Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za

A BITTER PILL TO SWALLOW

- Case presentation

Dr E Shoul
Wits University, Dept of Medicine
SA HIV Clinicians Society Conference
April 2016

Mr HM – 42 year old male from Johannesburg

Background history:

- Previously well
- Known with HIV, on ARVs since 2006
- Uncertain initial regimen:
- likely 3TC/ D4T/ EFV
- then 3TC/ TDF/ EFV
- now on FDC: FTC/ TDF/ EFV since April 2015
- No previous episodes of TB/ no other opportunistic infections
- No other chronic treatment taken apart from ARVs

Social history:

Works in construction - since 2004

Lives in a flat in Hillbrow with all amenities, with his 2 sons (aged 15 and 20) who are well

No exposure to pets, birds, livestock

Originally from Zimbabwe, last visited Zimbabwe over the December 2015 period

Presenting complaint

Noted lesions on the palate since 22/12/2015

- Lesions are painless, no difficulty swallowing or with phonation
- Denies any masses or ulcerations on the palate prior to this
- No preceding dental problems
- No history of sinus problems

History of the Presenting Complaint

- Mass enlarging - starting to impede phonation
- Remained painless, still able to swallow with no problems

- <u>Referred to ENT for assessment and further management:</u>

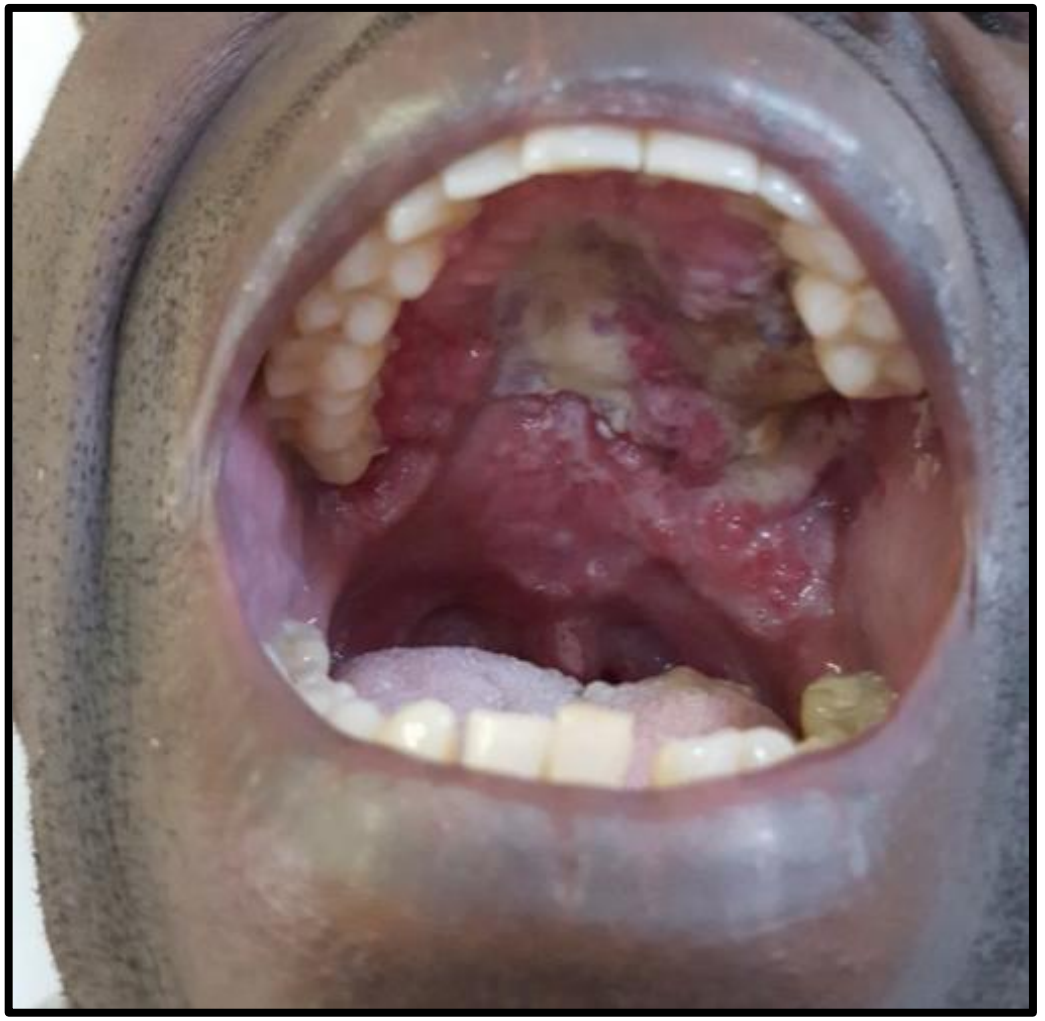
  Skull x-ray done

  Biopsy taken; told to follow up for results

  CT scan booked for 2 days after initial consultation

  Working diagnosis:

