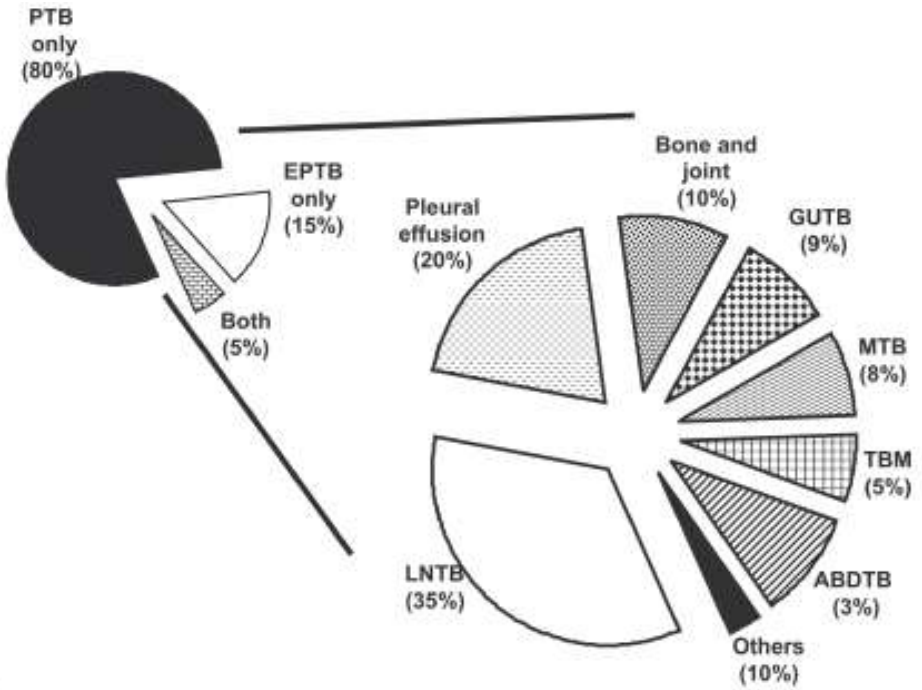
Department of Medical Microbiology, Liverpool University, UK.

  - 19% of smear+ cases detected by SI

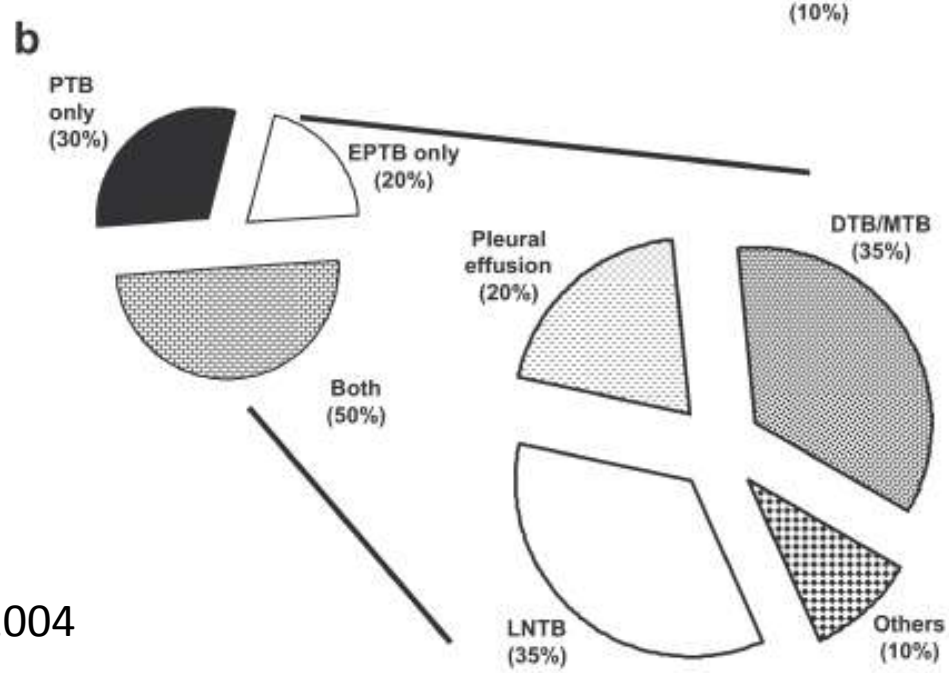
- Key role in diagnosis of DR TB in those with low bacillary burden in sputum

