Opportunistic Infections and ART

CASES

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CASE 1

Anaemia on ART

- 36 year old woman
- HIV+ with CD4 = 202
- Disseminated TB Nov 2010
  - Sputum cultured MTB, no DST
  - Cervical lymphadenopathy
- TB symptoms improved on TB treatment and LN decreased in size
- Commenced TDF, 3TC, EFZ Dec 2010
- Baseline Hb = 7.6
- Never on co-trimoxazole
- Reports adherence

- Presented in March 2011
  - Severe symptoms of
    - dizziness, palpitations, weakness, headaches
  - No history of blood loss
  - Hb = 2.4 (MCV = 96)
  - WCC = 3.9 (Neut = 2.0)
  - Plt = 280

- What are the possible causes?

Causes of anaemia in HIV

- Nutritional
  - Iron, folate, B12 deficiencies
- Haemolysis
  - Auto-immune, drugs, TTP
- Anaemia of chronic disorders
- Bone marrow infiltration
- Drugs
- Parvovirus B19
- Malaria
- GIT blood loss (KS)

Results

- Iron studies: no deficiency
  - Fe = 39,5 TF = 1,5 TF sats = 100% Ferritin = 451
- B12 = 592
- RBC folate = rejected
- No fragments on smear, Rouleaux formation only
- LDH = 453
- Total bilirubin = 4
- Reticulocyte count = 0.1% and RPI = 0
- Parvovirus B19 PCR negative

- Transfused 4 units
- What next?

Bone marrow biospy

- Features of pure red cell aplasia
  - Erythropoeisis = markedly hypocellular
- No infiltration
- Cause?

Possible causes

- Parvovirus B 19 (excluded)

- 3TC
- INH

Management

- Switched ART to TDF, D4T, EFZ
- Required further transfusions
- Then Hb normalised (13.2) and remained stable
- Reticulocyte count normalised (1.1%) and RPI = 1
- Switched to TDF, AZT, EFZ in Aug 2011 and monitored

- Discharged back to primary care in Oct 2011
  - Diagnosis: 3TC-induced pure red cell aplasia
  - Hb 12.1 WCC 3.5 Plt 185
  - HIV VL = LDL

3TC Pure Red Cell Aplasia

- 3TC is generally very well tolerated
- Rare, isolated case reports of PRCA
- 5/269 (1.9%) developed 3TC PRCA in 1 cohort
  - Hb dropped from median 11.8 to 5.2 g/dl after median 12 weeks
  - Rapid response after stopping 3TC (within 6 weeks)
- Bone marrow biopsy
- Exclude Parvovirus B19 and other drugs

Maijluf-Cruz, Am J Hematol 2000
John, J of Med Micro 2008

CASE 2

An unusual combination of conditions

Case

- 52 year-old man
- Ex-prisoner, living in an informal settlement
- Heavy smoker
- Previous PTB 2004, completed TB treatment

- HIV diagnosed 2009
- Defaulted ART on 3 occasions since 2009
- HIV-related thrombocytopaenia (Plt 50-80)
- Back on AZT/3TC/EFV since Nov 2011

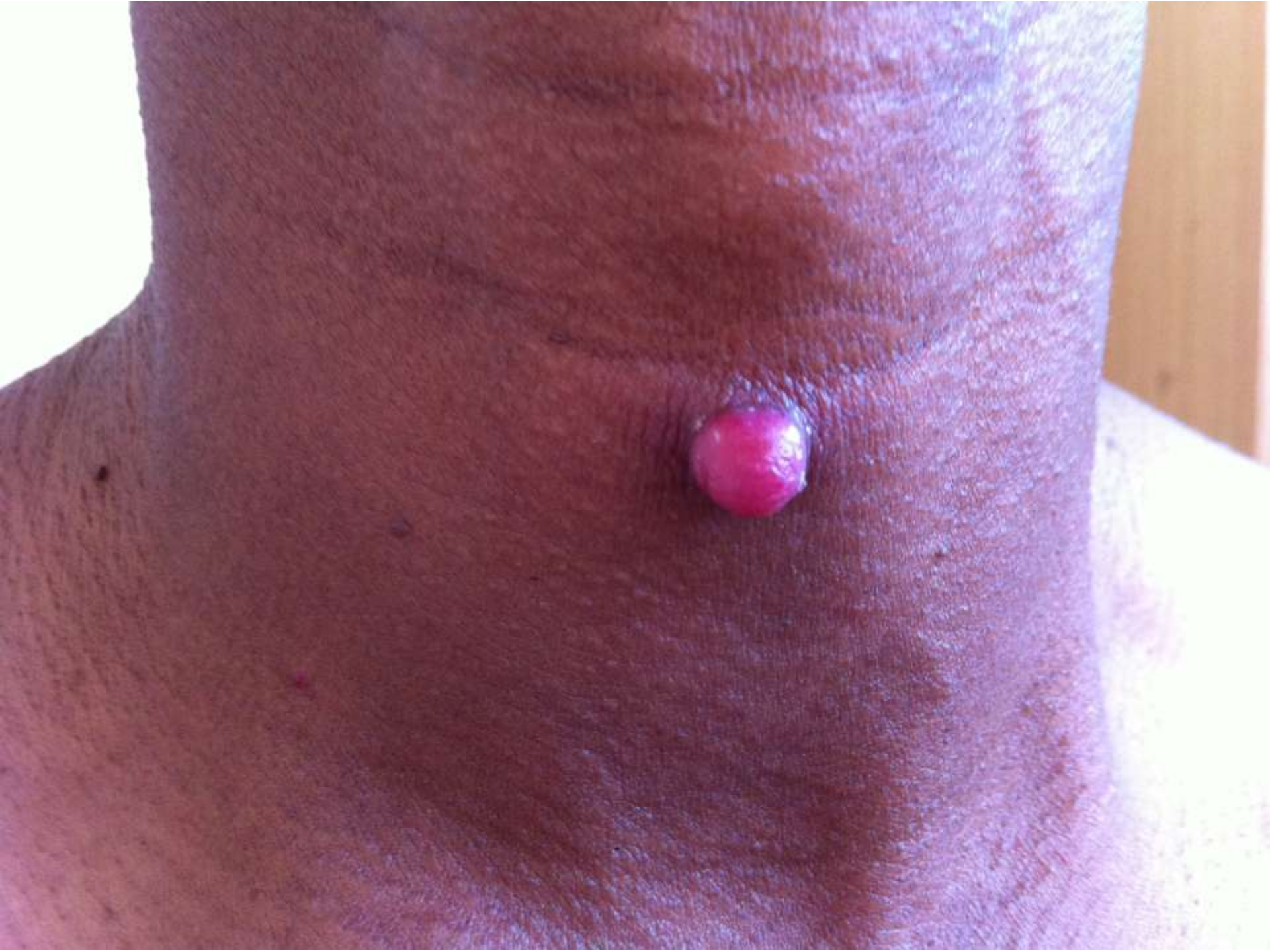
- Presented in Feb 2012 with 2 month history
  - Nodular skin rash. Started on face. Spread to trunk and limbs. Associated pruritus and pain.
  - Chronic productive cough. Green and white sputum.
  - Loss of weight