  - Non-benign lesion of the palate for investigation



Initial blood results

Taken at ENT OPD on 11/01/2016

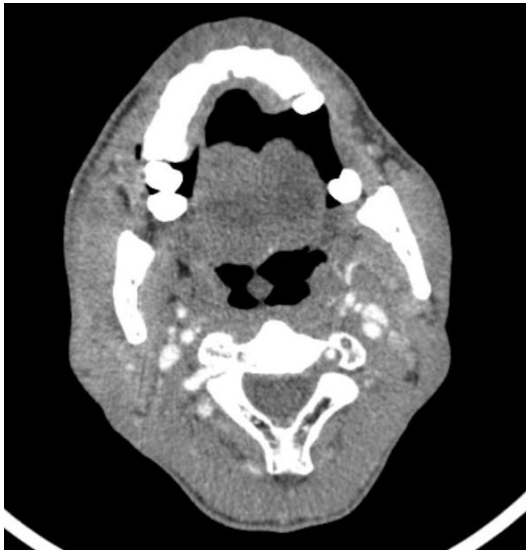
- **FBC:** 2.33 / 11.2 (MCV 88.5) / 280
- **Differential:** Not requested
- **U&E:** 136 / 4.6 / 98 / 27 / 6.7 / 71
- **CRP:** 14

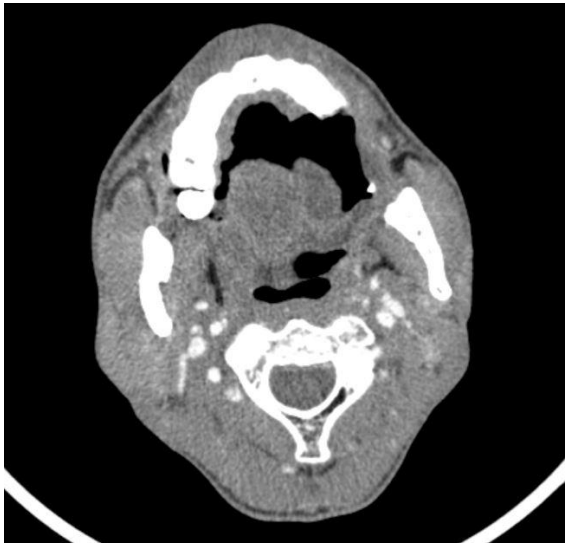
Imaging

ABDO U/S: Micro-abscesses noted in the spleen; mesenteric lymph nodes noted

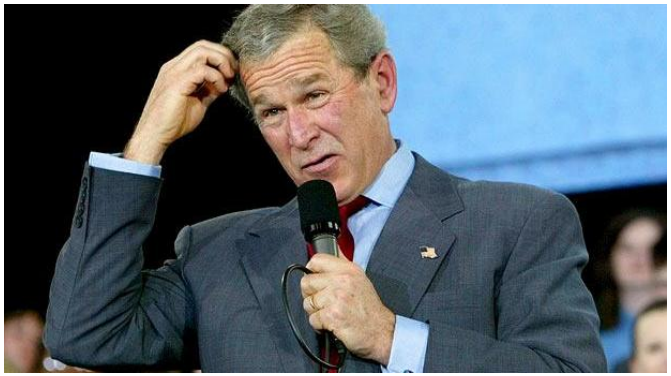
CT BOS to clavicle:

- **Locally destructive soft tissue lesion left side of the palate:**
- Superiorly: inferior part of the maxillary bone with destruction of the bone
- Inferiorly: base of the tongue on the left with poor separation from the tongue
- Laterally: into the anterior masticator space and infratemporal region
- Medially: into the soft palate
- Associated areas of necrosis



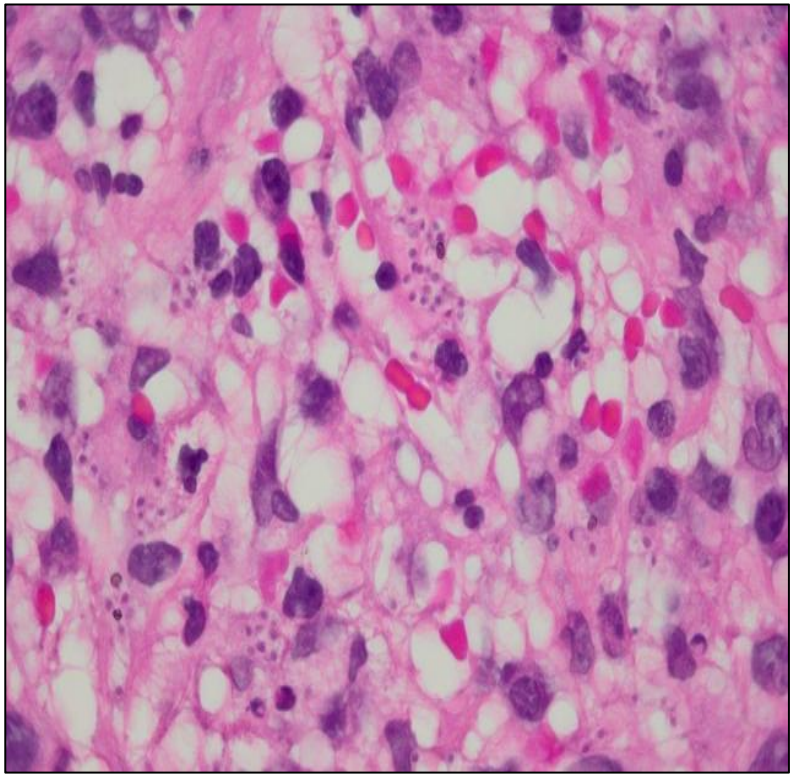


What's your differential diagnosis?