2. Extrapulmonary TB

HIV-negative

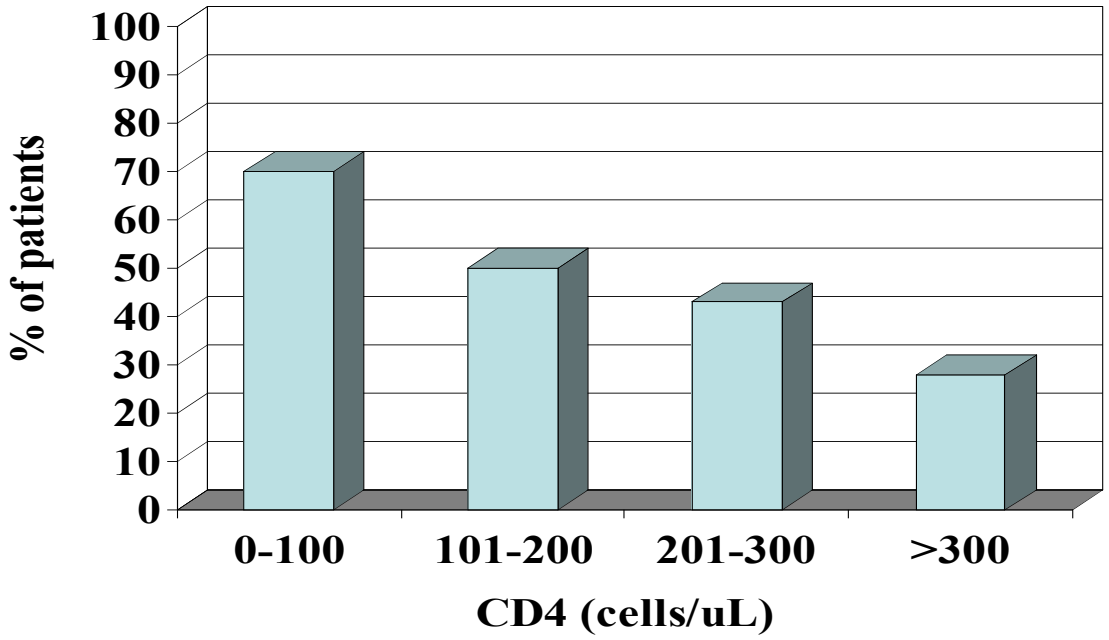


HIV-positive



Sharma, Indian J Med Research 2004

Frequency of extrapulmonary TB according to CD4 count



Jones BE, *Am Rev Respir Dis* 1993: 148(5): 1292-1297

Extrapulmonary TB in HIV

- Majority of patients with low CD4 counts have EPTB even if not clinically evident
  - Post-mortem data

- Theoretical possibility that MTB could evolve differentially in different anatomical compartments contributed to by:
  - High organism burden
  - Adherence issues
  - Drug absorption and penetration issues

Samples for diagnosis of extrapulmonary DR TB

- Lymph node or cold abscess needle biopsy
  - Aspirate pus
  - Flush needle with saline / liquid transport medium
- Lymph node excision biopsy
- Ultrasound-guided needle biopsy of intra-abdominal nodes or pus collections
- Aspirate of effusion
- Lumbar puncture
  - but diagnostic delays in MDR TBM frequently fatal (Xpert)

- Extrapulmonary specimen may be the only way to make diagnosis in some cases

Extensively Drug-Resistant *Mycobacterium tuberculosis* from Aspirates, Rural South Africa

Scott K. Heysell, Anthony P. Moll, Neel R. Gandhi, François J. Eksteen, Palav Babaria, Yacoob Coovadia, Lynn Roux, Umesh Lalloo, Gerald Friedland, and N. Sarita Shah

The yield from aspirating lymph nodes and pleural fluid for diagnosing extensively drug-resistant (XDR) tuberculosis is unknown. *Mycobacterium tuberculosis* was cultured from lymph node or pleural fluid aspirates of 21 patients; 7 (33%) cultures grew XDR *M. tuberculosis*. Additive diagnostic yield for XDR *M. tuberculosis* was found in parallel culture of sputum and fluid aspirate.