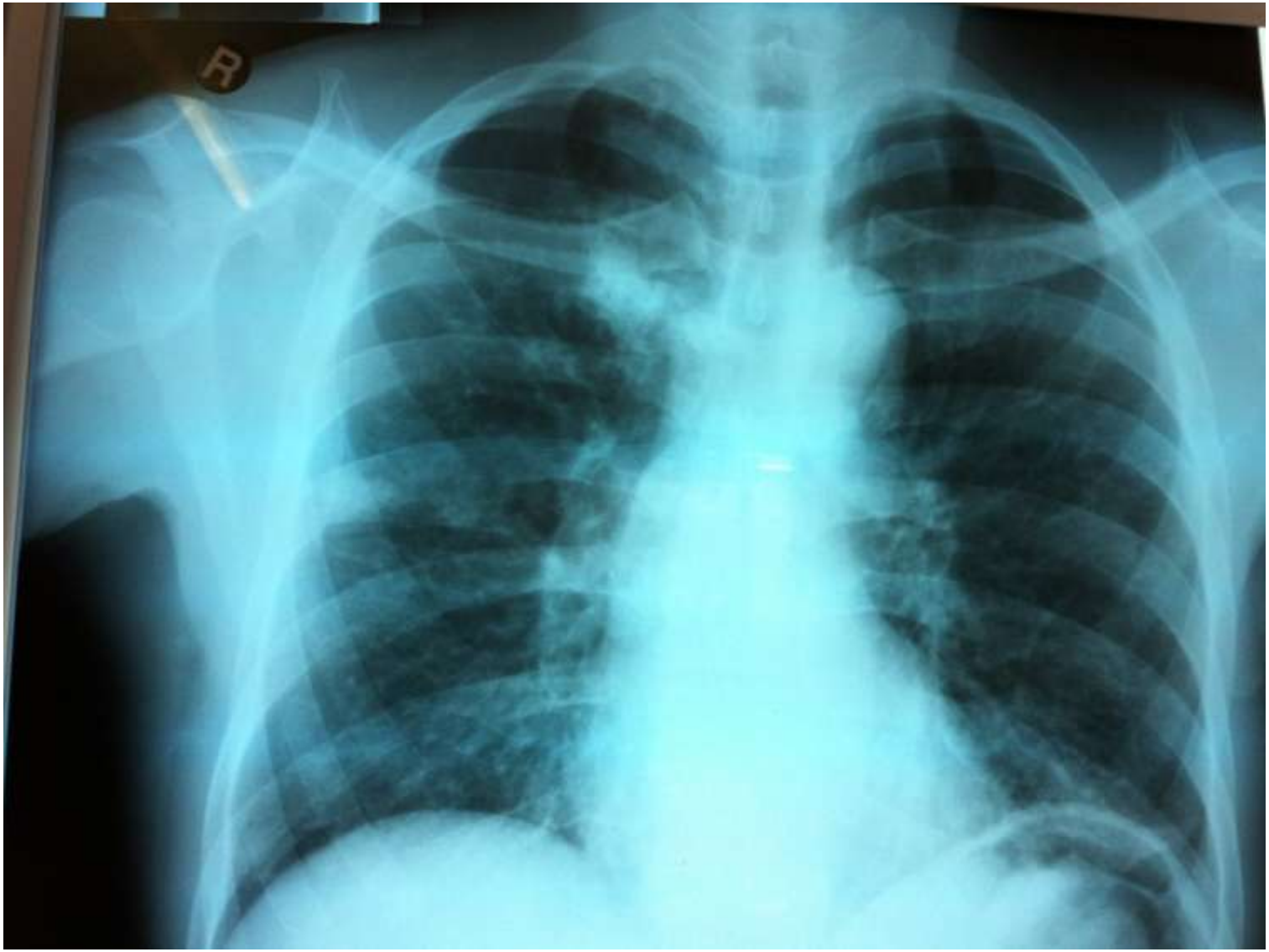
- Failing ART
  - CD4 = 139
  - HIV viral load = 401795

Examination

- Multiple red-purplish nodular lesions up to 2cm in size
  - Eyelids, neck, shoulders, chest, back and limbs
  - Some pedunculated and some ulcerated
  - No oral lesions
- Tinea unguium

- Temp 36 Pulse 84 BP 106/68
- Heart sounds normal
- Chest clear
- No hepatosplenomegaly
- No meningism and no neurological deficits
- Dipstix NAD