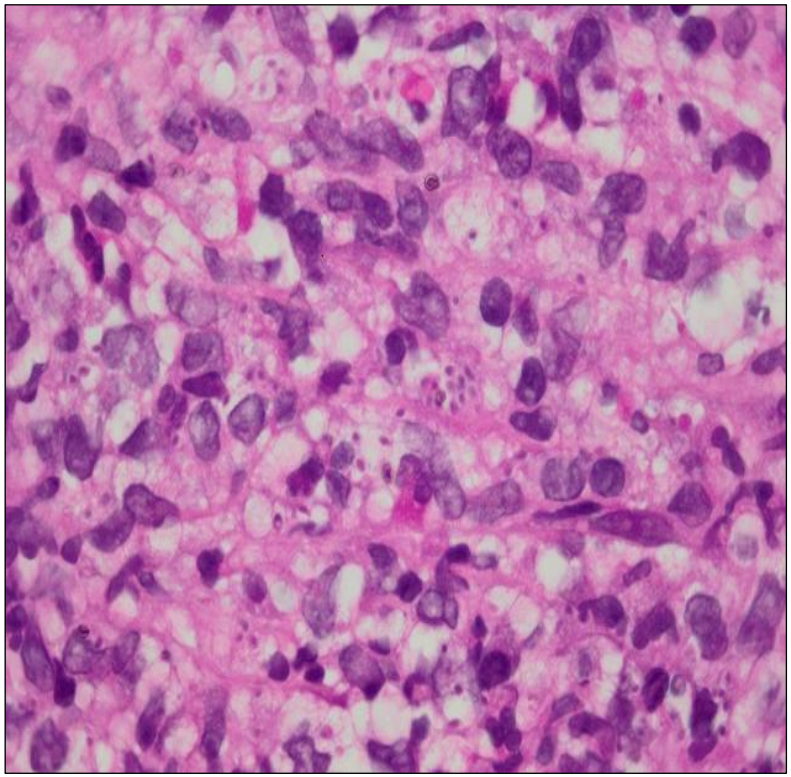


Patient H.M.

Intracellular fungal spores with discernible clear halos within macrophages



400X Magnification (Oil)



400X Magnification (Oil)

	22/01/2016	27/01/2016	29/01/2016
WCC	11.9	2.02	1.76
HB	11.5	10.7	9.1
MCV	97.9		
PLTS	266	200	135
TPHA	Negative		
CD 4	**10**		
HIVVL		**376000**	
TP	58		
ALBUMIN	34		
GGT	26	375	542
ALT	15	192	326
AST	18	337	458
ALP	81	234	336

Issues to consider

1. What is the clinical picture of histoplasmosis?

1. How do we diagnose it in our setting?

2. What is the recommended management and how can it be applied to the local context?

4. What are implications of treating histoplasmosis in someone on ARVS?

Different clinical spectra of histoplasmosis

Immune-competent

- Mild, self-limiting pulmonary illness
- Subacute pulmonary infection
- Acute diffuse pulmonary histoplasmosis
- Chronic pulmonary histoplasmosis

Immune-compromised

- Progressive disseminated histoplasmosis

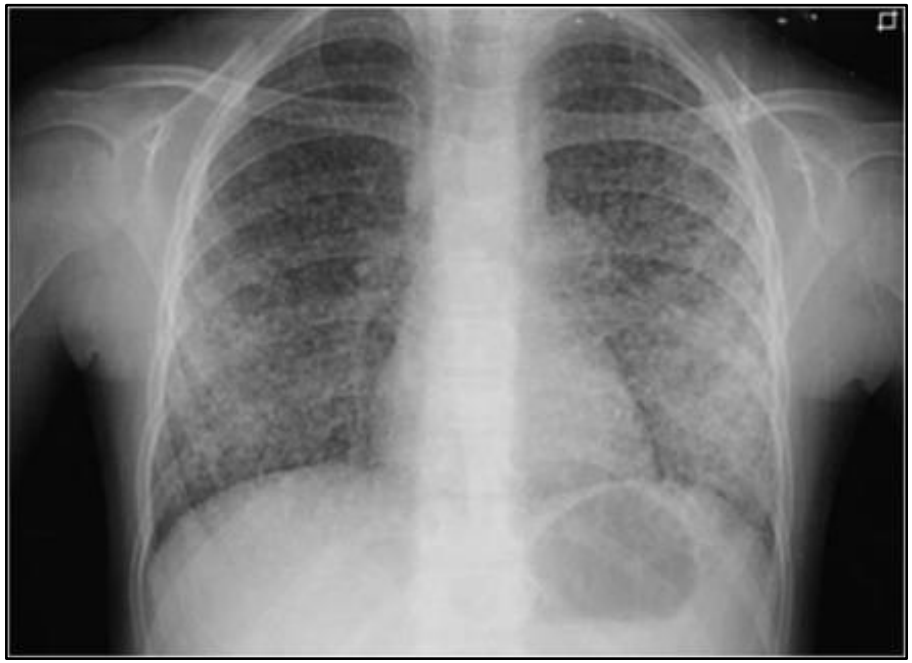
Kaufman CA. *Clin Micro Rev* 2007;20(1):115