Emerging Infectious Diseases 2010

Heysell et al. BMC Infectious Diseases 2010, 10:344
http://www.biomedcentral.com/1471-2334/10/344

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Blood cultures for the diagnosis of multidrug-resistant and extensively drug-resistant tuberculosis among HIV-infected patients from rural South Africa: a cross-sectional study

Scott K Heysell[1,2*], Tania A Thomas[1,2], Neel R Gandhi[1,3], Anthony P Moll[1,4], François J Eksteen[1,4], Yacoob Coovadia[5,6], Lynette Roux[5], Palav Babaria[1,7], Umesh Lalloo[6], Gerald Friedland[1,7], Sarita Shah[1,3]

Abstract

Background: The yield of mycobacterial blood cultures for multidrug-resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB) among drug-resistant TB suspects has not been described.

Methods: We performed a retrospective, cross-sectional analysis to determine the yield of mycobacterial blood cultures for MDR-TB and XDR-TB among patients suspected of drug-resistant TB from rural South Africa. Secondary outcomes included risk factors of *Mycobacterium tuberculosis* bacteremia and the additive yield of mycobacterial blood cultures compared to sputum culture.

Results: From 9/1/2006 to 12/31/2008, 130 patients suspected of drug-resistant TB were evaluated with mycobacterial blood culture. Each patient had a single mycobacterial blood culture with 41 (32%) positive for *M. tuberculosis*, of which 20 (49%) were XDR-TB and 8 (20%) were MDR-TB. One hundred fourteen (88%) patients were known to be HIV-infected. Patients on antiretroviral therapy were significantly less likely to have a positive blood culture for *M. tuberculosis* ($p = 0.002$). The diagnosis of MDR or XDR-TB was made by blood culture alone in 12 patients.

Conclusions: Mycobacterial blood cultures provided an additive yield for diagnosis of drug-resistant TB in patients with HIV from rural South Africa. The use of mycobacterial blood cultures should be considered in all patients suspected of drug-resistant TB in similar settings.

130 blood cultures in DR TB suspects: 41 positive
MDR or XDR TB diagnosis made by blood culture alone in 12

Xpert on extrapulmonary specimens

Table 1. Summary of studies (n = 8) published before 7 March 2012 in which the diagnostic accuracy of Xpert® MTB/RIF for extrapulmonary TB was assessed.

Study (year)	Country	TB gold standard diagnoses (n)	TB not diagnosed (n)	Main sample types testing positive for TB (n)	Gold standard for TB diagnosis	Xpert sensitivity, % (95% CI)	Xpert specificity, % (95% CI)	Ref.
Index study								
Tortoli *et al.* (2012)	Italy	268	1206	Tissue biopsies/fine-needle aspirates (94); pleural fluid (18); gastric aspirates (61); pus (55); CSF (14); urine (16); peritoneal/ synovial/pericardial fluid (10)	Culture (solid and liquid) or suggestive radiology/ histology with documented positive response to TB treatment	81.3 (76.2–85.8)	99.8 (99.4–100)	[5]
Other studies								
Armand *et al.* (2011)	France	32	NA	LNs (16); pleural (7); bone (5)	Culture (solid and liquid media)	53.1 (34.7–70.9)	NA	[6]
Causse *et al.* (2011)	Spain	41	299	Tissue biopsies (18); CSF (6); gastric aspirates (8); pleural fluid (4); purulent exudates (5)	Culture (solid and liquid media)	95.1 (83.5–99.4)	100 (98.8–100)	[7]
Friedrich *et al.* (2011)	South Africa	20	5	Pleural fluid (25)	Culture (liquid media)	25.0 (8.7–49.1)	100 (47.8–100)	[8]
Hillemann *et al.* (2011)	Germany	45	476	Tissue (30); gastric aspirate (8); urine (5)	Culture (solid and liquid media)	77.3 (60.5–87.1)	98.2 (96.0–98.9)	[9]
Ligthelm *et al.* (2011)	South Africa	30	18	Fine-needle aspiration LN biopsy	Composite standard: positive cytology + AFB and/or culture of MTB	96.6 (86.6–100)	88.9 (69.6–100) (note: only 18 samples)	[10]
Moure *et al.* (2011)	Spain	108	41	All smear-negative. Pleural fluid (26); LNs (34); abscess aspirates (17); tissues (12)	Culture (solid and liquid media)	58.3 (48.5–67.8)	100 (91.4–100)	[11]
Vadwai *et al.* (2011)	India	283	250	Tissue biopsies (105); pus (98); body fluids (24)	Composite of smear, culture, clinical, radiology and histology	80.6 (75.5–85.0)	99.6 (97.8–100)	[12]