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Other investigations

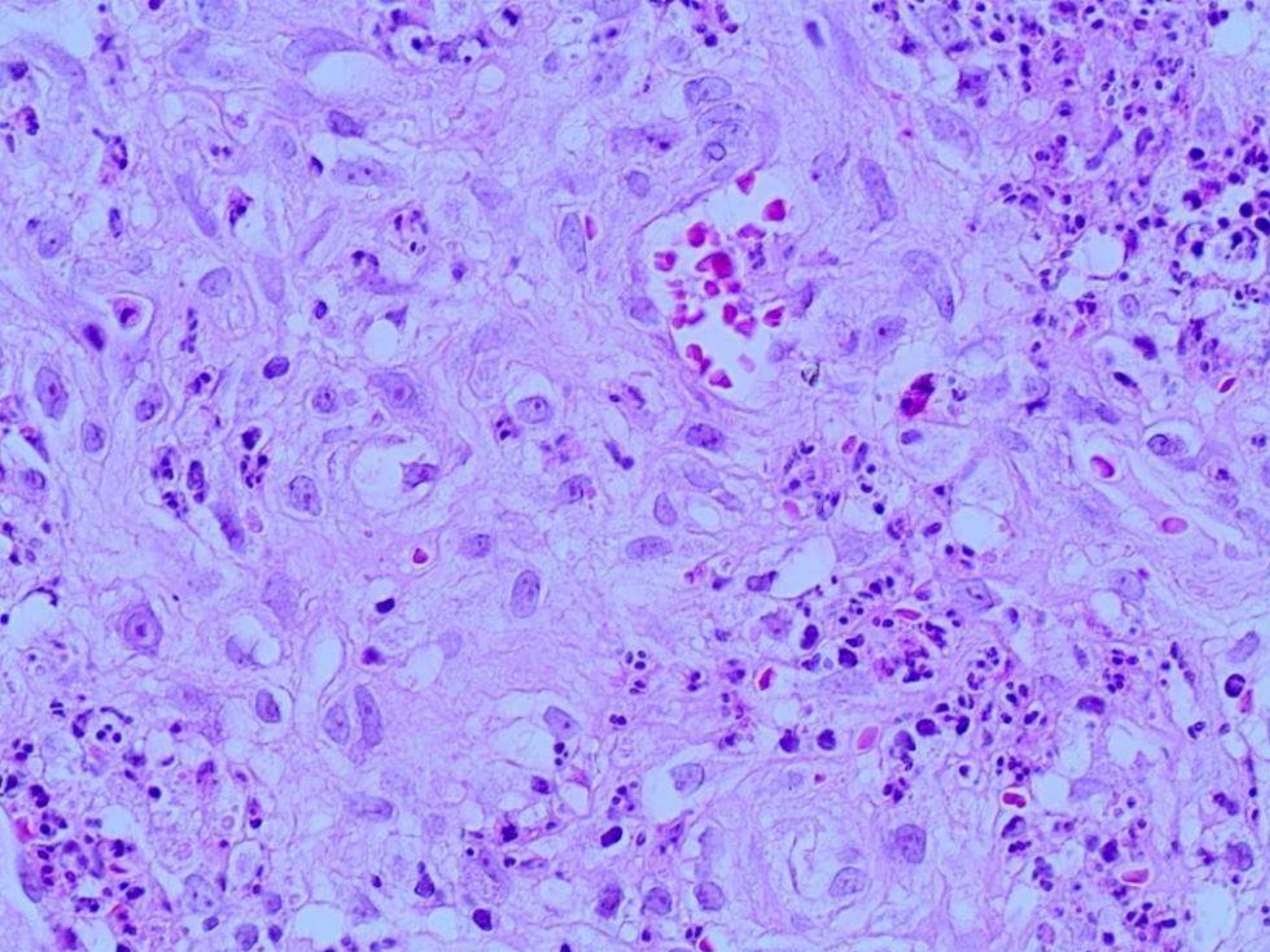
- FBC
  - Hb = 11.1 (MCV 96)
  - WCC = 5.7
  - Platelets = 228
- Creatinine = 73
- ALT = 15
- CRP = 24

What is your diagnosis?

