

# ***Meningitis***

## **in the context of the**

# ***HIV epidemic***

**14<sup>th</sup> March 2013**

**Kerrigan McCarthy**

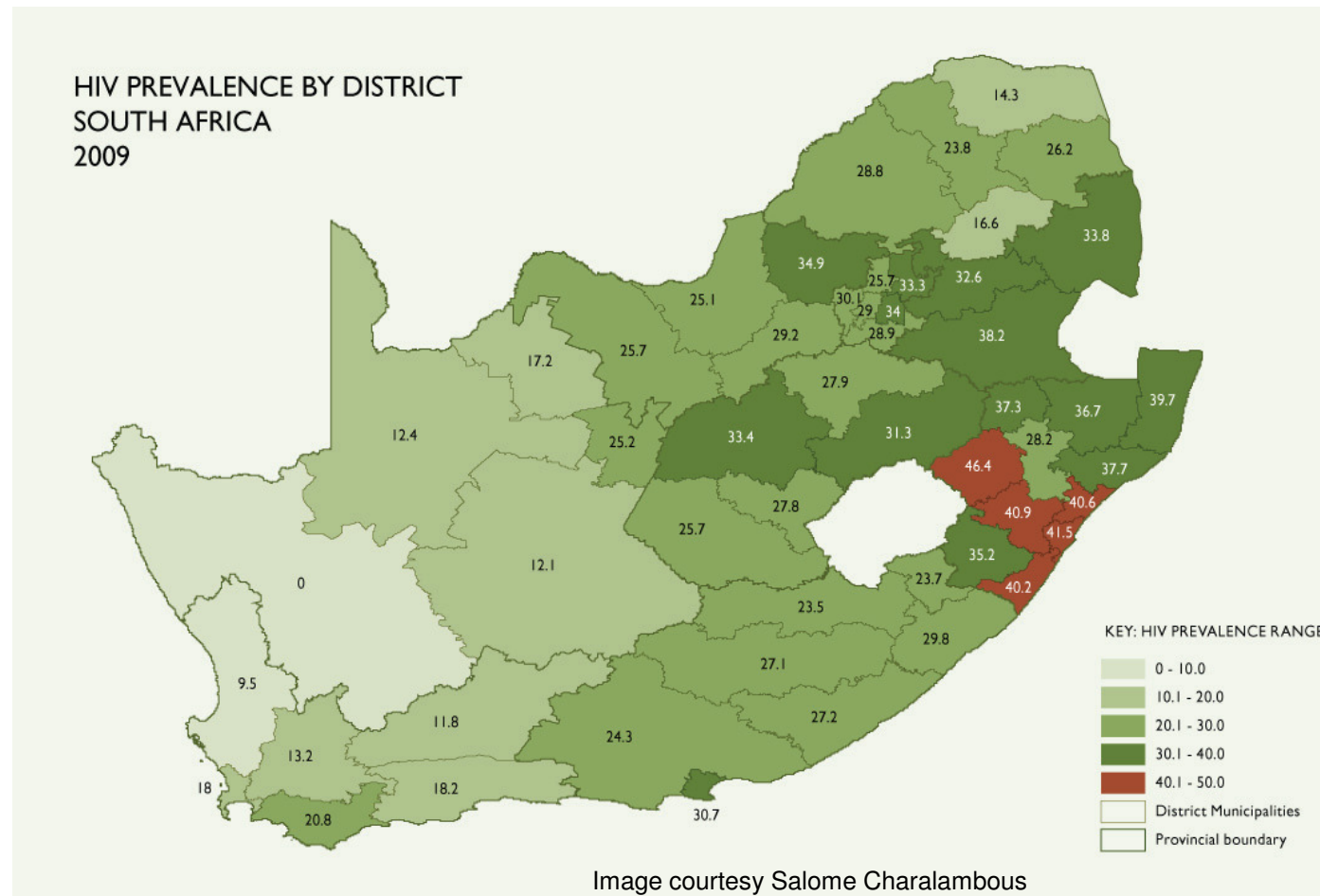
**MBBCh, DTM+H, FCPATH (Micro)**



**XTEND**

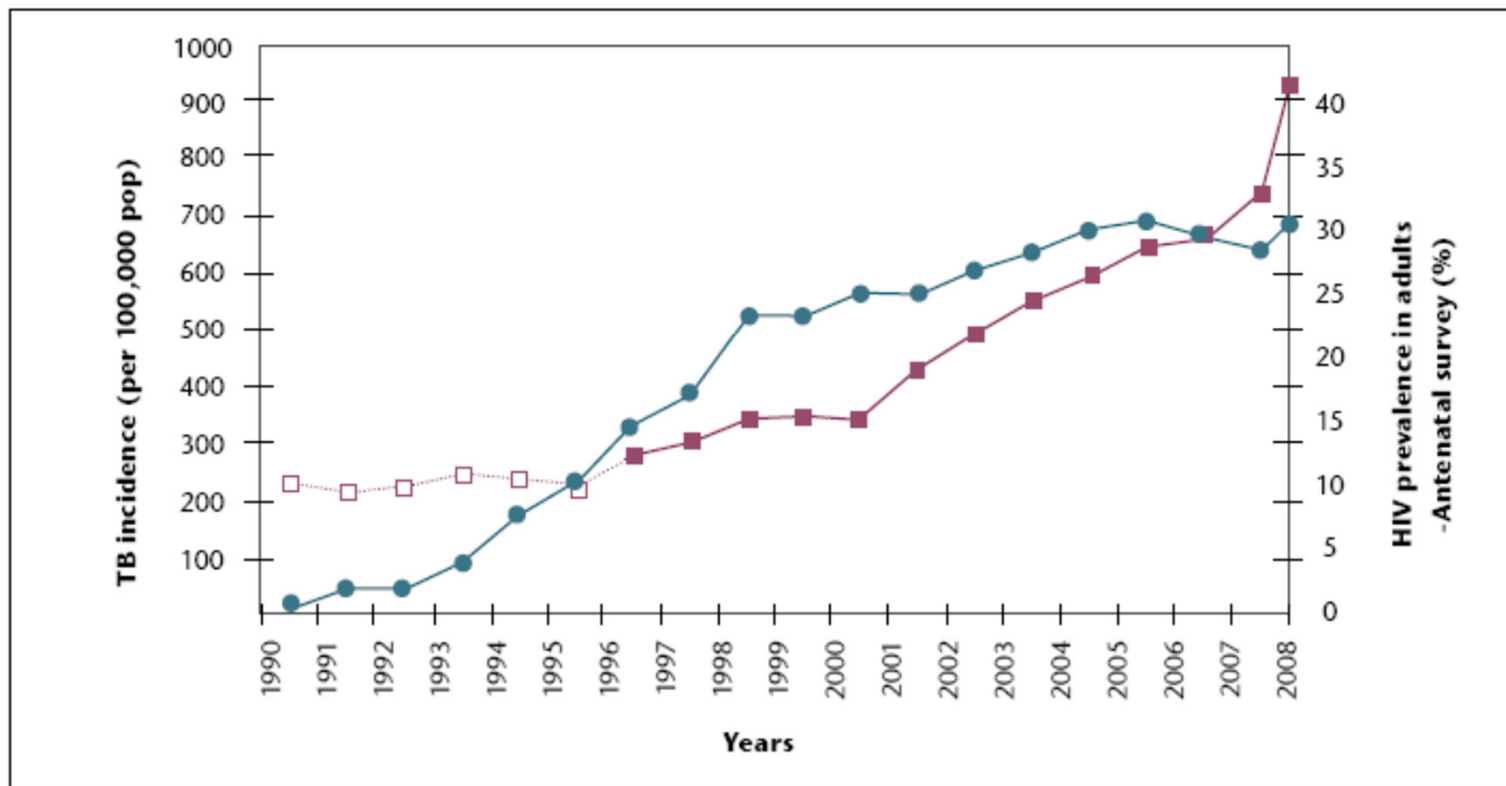


# KZN is the epicentre of the epidemic



# A note on our context.....

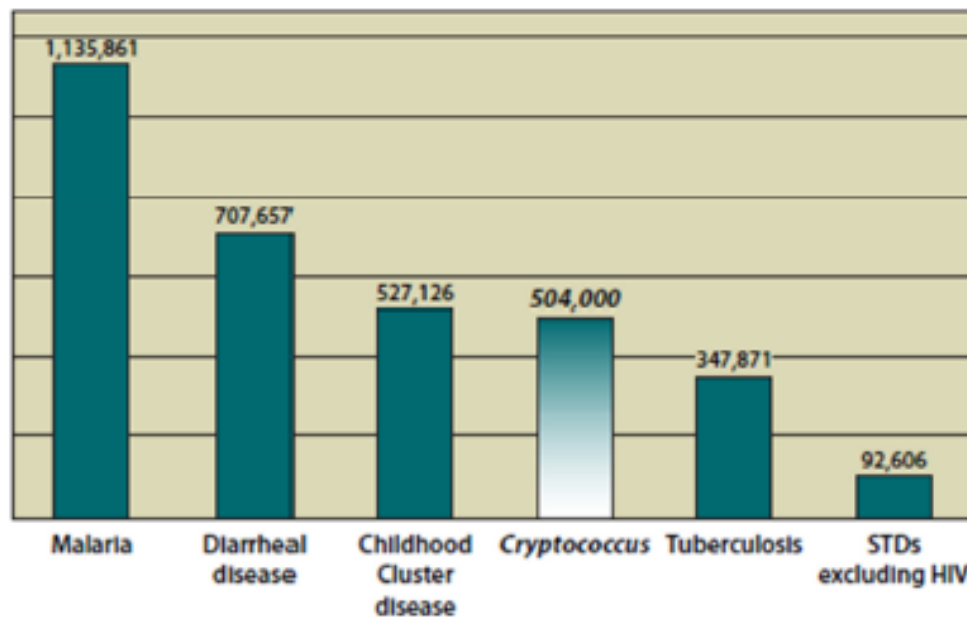
**Figure A1: TB Incidence and HIV Prevalence, South Africa, 1980-2007<sup>4</sup>  
(updated 2008)**



## A note on our context....

- Meningitis and TB across the globe
  - It's a killer.....

Leading causes of death in sub-Saharan Africa, excluding HIV



Images adapted from B.J. Park et al. AIDS 2009; 23: 525-30.

# Meningitis - overview –

- A case study...

.....and all the things that go through our heads

- ? Any immediate action
- Diagnostic procedures
- Anti-infective chemotherapy
- Palliative and nursing care
- HIV diagnosis and management
- Prognosis and long term sequelae.....
- An note on prevention

# A presentation we are all too familiar with:

- Ms PN, brought in by boyfriend
- 26 yrs old, resident with her boyfriend in local township, unemployed mother of 2
- History taking is difficult –but it appears that
  - M/C is headache & confusion, progressive over 2 weeks
  - Occasional cough, fever and nightsweats, loss of weight
- No previous illness
- No previous admissions
- Not tested ever for HIV, apparently