Only studies with at least 20 gold standard diagnoses of extrapulmonary TB were included.
AFB: Acid-fast bacilli; CSF: Cerebrospinal fluid; LN: Lymph node; MTB: *Mycobacterium tuberculosis*; NA: Not available.

Lawn, Expert Rev Anti-Infect Ther 2012

Xpert sensitivity on EPTB specimens

Specimens	Sensitivity
Biopsies Pus CSF	> 85%
Cavitary fluids	< 50%

Tortoli, Eur Resp J 2012

3. Broad spectrum of differential diagnoses

Clinical deterioration requiring hospital referral

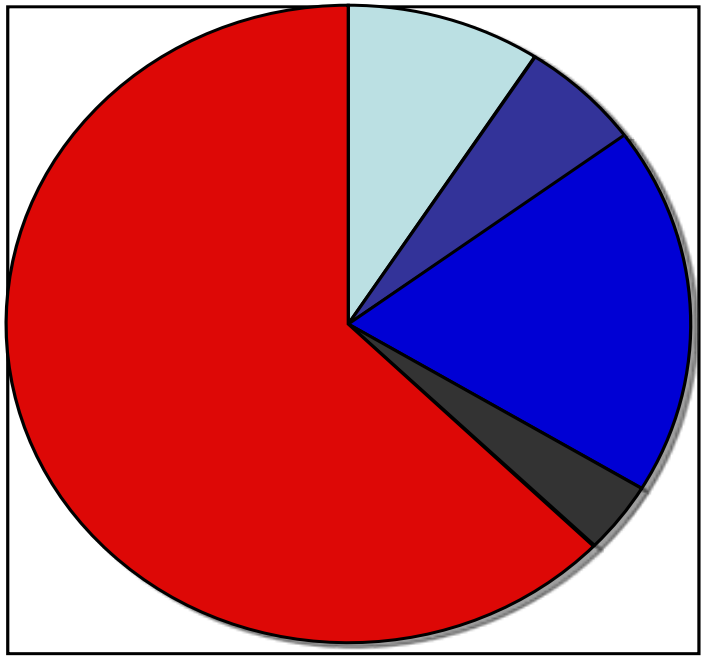
- GF Jooste Hospital in Cape Town
- 352 patients over a 3 month period
- 296 admitted (17% of medical admissions)

- 83% HIV-infected with median CD4 = 89

- 16% died
- Median duration of admission 9.5 days

Pepper, PLoS ONE 2009

Causes of deterioration
HIV-infected patients (n=291)



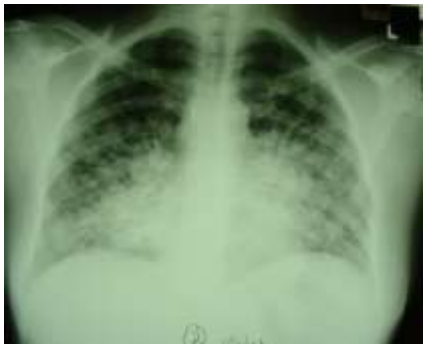
- Rifampicin-resistant TB - 10%
- Poor adherence - 7%
- TB-IRIS/Paradoxical reaction -21%
- Alternative illness to TB - 4%
- Additional illness to TB - 72%