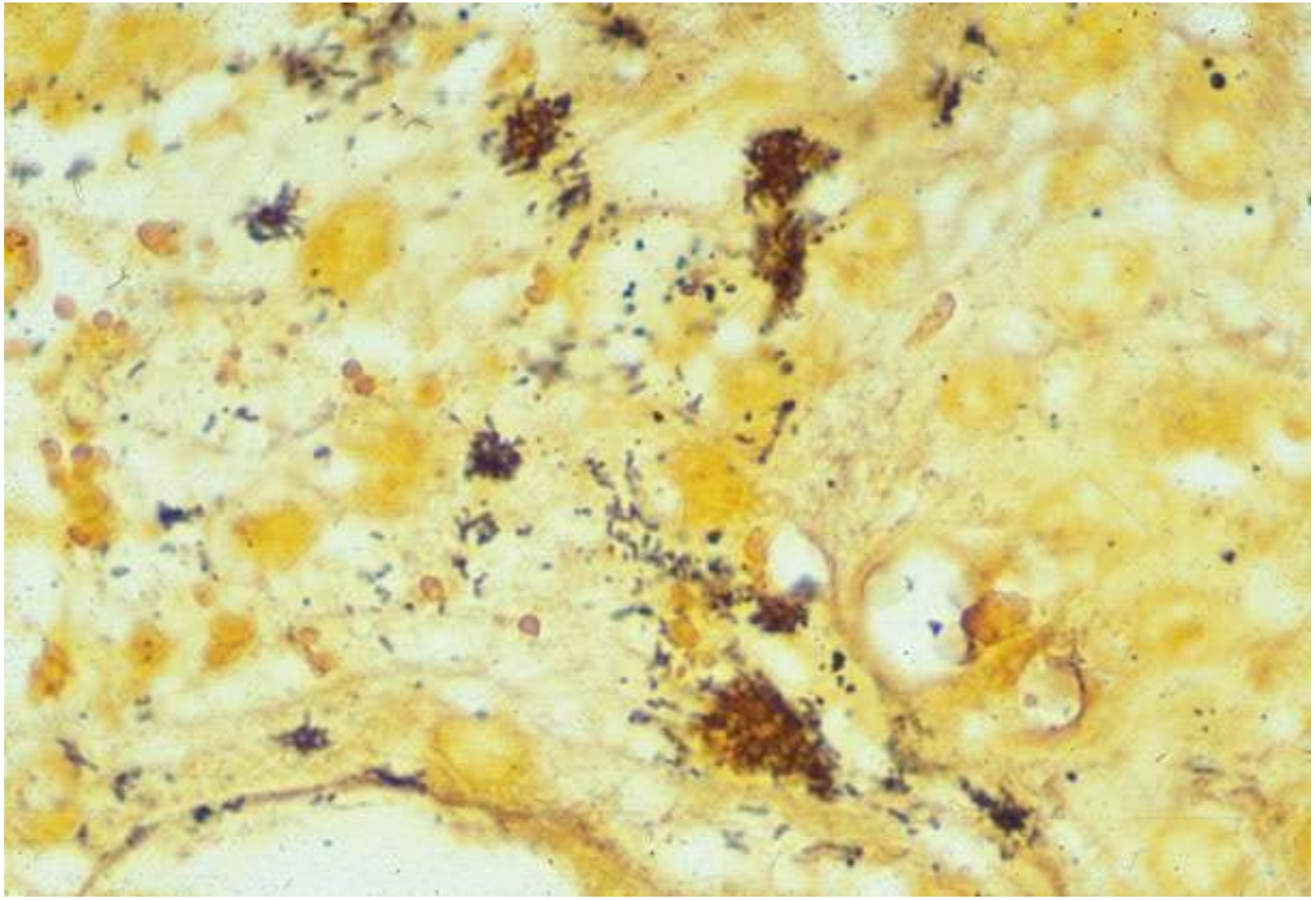
Assessment

- Skin lesions
  - Bacillary angiomatosis (Treatment?)
  - Kaposi's sarcoma
- CXR infiltrates
  - Active or past TB or due to one of above
- Virological failure

- Started Erythromycin 500mg qid
- Skin biopsy



Warthin – Starry stain



Then received CLAT result

- Serum CLAT = positive, titre < 1:8
- Repeat CLAT also positive, titre < 1:8
- 2-week conventional and MycoFlytic blood cultures negative
- Declined LP to exclude meningitis
- No neurological symptoms

- Sputum AFB - and TB culture -

Management

- Fluconazole
  - 800mg/d x 2 weeks
  - 400mg/d x 8 weeks
  - 200mg/d x 1 year and CD4 > 200
- Changed Erythromycin to Doxycycline when Fluconazole started (3 months treatment planned)
- Change to 2nd line ART (TDF/3TC/Aluvia) 2 weeks later

- Skin lesions resolved, 2kg weight gain, CXR unchanged
- Returned after defaulting ART again

Discussion

1. Bartonella infection in HIV

2. Cryptococcal antigenaemia

3. Erythromycin, Fluconazole, Aluvia and prolonged QT

Bacillary angiomatosis (BA)

- Bartonella
  - Gram-negative slow-growing intracellular bacillus
  - 19 species, 5 cause human disease
  - B.henselae and B.quintana cause BA in HIV+ patients (typically CD4 < 100)
  - BA manifests with skin rash, intermittent bacteraemia and other organ involvement
- B. henselae
  - Vector = cat flea (cat scratch or bite)
  - Peliosis hepatis
- B.quintana
  - Vector = body louse (homeless people)
  - Osteomyelitis
- Many other organs can be involved
  - Endocarditis, spleen, CNS, eye, lung
  - Chronic fever and weight loss

BA: Diagnosis

- Skin biopsy
  - Characteristic histology
  - Warthin-Starry stain positive
  - Does not stain on Gram stain
- Prolonged blood culture
- Blood PCR
  - 10.1% of 188 HIV+ patients were PCR+ in Joburg
- Current NICD study (EDTA tube for culture & PCR)

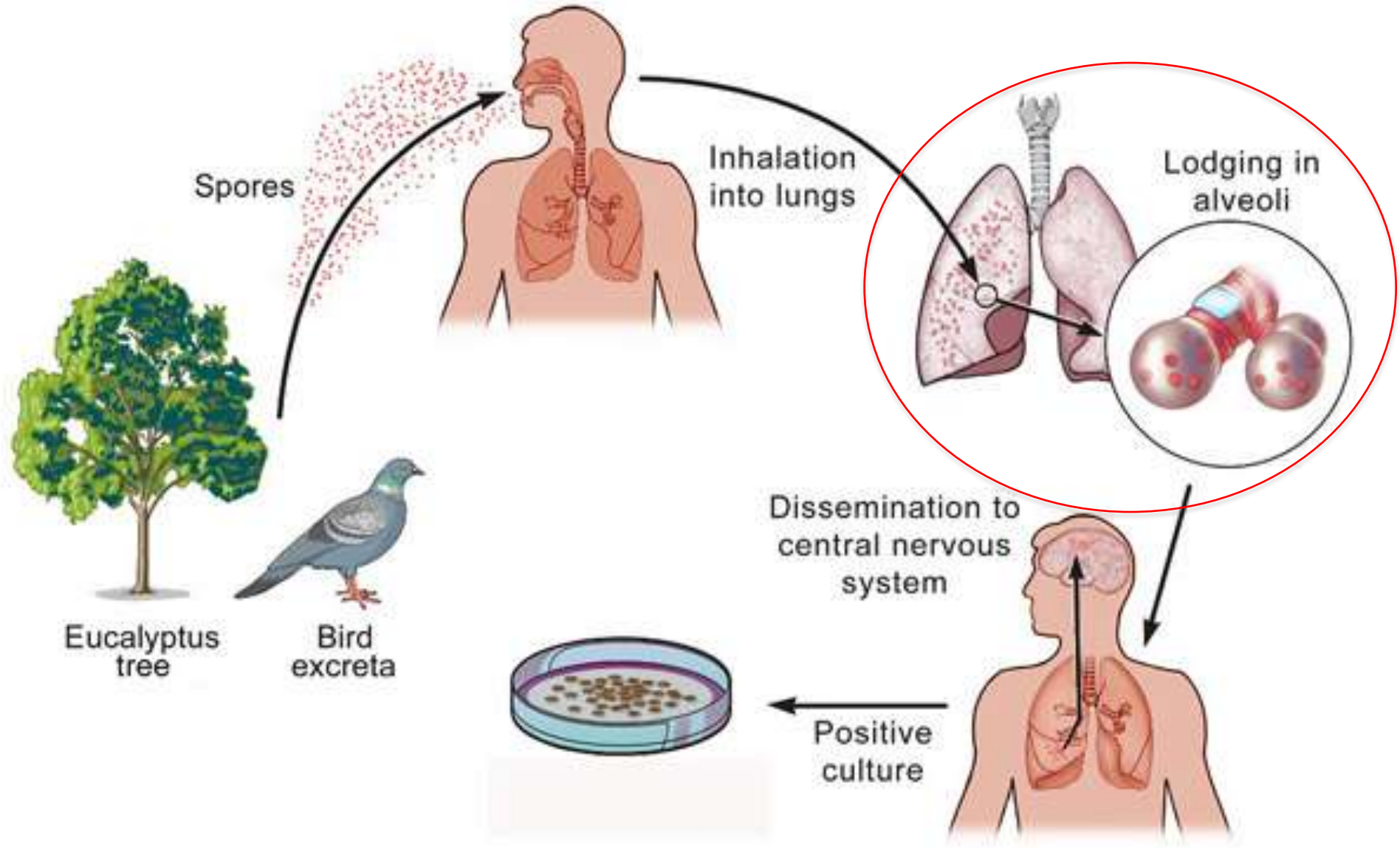
Frean, Trans Royal Soc Trop Med & Hyg 2002