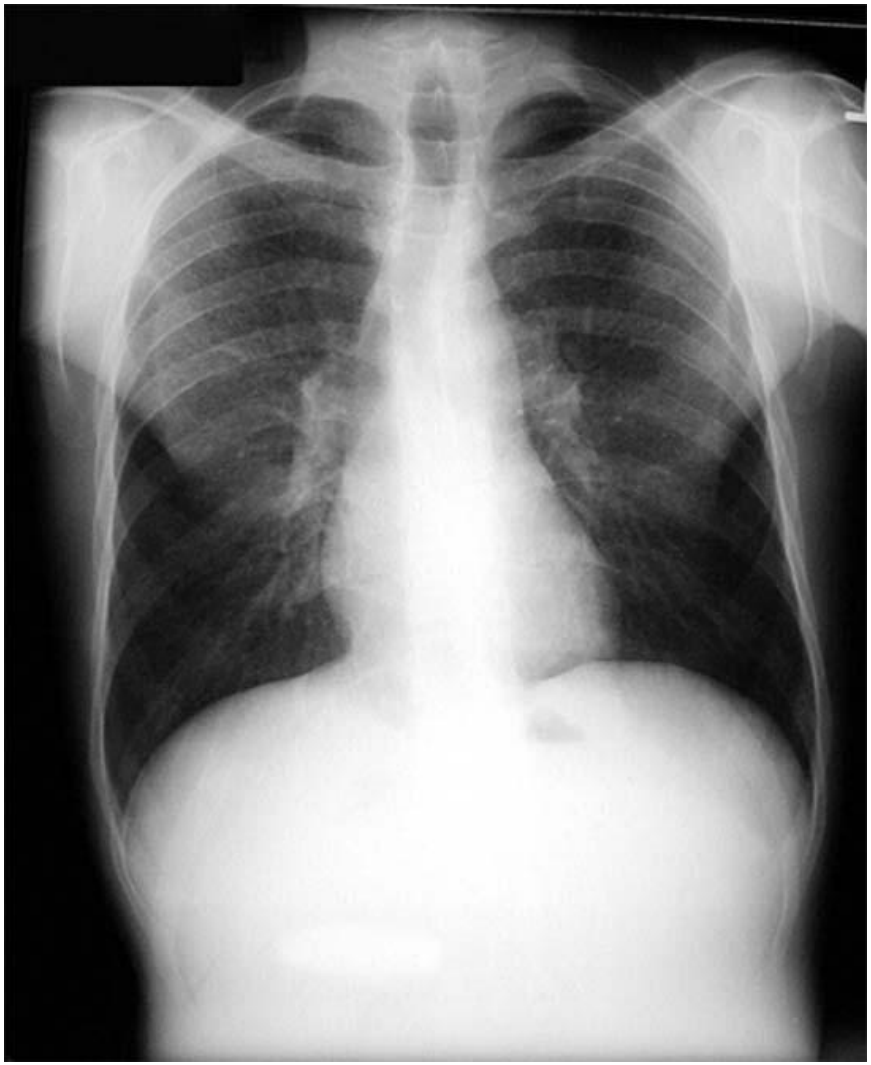
Clinical picture – mimicking the mimicker
Disseminated Progressive Histoplasmosis

- Constitutional symptoms: fever, fatigue, weight loss - ±always
- Respiratory findings: cough and dyspnoea (about half)
- Hepatosplenomegaly
- Superficial lymph nodes
- Mucocutaneous features
- GIT/ Neuro (less common)

Adenis AA, *et al. CurrTrop Med Rep* 2014;1:119-128

If you're thinking TB – think Histoplasmosis





Garcez CSG, *et al. Arch Dis Child* 2012;97:A272-A273
Al-Hameed F. Histoplasmosis Imaging. Medscape, Jan 2016

What is the value of "splenic microabscesses" on ultrasound?