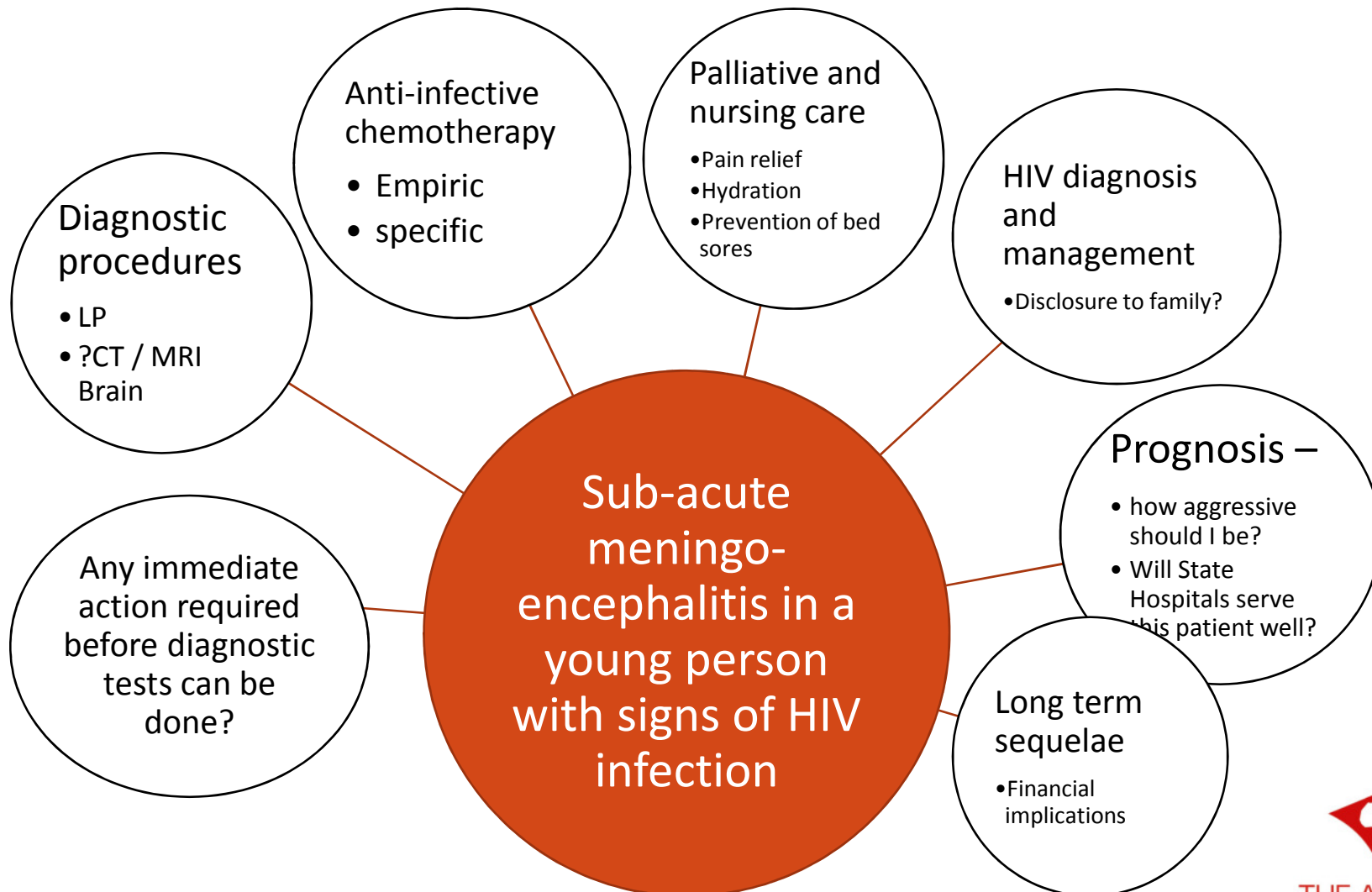


# A presentation we are all too familiar with:

- General examination:
  - Axillary temperature 37.5°C
  - Resp rate 18/min
  - Bp 90/60mmHg
  - Pulse rate 110/min
  - Generalised LNs, pale mucous membranes, diffuse seborrheic dermatitis, oral thrush
- On examination of CNS
  - Mini-mental status exam
    - GCS 14; poor recall, not orientated to time, person or place
  - ?neckstiffness
  - Fundi not visualised
  - No localising signs
- Other organ systems
  - Chest clear
  - Cor – no abnormalities detected
  - Abdomen – soft, non-tender