BA: Treatment

- Erythromycin or Doxycycline for 3 months
- Alternatives
  - Azithromycin, Clarithromycin
- CNS: Doxycycline +/- Rifampicin

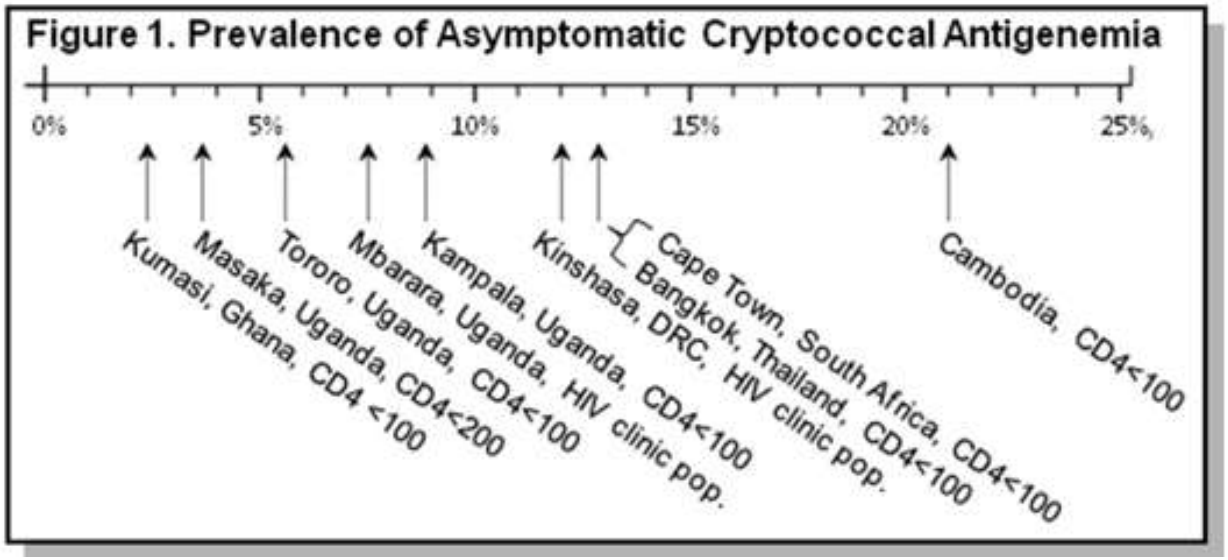
NIH/CDC/HIVMA-IDSA guidelines 2008

Cryptococcal transmission and disease



Cryptococcal antigenaemia

- Ugandan study: preceded symptoms by median 22 days (>100 days in 11%)
- Serum cryptococcal antigen + in 7% entering ART programme in Guguletu without previous CM



French,
AIDS 2002

Jarvis,
Clin Infect Dis 2009

Rajasingham,
JAIDS 2012

CLINICAL PRACTICE: POLICY

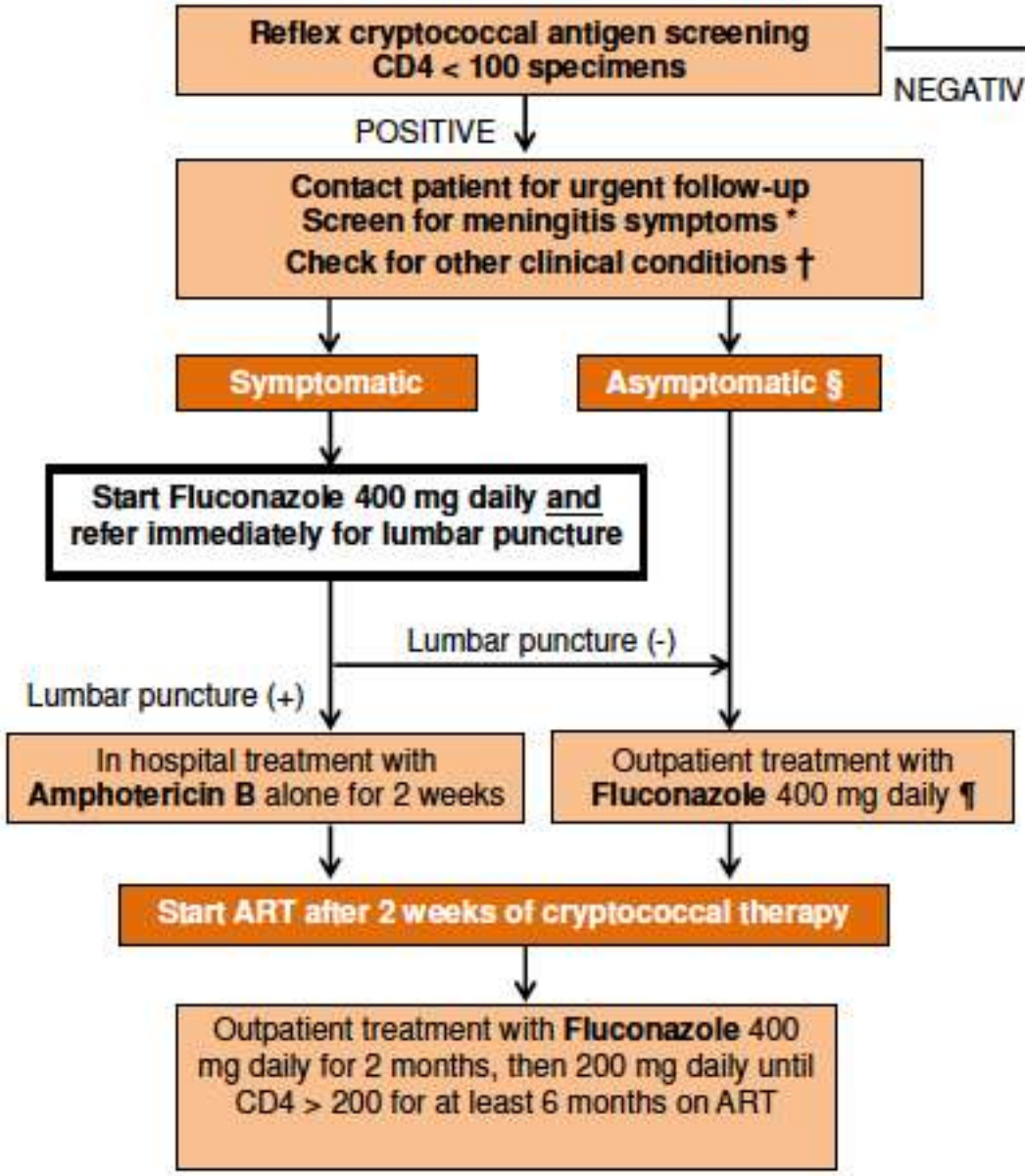
Routine cryptococcal antigen screening for HIV-infected patients with low CD4+ T-lymphocyte counts – time to implement in South Africa?