Bacterial infections	n= 53
Gastroenteritis	n = 37
Drug toxicity	n = 35
PCP	n = 20
Cryptococcal meningitis	n = 18
DVT	n =12

Pepper, PLoS ONE 2009

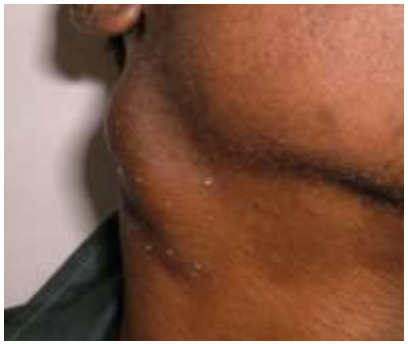
Important non-TB differentials

PULMONARY



Kaposi's
PCP
Cryptococcosis
Histoplasmosis

NODAL



Lymphoma
Kaposi's
Castleman's
NTM

WASTING SYNDROME

Lymphoma
Kaposi's
NTM
Enteric pathogen

APPROACH TO DETERIORATION DURING TB TREATMENT

DETERIORATION DURING TB TREATMENT

1 POOR ADHERENCE

- See green TB card.
- Get collateral from TB clinic and relatives.
- Exclude oesophageal candida & GIT intolerance as cause of non-adherence.

2 DRUG SIDE EFFECTS

TB drugs/HAART/Co-trimoxazole

3 MDR TB

- Proven on TB culture & sensitivities
- Suspect if clinical deterioration despite 2/52 of compliant TB therapy.
- Request drug sensitivities (PCR or formal testing) on initial isolate in laboratory as well as current specimen.

4 ALTERNATE*/ADDITIONAL DIAGNOSIS

PULMONARY/PLEURAL	Bacterial/nosocomial pneumonia, PJP, Kaposi's sarcoma, pulmonary embolus, lymphoma, fungal infection (cryptococcosis, histoplasmosis), mtb tung, sarcoid, lung carcinoma, bacterial empyema, nocardiosis	
CNS	**SOL**	Toxoplasmosis, lymphoma, cryptococcoma, brain abscess
	Meningeal	Cryptococcal, lymphoma, syphilitic
	Spinal cord	CMV, lymphoma
ABDOMEN/WASTING SYNDROME	Lymphoma, Kaposi's sarcoma, MAC, enteric pathogens, CMV, systemic fungal infection (cryptococcosis, histoplasmosis)	

Δ Δ Pulmonary

- Consolidation
- Patchy infiltrate
- Reticulonodular infiltrate
- Pleural effusion
- Mediastinal/hilar LN
- Mass lesion

- Follow up all TB (M,C,S) from this TB episode
- * NB to consider in patient where initial TB diagnosis not proven microbiologically

5 TB-IRIS

- Initial improvement of TB symptoms prior to ART
- New, worsening or recurrent symptoms 1-4 weeks after ART initiation
- Inflammatory in nature, eg nodes, pulmonary infiltrates, tuberculomata
- Risk factors: low CD4 nadir, disseminated TB, short interval (< 4-6/52) b/w TB Rx + ART
- Consider steroids in severe cases and if drug-resistant TB/other opportunistic illnesses excluded

6 PARADOXICAL REACTION

- No ART prior to deterioration
- No MDR TB
- Recurrence of initial or new TB symptoms/signs
- Exclusion of other causes

7 MALABSORPTION

- Ensure correct TB dose for weight.
- Consider rifampicin level (peak).
- Chronic diarrhoea? – but may be absent.

REGIMEN I Intensive phase	
Weight	TB dose
30-37 kg	2 tabs RHZE
38-54 kg	3 tabs RHZE
55-70 kg	4 tabs RHZE
> 70 kg	5 tabs RHZE

SOURCE: POSTER BY DR DOMINIQUE PEPPER, COMPLETED UNDER THE SUPERVISION OF PROF ROBERT WILKINSON, UNIVERSITY OF CAPE TOWN AND GF JOOSTE HOSPITAL