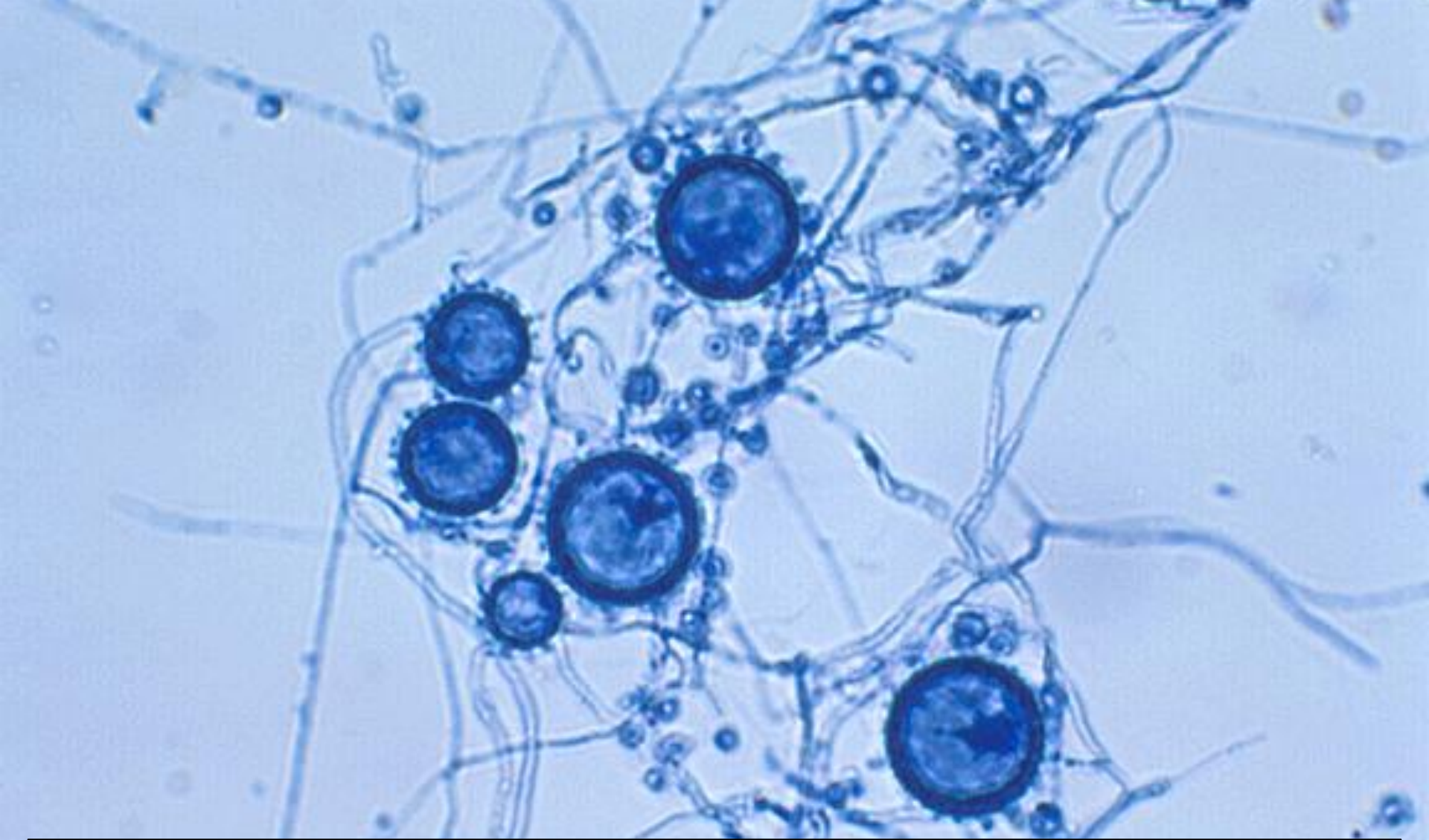
-thinking outside the TB box

Most will be TB

HOWEVER

- Non-tuberculous mycobacterial infection eg. *Mycobacterium avium* complex infection (MAC)
- Salmonella spp.
- Lymphoma/ Leukemia/ Solid tumour metastasis
- Disseminated fungal infection (Candida spp., cryptococcus)
- Leishmaniasis

Bernabeu-Wittel M, *et al. Eur J Clin Micro Infect Dis* 1999;18(5):324-9
Kamaya A, *et al. Semin Ultrasound CT MR* 2006;27(5):389-403

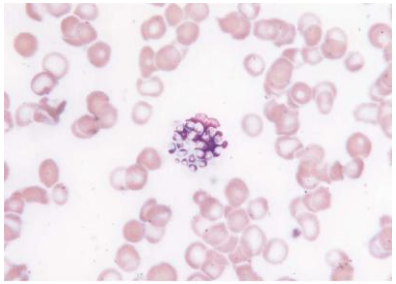


Diagnosing Fungal Infections

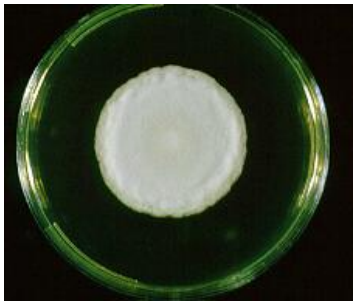
Diagnosing Fungal Infections

- **Culture** – blood or other tissue samples BUT long turn-around up to 4-6wks, coin-flip yield (around 50%)
- **Serology** – complement fixation or immunodiffusion (BUT: results delayed by few weeks)
- **Antigen detection** – *Histoplasma* antigen in urine and serum using antigen enzyme immunoassay – very sensitive
- **Direct microscopy** – peripheral blood or bone marrow aspirate: very low sensitivity
- **PCR –** directly from tissue or culture
- **Histology**

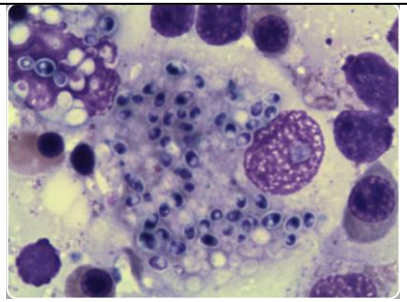
Edelman M, *et al. N Eng J Med* 2000; Jan 6:28