Joseph N Jarvis, Thomas S Harrison, Nelesh Govender, Stephen D Lawn, Nicky Longley, Tihana Bicanic, Gary Maartens, Francois Venter, Linda-Gail Bekker, Robin Wood, Graeme Meintjes

- Screening advocated for those with CD4 < 100
- Pre-emptive treatment to prevent meningitis
  - CM mortality 30-70% in SA
- No evidence-based pre-emptive treatment but an approach suggested
- Phased implementation in SA starting in Free State, Gauteng and W.Cape government clinics

Jarvis, SAMJ 2011

Decision-Making Guide for Cryptococcal Screening



* **Patient is symptomatic if they have any of the following:**

1. Headache greater than 24 hours
2. Fever
3. Confusion or coma
4. Blurry vision
5. Neck stiffness

† **Other clinical conditions include:**

- Patients on tuberculosis medications
- Patients on nevirapine
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Liver disease
- Children

§ A lumbar puncture may be considered if available.

¶ Some clinicians prefer to use a higher dose.

Low titre CLAT (<1:8)

- False positive
- Early disease (2 anecdotes)

Erythromycin, Fluconazole and Aluvia

- Case reports of QT prolongation and Torsades with Erythromycin and Fluconazole
- Aluvia may also prolong QT and PR, particularly in patients with underlying cardiac disease
- Likely additive risk, thus avoid combination where possible or monitor ECG

Khazan, Pharmacotherapy 2002
Wassmann, Ann Intern Med 1999
Oberg, Pharmacotherapy 1995
Poluzzi, Drug Saf 2010
Aluvia package insert

CASE 3

Severe weakness on ART

- 29 year old HIV+ woman
- Previous PTB 2003
- Recurrent PTB Jan 2012 (Rif susceptible)
- Started ART 2 weeks after TB treatment with baseline CD4 = 17 (TDF/3TC/EFZ)
- Referred to hospital 3 Apr 2012
  - 3 day history of generalised weakness and painful limbs and back
  - 2 x vomit, but no diarrhoea
- On ART, RHZE, Co-trimoxazole, BCo

Examination

- Afebrile
- BP 99/57 P98 RR30 Sats 100%
- Visidex 5.8
- Dipstix: Trace glucose 4+ RBC
- Oral candida and pale
- Power 2/5 proximally, 3/5 distally
- Reduced reflexes
- No cranial nerve or sensory deficits
- Tender muscles

“A diagnostic test was performed” ?

- Na = 134
- K = 1.5
- Urea = 5.1
- Creat = 210
- Mg = 1.08
- Phos = 0.77
- Corr Ca = 2.26
- CK peak = 2760

- pH = 7.29
- pO2 = 13.7
- pCO2 = 2.4
- sHCO3 = 12.1

- Urine K = 5.4 mmol
- Urine Creat = 1.0 mmol
- Ratio = 5.4 (>1.5 suggests renal wasting)

- Cause?

AIDS. 2006 Aug 1;20(12):1671-3.

Hypokalemia in HIV patients on tenofovir.

Cirino CM, Kan VL.

Infectious Diseases Section, Veterans Affairs Medical Center, Washington, DC, USA.

Abstract

Although adverse events in HIV patients taking tenofovir are relatively rare, postmarketing reports of nephrotoxicity have alerted physicians to other potentially serious outcomes. We present a series of 40 patients who developed hypokalemia associated with tenofovir. Identified risk factors included concomitant ritonavir or didanosine use, a lower weight and longer duration of tenofovir use. Recovery or improvement was seen in the majority of patients (66%) after the discontinuation of tenofovir; however, four deaths occurred. The associated consequences of tenofovir-related hypokalemia may be profound and life-threatening.

Management

- Intravenous and oral potassium supplementation
- IVI fluids
- Switched to TDF to D4T (anaemic)
- At discharge
  - K = 4
  - Creat = 70