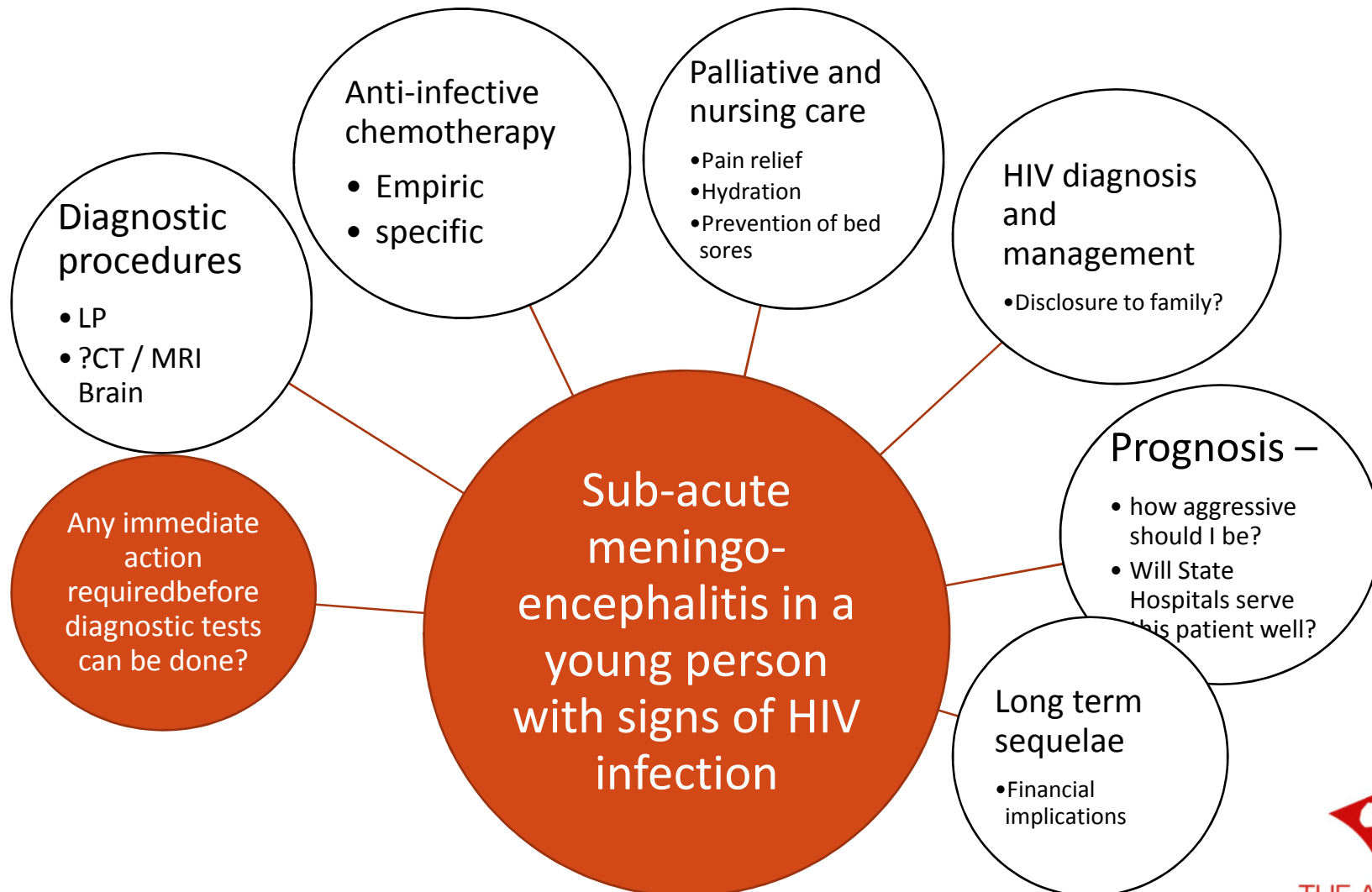


# Going through our minds.....





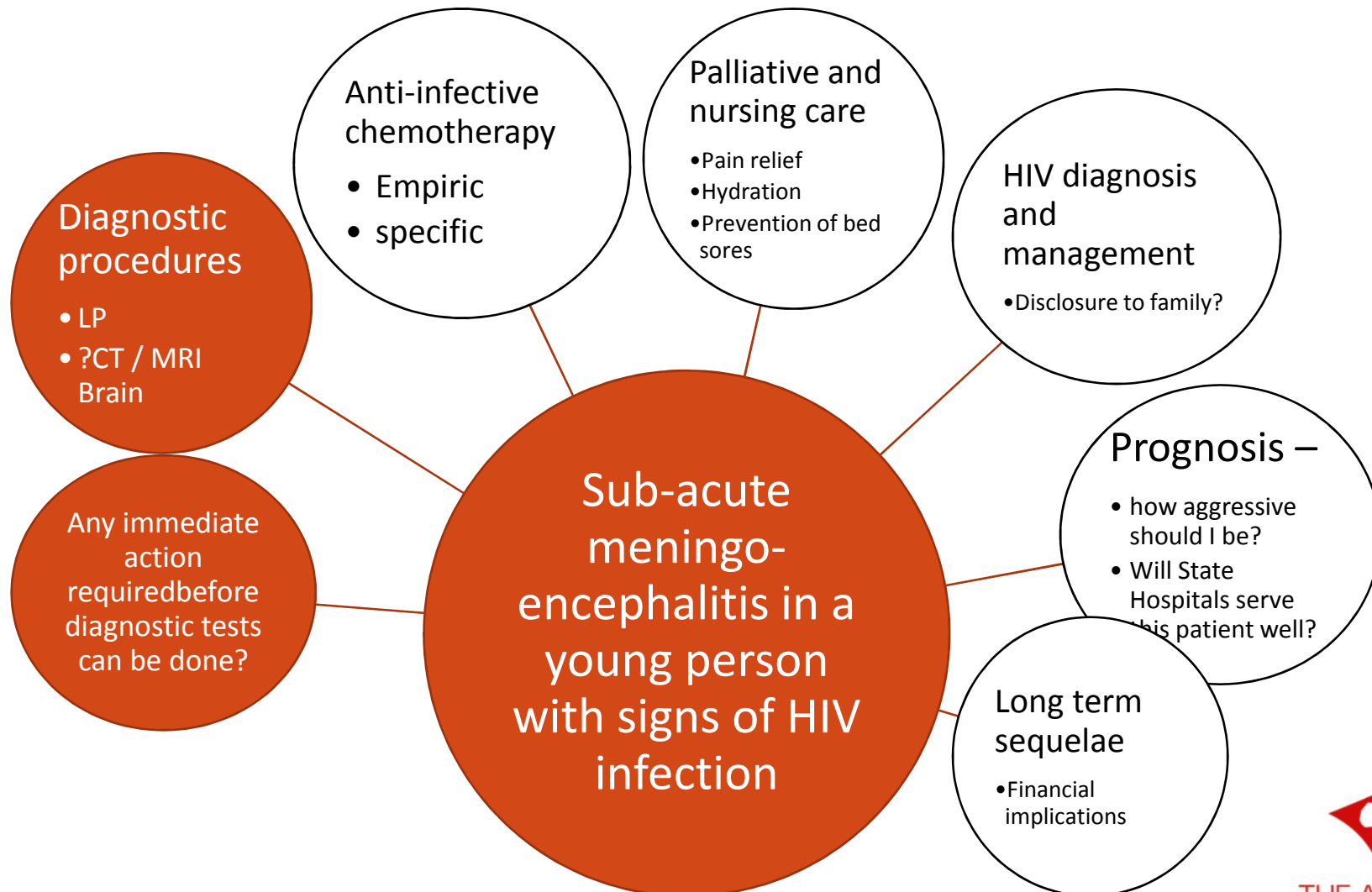
# Going through our minds.....



## Immediate action....

- If LP can't be done immediately...
  - (E.g. patient at primary health clinic (PHC)/other venue and needs transfer or patient has localising signs and needs CT brain)
- Antibacterials?      Should we start ivi antibiotics?
- Antifungals?      Do serum cryptococcal antigen using LA or LFA;  
if positive, start on oral fluconazole 800mg until LP can be done
- Steroids?      If bacterial or TB meningitis suspected – should we give steroids?

# Going through our minds.....



# LP and laboratory tests to facilitate diagnosis of cause of meningitis

- Should I do a lumbar puncture?
  - Is it safe?
    - Is there raised intra-cranial pressure?
    - Are there localising signs?
    - Is there gross impairment of consciousness?