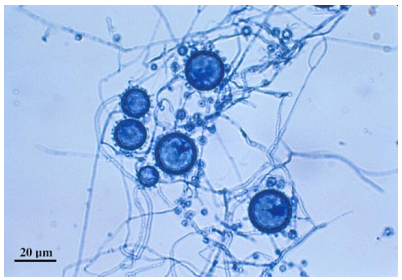
Peripheral smear



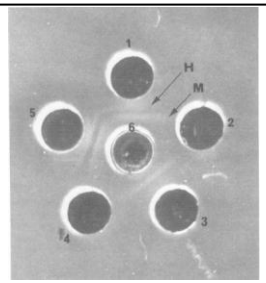
Culture



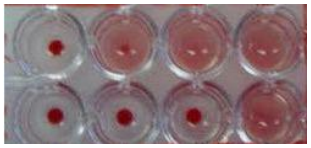
Bone marrow aspirate



Microscopy



Immunodiffusion

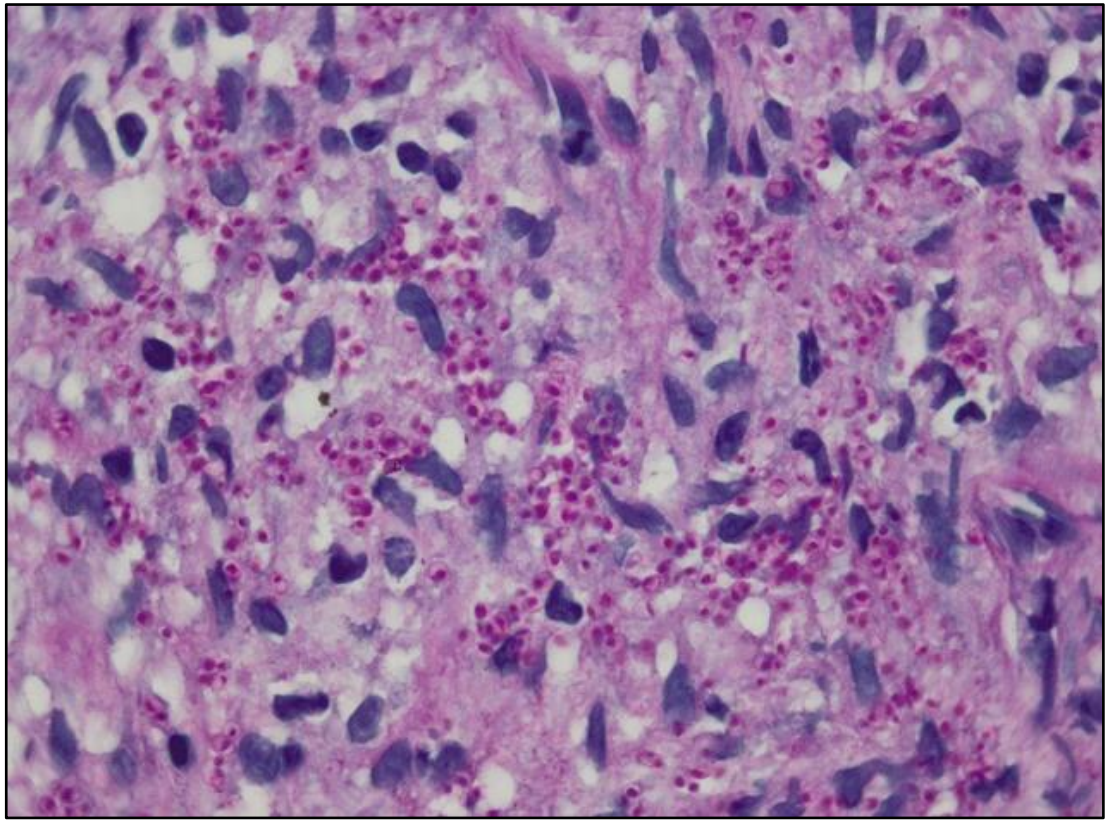


Complement fixation

Edelman M, *et al. N Eng J Med* 2000; Jan 6:28
Emani M, et al. Blood 2014;123(7):957

Bauman DS, Smith CD. *J Clin Micro* 1975;2(2):77
http://www.mycology.adelaide.edu.au/

In Mr HM – combination of:



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Laboratory Report
Date of report: 04-02-2016

Patient name	[redacted]
Hospital number	
Referring laboratory	NHLS Charlotte Maxeke Johannesburg Academic Hospital
Reason for referral	Urine for *Histoplasma* antigen test
Test requestor	Dr M Venter
Contact details	Michelle.venter@gmail.com
Clinical history	42-year-old man from Zimbabwe. HIV-infected with a CD4 count of 10 cells/µl. Has been on ART since 2006, claims adherent to ART, currently on FDC. He works as an excavator on construction sites (12 years), stays in Hillbrow and has no known exposure to birds. 1-month history of an enlarging palatal mass. On amphotericin B.
Specimen type	Urine for *Histoplasma* antigen test
Specimen collection date	28/01/2016
Lab number	Unknown

Date of receipt at NICD: 28-01-2016

Histoplasma antigen assay (04-02-2016)
An investigational EIA was performed in duplicate on the urine sample:

1. Test run 1: 24.235 EIA units (POSITIVE)
2. Test run 2: 23.933 EIA units (POSITIVE)

Interpretation: A POSITIVE EIA implies the presence of *Histoplasma* galactomannan antigen in the urine. However, since this is an investigational assay that is currently being validated, culture and histopathological results must be considered before patient management is altered.