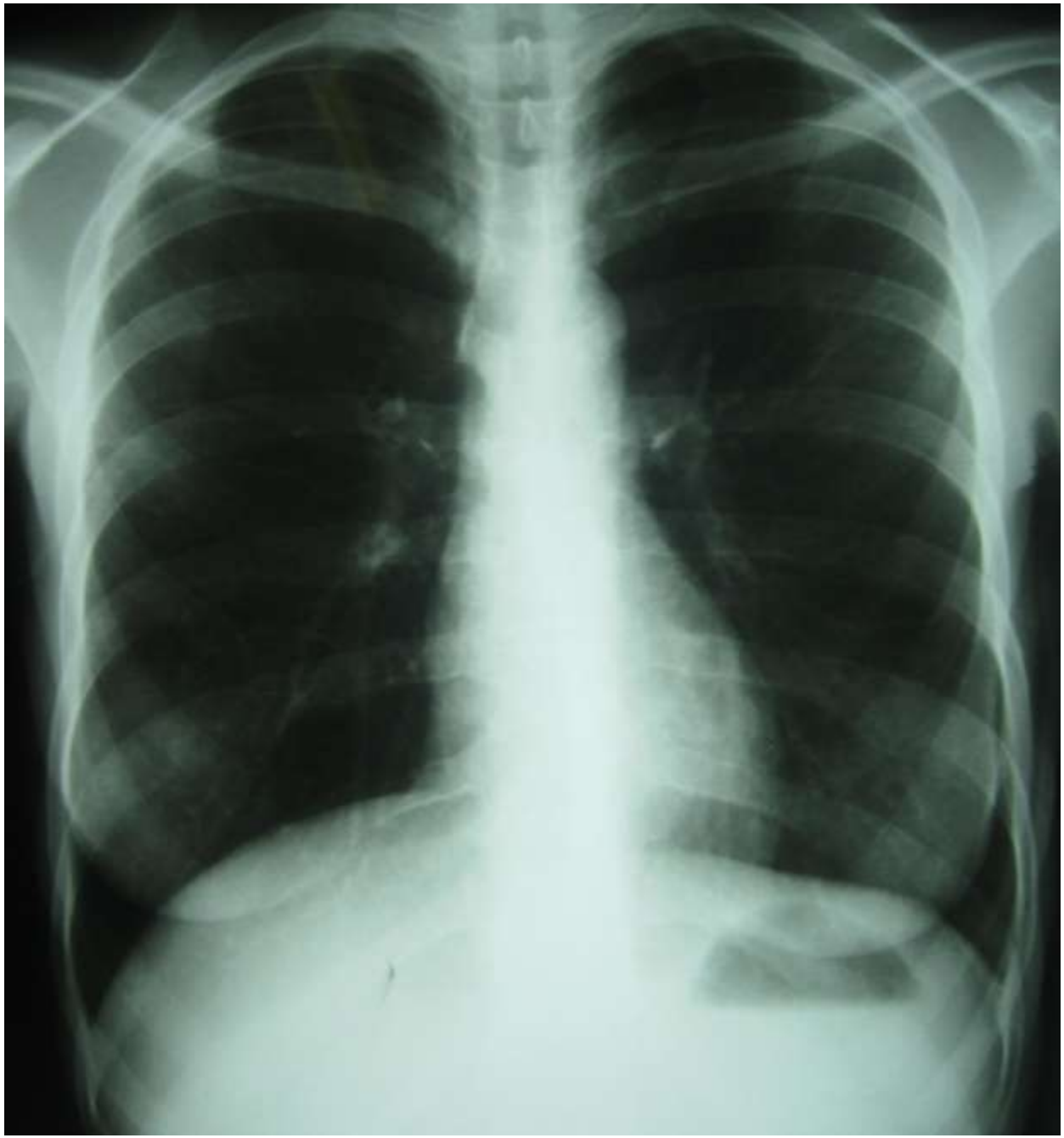
CASE 5

Deterioration despite TB treatment

- 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 (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?

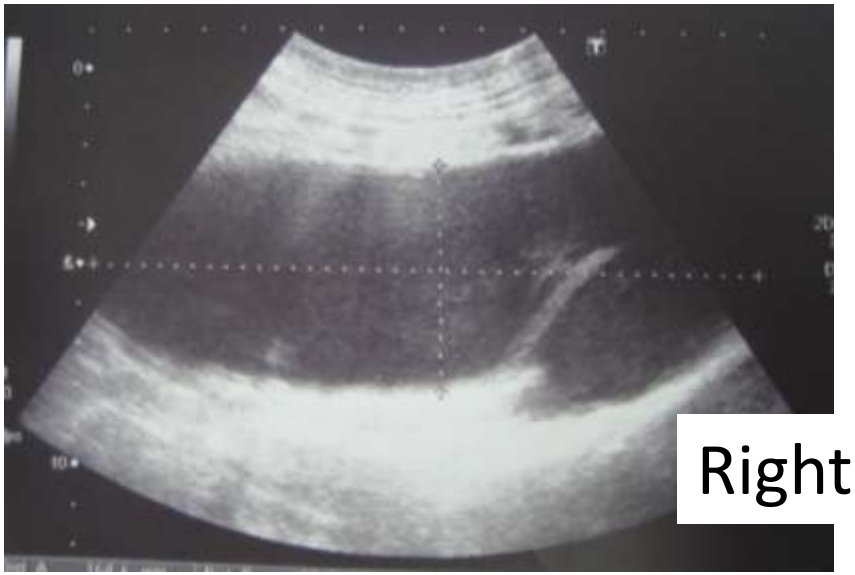
What next?

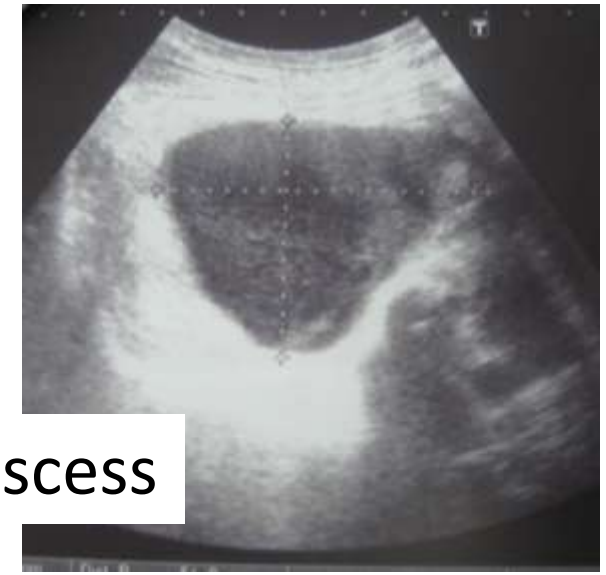
- Assessed adherence
  - ART: Possible inadequate adherence noted on pill count. Viral load in Jan LDL, but viral load in Apr was 1100 copies/ml.
  - TB: Self-reported good adherence, and TB card reviewed in Jan showed this. Phoned TB clinic and they could not provide information.
- Review of sputum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