Approach to deterioration

Is the diagnosis of TB correct?	Review TB results
Is patient adherent & dose correct?	History and collateral
Exclude MDR	Drug susceptibility testing (preferably rapid test)
Consider malabsorption	Rifampicin level (2 and 6hrs)
If rapid deterioration or clinical suspicion of bacterial infection	Blood culture Other bacterial cultures Antibiotic
Exclude other opportunistic infection/malignancy	Examine for Kaposi's sarcoma Serum cryptococcal antigen Mycobacterial blood culture Tissue biopsy
Chronic gastro-enteritis	Stool for stains Endoscopy and biospy

Paradoxical TB-IRIS

Patient diagnosed with TB and started on TB treatment

↓

Typically improving on TB treatment then start ART

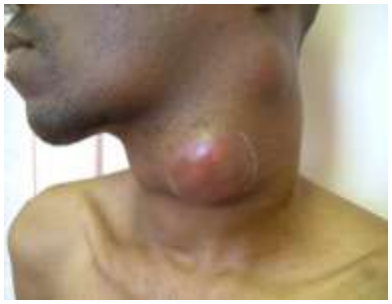
↓

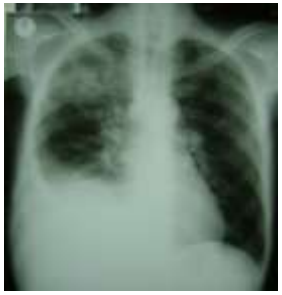
Recurrence of TB symptoms and new or recurrent clinical manifestations of TB

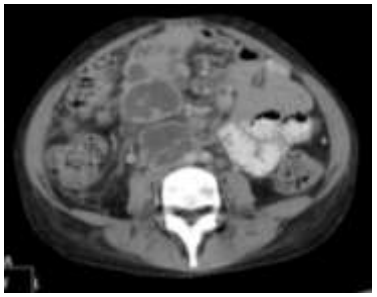
(Usually 1-4 weeks after starting ART)

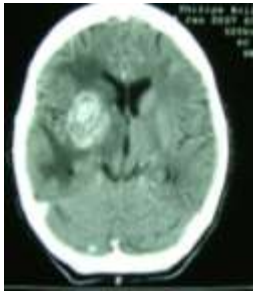
Up to 40% of patients starting ART are on TB treatment in Cape Town