This test should not be used in isolation for diagnostic purposes.

Laboratory tests completed by: Mabatho Mhlanga
Authorised: Nelesh Govender

Management

Histoplasmosis alone
and
implications in HIV with ARVs

Management depends on clinical syndrome

No indication for antifungal therapy

1. Mild acute pulmonary histoplasmosis
2. Localized pulmonary disease (Symptoms < than 4 weeks)
3. Rheumatologic complications
4. Pericarditis

(Unless steroids given for severe pericarditis)

4. Mediastinal lymphadenitis
5. Asymptomatic granulomatous mediastinitis

Treatment recommended

1. Severe acute pulmonary disease (antifungal therapy + steroids)
2. Chronic cavitary pulmonary disease
3. Mild to moderate disseminated disease vs severe disseminated disease

Wheat LJ, *et al. Clin Infect Dis* 2007;45:807-825

Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America

L. Joseph Wheat,[1] Alison G. Freifeld,[3] Martin B. Kleiman,[2] John W. Baddley,[4,5] David S. McKinsey,[6] James E. Loyd,[7] and Carol A. Kauffman[8]

	Induction phase	Maintenance phase
Disseminated Progressive Histoplasmosis	Liposomal Amphotericin B x 1 – 2 weeks	Itraconazole 200mg tds x3/7 200mg bd x12mo.
Alternative options	Other lipid formulations Deoxycholate Ampho B	?Fluconazole at high doses – less effective

Wheat LJ, *et al. Clin Infect Dis* 2007;45:807-825

Great if you live
in the US

Not so great if you
live
in Southern Africa

No liposomal Ampho B
No itraconazole
No urinary antigen monitoring
No itraconazole monitoring

Murphy RA, *et al. Open Forum Infect Dis* 2015; March 23

Antifungal discontinuation in AIDS patients:

- At least 1 year of Itraconazole
- Negative blood cultures
- Serum and urine antigen levels <2 ng/mL
- CD 4 count above 150 cells/mm^3
- On HAART

Drug interactions – HAART vs Azoles

HAART

NRTIs – AZT/ ABC – not metabolised by cytochrome P450
NNRTIs – EFV: cleared by cytochrome P450, inhibitor of certain P450 enzymes – can increase levels of RTV
PIs – RTV potent inhibitor of cytochrome P450
LPV/ ATV – metabolised by P450 system, weak inhibitors of certain enzymes

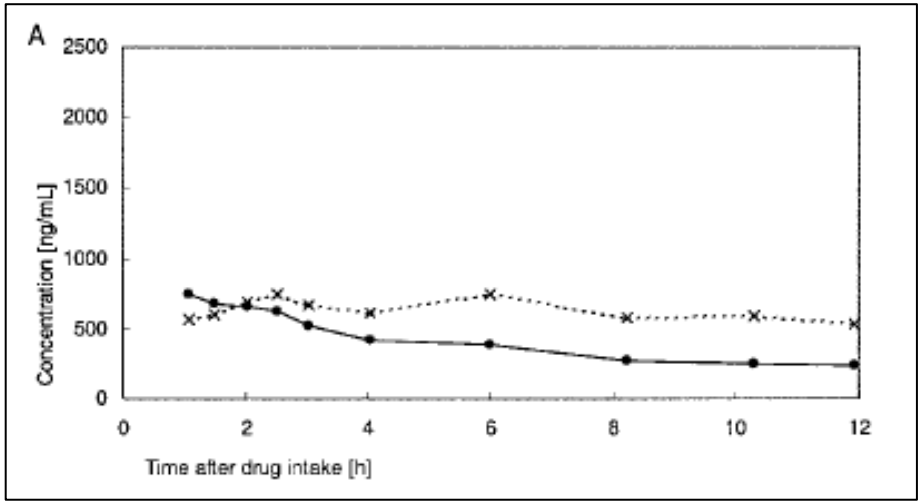
Dooley KE, *et al. J Infect Dis* 2008;198:1-14