Abdominal ultrasound

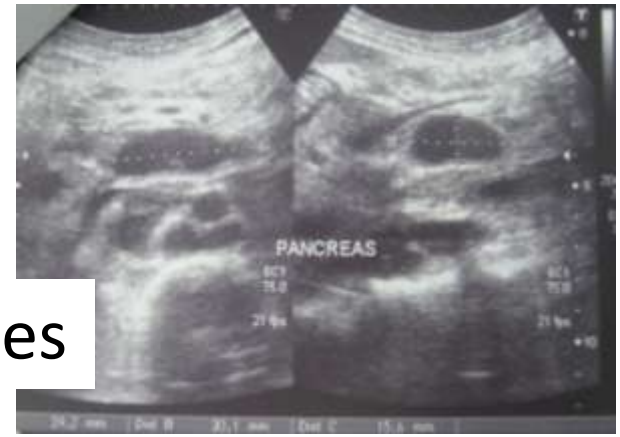
- Hypoechoic area inferior to pancreas, likely necrotic LN (4 x 3 x 2 cm)
- Right psoas abscess extending from kidney to femoral head (17 x 8 x 6 cm)
- Splenic microabscesses
- Free fluid in pouch of Douglas
- DVT in right common and superficial femoral veins

Abdominal USS





Right psoas abscess



Necrotic lymph nodes

Next step?

USS guided aspirate of psoas abscess (and further sputa sent) and requested Xpert

- 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 TB treatment with Rifafour plus Kana/Moxi/Ethio/Terizidone

- Two recent sputum cultures negative and discharged for outpatient treatment

Questions and issues

- Should she have been started on empiric MDR TB treatment earlier?
- Adherence difficult to assess at referral hospital
  - How does clinician differentiate poor adherence from possible drug resistance?
  - What are your experiences in this regard?
- 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
- Diagnosis of drug-resistant TB can be very difficult

Diagnosing extrapulmonary MDR TB

- Lymph node or cold abscess needle biopsy
  - Aspirate pus
  - Flush needle with saline
- 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 showing promise in extra-pulmonary samples

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.

Xpert on extrapulmonary specimens

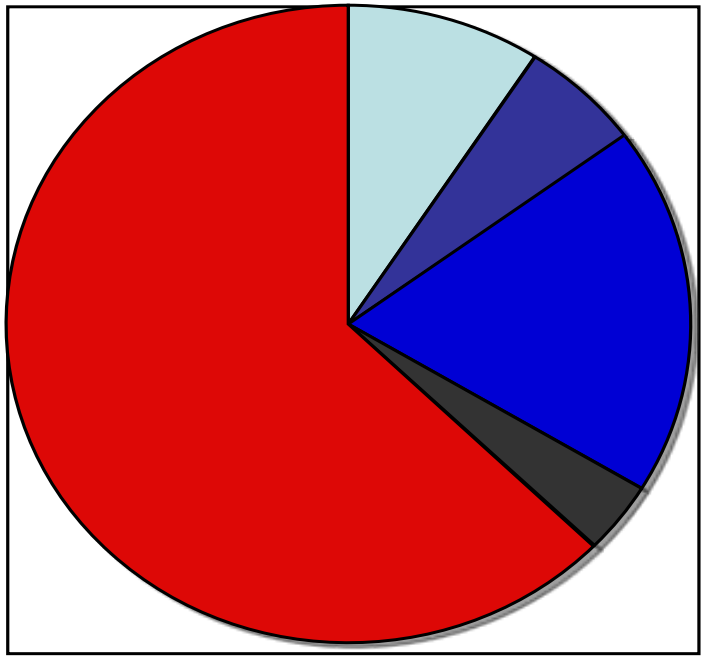
Table 1. Summary of studies (n = 8) published before 7 March 2012 in which the diagnostic accuracy of Xpert® MTB/RIF for extrapulmonary TB was assessed.

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

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%**

Pepper, PLoS ONE 2009

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

Approach to deterioration

Is the diagnosis of TB correct?	Review TB results
Is patient adherent?	History and collateral
Exclude MDR	Drug susceptibility testing (preferably rapid test)
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

CASE 6

Breast enlargement on ART

Breast enlargement

- What are the three mechanisms of breast enlargement in HIV+ patients on ART?

- Name the commonest causes of each

Breast enlargement

Mechanism	Common causes
Gynaecomastia	Efavirenz ddI
Lipomastia (associated with lipodystrophy)	Weight gain on ART
Infiltrative processes	TB Lymphoma Breast Ca

Gynaecomastia in HIV-infected men on HAART: association with Efavirenz and Didanosine treatment

Mira et al, Antivir Ther 2004; 9(4): 511-7

- Prospective study of 1304 men on HAART
- 30 (2.3%) gynaecomastia
- 22/30 (73%) resolved completely after median of 9 months (range 5-22)
- Association with
  - EFV 57% vs 17% ($p = 0.004$)
  - ddI 50% vs 13% ($p = 0.003$)
  - Lower bioavailable testosterone levels

CASE 8

Hypertensive patient with HIV-TB

CASE

- 47 year old man

- HIV+ with CD4 = 61
- Hypertensive
- Creatinine 131 prior to ART
- RHZE plus Streptomycin for retreatment TB

- Commenced TDF, 3TC and Efavirenz

- What are the problems?

- Admitted 3 weeks later with vomiting, weakness and confusion
- Creat = 1902
- TDF and streptomycin stopped and IVI fluids
- Creat decreased to 160 over 3 weeks

International AIDS Conference 2008 Castellano, WEAB0104

- Duke University, North Carolina HIV Clinic
- 35/744 (4.7%) on TDF developed renal impairment, similar rate to non-TDF controls
- 20 discontinued TDF
  - 16 significant renal improvement
- 15 continued TDF
  - 10 continued to have abnormal renal function

Risk factors

- Concurrent nephrotoxic mediactions
  - ACEI, NSAIDs, AmphoB
- Medical comorbidities
- Hypertension
- Chronic pain
- Concurrent and previous PI use
- History of OI

Risk factors

- Nephrotoxicity seen in all 25 patients who had both hypertension and were using other nephrotoxic drugs
- Only one patient (1/39) experienced nephrotoxicity when both were absent
- NNRTI use with TDF - nephrotoxicity rare