8-43% of patients on TB treatment when starting ART develop paradoxical TB-IRIS

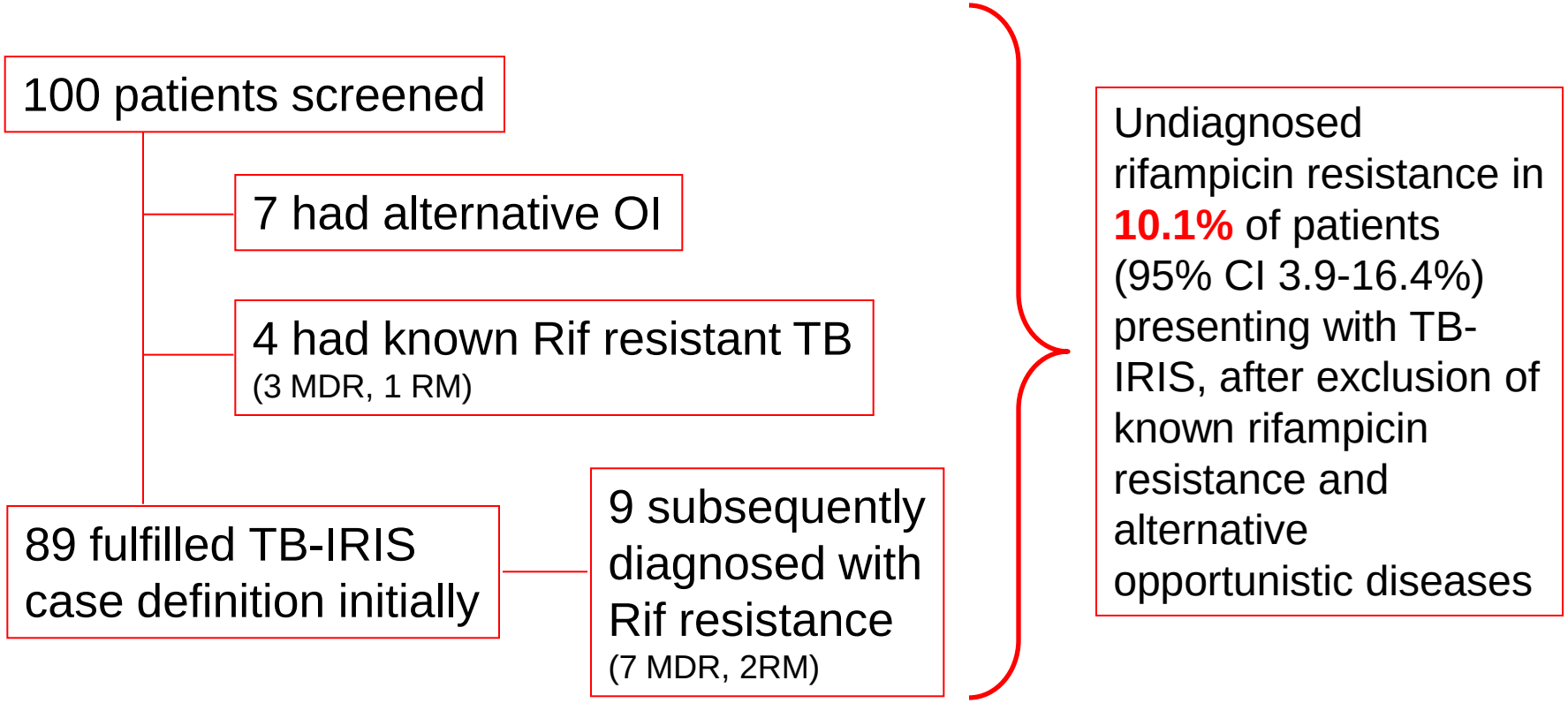








Observational study of 100 suspects screened using a paradoxical TB-IRIS case definition



66 female and 34 male
Median age: 31 years (IQR 26-35)
Median baseline CD4 = 50 (IQR 26-94)
26 retreatment TB cases
IRIS symptoms: 14 days (IQR 7-25) after starting ART

Meintjes et al,
Clin Infect Dis 2009

- **The 9 patients diagnosed with rifampicin resistance after presenting with TB-IRIS**
  - Had improved on TB treatment prior to ART
  - Deterioration median of 13 days after starting ART (range 3-48)
  - Clinical, radiologic and laboratory features not statistically different to those diagnosed with TB-IRIS without rifampicin resistance

- **Conclusions**
  - Patients with undiagnosed DR TB may initially improve on first line TB treatment then deteriorate on starting ART with TB-IRIS which accelerates clinical deterioration
  - TB drug resistance should be excluded in all TB-IRIS suspects

4. Temporary improvement on first line TB treatment

Not only in HIV-infected patients

Why do some MDR patients improve clinically on Regimen 1 or 2?

- Some drugs still have efficacy
  - PZA, Ethambutol, Streptomycin, (INH)
- Selection out of minority population of resistant mutants
- Dual strain infection
- Secondary infection with MDR during treatment

- A proportion of patient with MDR TB culture convert on first line treatment
  - 11% of HIV+
  - 33% of HIV-

Brust, PLoS ONE 2012

5. Empiric MDR TB treatment

- Decision should be made by experienced TB clinician
- First try to make the diagnosis with a rapid diagnostic test
- Ensure TB diagnosis confirmed
- Ensure adherence and dosing adequate
- Consider and exclude potential differential diagnoses
  - Malignancy, NTM, fungal infections, GI pathogen, TB-IRIS
- Ask the question: is there a risk this patient may die or suffer irreversible organ damage if he/she indeed has MDR and MDR treatment is delayed?
- Send multiple (3) specimens for TB cultures/DST
- Ensure follow-up

TAKE HOME MESSAGES

1. If initial tests for MDR negative, but patient deteriorates keep investigating
2. Extrapulmonary specimens have additive diagnostic yield
3. Consider the many differential diagnoses in HIV-infected patients
4. Don’t be falsely allayed by initial improvement
5. Empiric MDR treatment should only be started after a thorough diagnostic work-up and by an experienced TB clinician

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