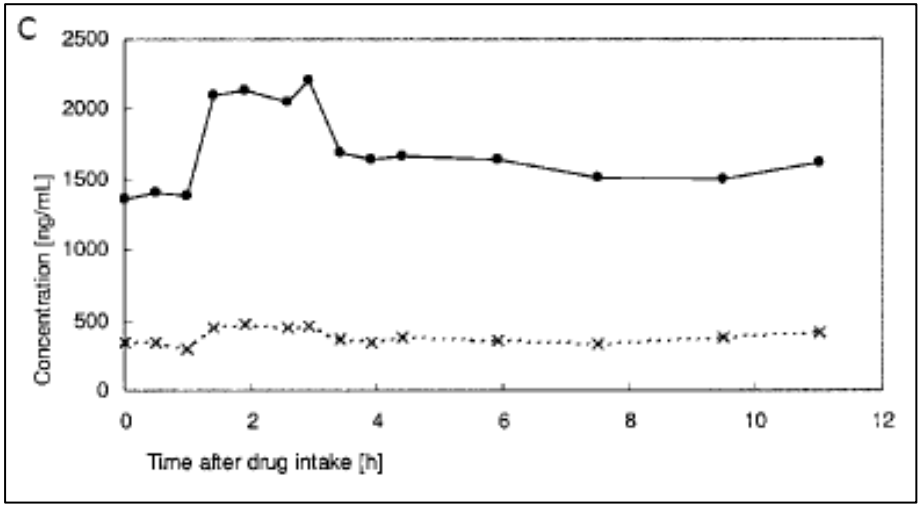
Azole Antifungals

- Extensively metabolised by cytochrome P450 system
- Competitive inhibitors of CYP isoenzymes
- Variable inhibitory capacity: ketoconazole > itraconazole > fluconazole
- Fluconazole and EFV: safe
- BUT fluconazole and NVP: increased NVP levels (monitor LFTs)
- Itraconazole and EFV/ NVP: decreased itraconazole levels (uncertain significance)
- Intraconazole and PIs: increased itraconazole concentration, prolong half-life, leads to accumulation

Dooley KE, *et al. J Infect Dis* 2008;198:1-14

Plasma concentrations of itraconazole (solid line) and droxyitraconazole (dotted lines) in an HIV-infected patient with histoplasmosis.
A: Concentrations before ARVs
C: Concentration when ARVs at steady state and itraconazole at 200mg daily

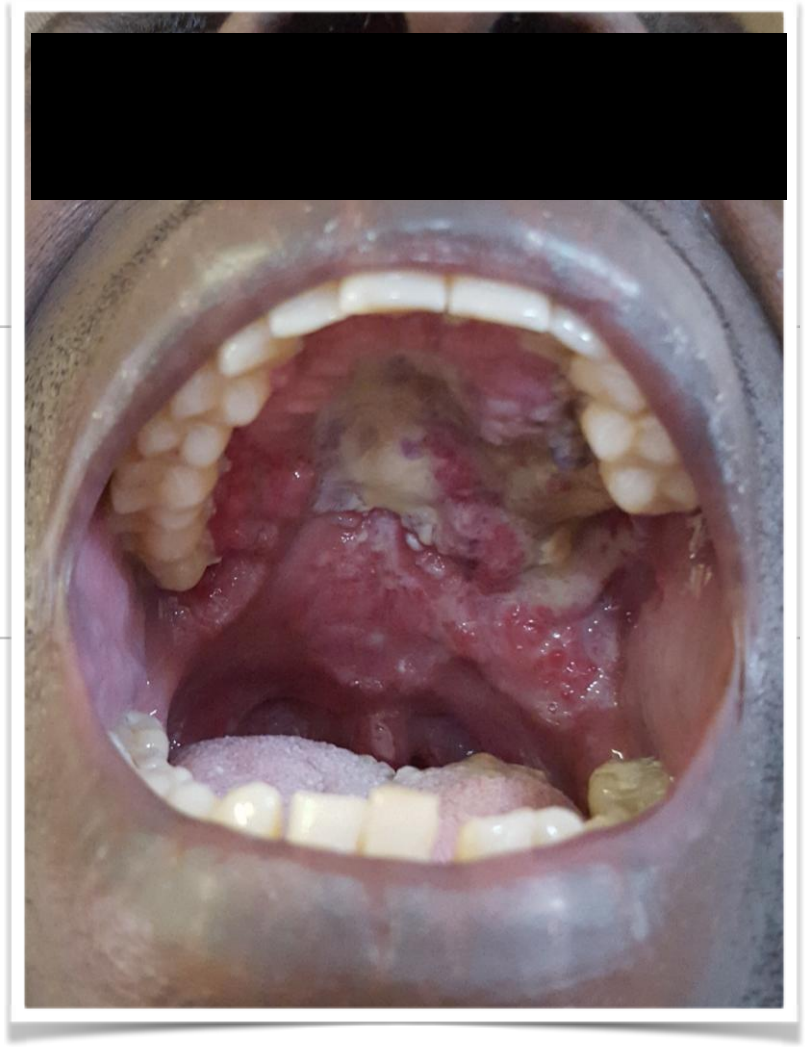




Crommetuyn KML, *et al. Clin Infect Dis* 2004;38:e73-75

Mr HM's course

- Completed >14 days of Amphotericin B
- Will need itraconazole maintenance.
- Virological Failure
- Patient now needs to be changed to second line ARV'S
- Follow-up in Infectious diseases clinic



At presentation

After 1 week of Treatment

Thank you

Special thanks to:
Dr Michelle Venter, Dept of Medicine
Dr Kirsty Fearnhead, Dept of Pathology
Dr Stacey Bhikha, Dept of Medicine