- Papilloedema is difficult to exclude in unco-operative patients
- ICP in persons with CM requires LP as part of mx

- VI cranial nerve palsy often associated with CM, requires LP



# LP and laboratory tests to facilitate diagnosis of cause of meningitis

- Should I do a lumbar puncture?

In settings with a high HIV seroprevalence, many patients with suspected acute community-acquired bacterial meningitis would qualify for cranial imaging before lumbar puncture because of the high likelihood of HIV infection,<sup>35-37</sup> yet CT equipment can be scarce in these settings.<sup>38</sup> The risk of death resulting from an inaccurate diagnosis through lumbar puncture deferral is considered greater than the risks that are associated with the procedure, irrespective of focal signs or a reduced state of consciousness, and therefore lumbar puncture should not be deferred.<sup>38</sup>



Brouwer et al. Dilemmas in the diagnosis of meningitis. Lancet 2013;380:1684-92

# LP and laboratory tests to facilitate diagnosis of cause of meningitis

- Should I do a lumbar puncture?
  - What if the CNS signs are subtle, such as
    - Very moderate neck stiffness
    - Slight/occasional confusion or subtle personality changes and/or memory loss

- ALWAYS DO LP if you have any reason to consider intra-cranial pathology



# The differential diagnosis - working within the HIV epidemic

- Could this be an acute/sub-acute bacterial meningitis?
- Suggestive si/sy
  - Acute onset
  - Marked neck stiffness
  - No antecedent history of LOW etc
  - High grade pyrexia on examination

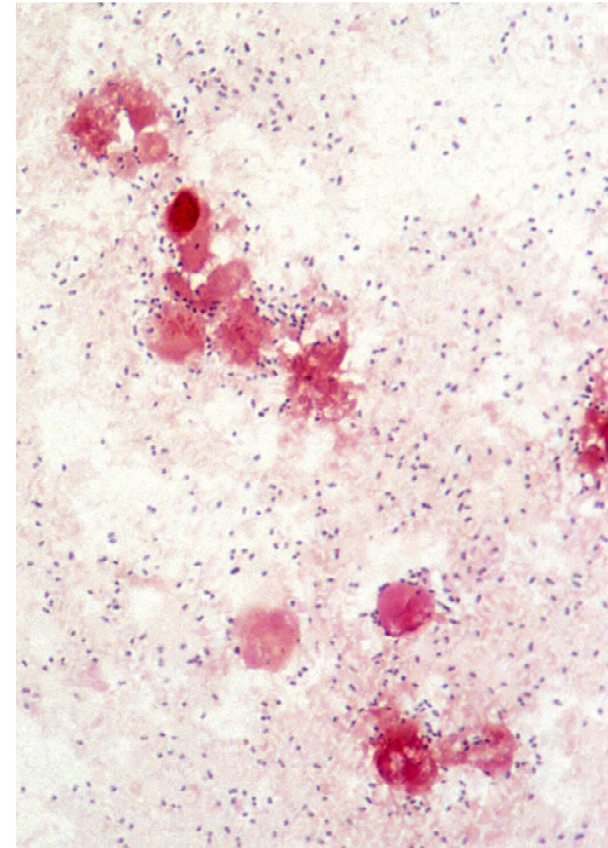


Image courtesy Anne von Gottberg, NICD

# LP and laboratory tests to facilitate diagnosis of cause of meningitis

Aetiology	Typical Cell count	Typical CSF chemistry	Microscopy and Culture	Specific tests
Bacterial	PMNs ↑↑↑ Lymphs ↑	Protein ↑	Gram's stain helpful Result due 24-48 hrs	Bacterial latex agglutination

## Commonly isolated organisms

Gram-positive diplococci – *Streptococcus pneumoniae*

Gram-negative cocci – *Neisseria meningitidis*

Gram-negative cocco-bacilli – *Haemophilus influenzae*

Gram-positive bacilli – *Listeria monocytogenes*

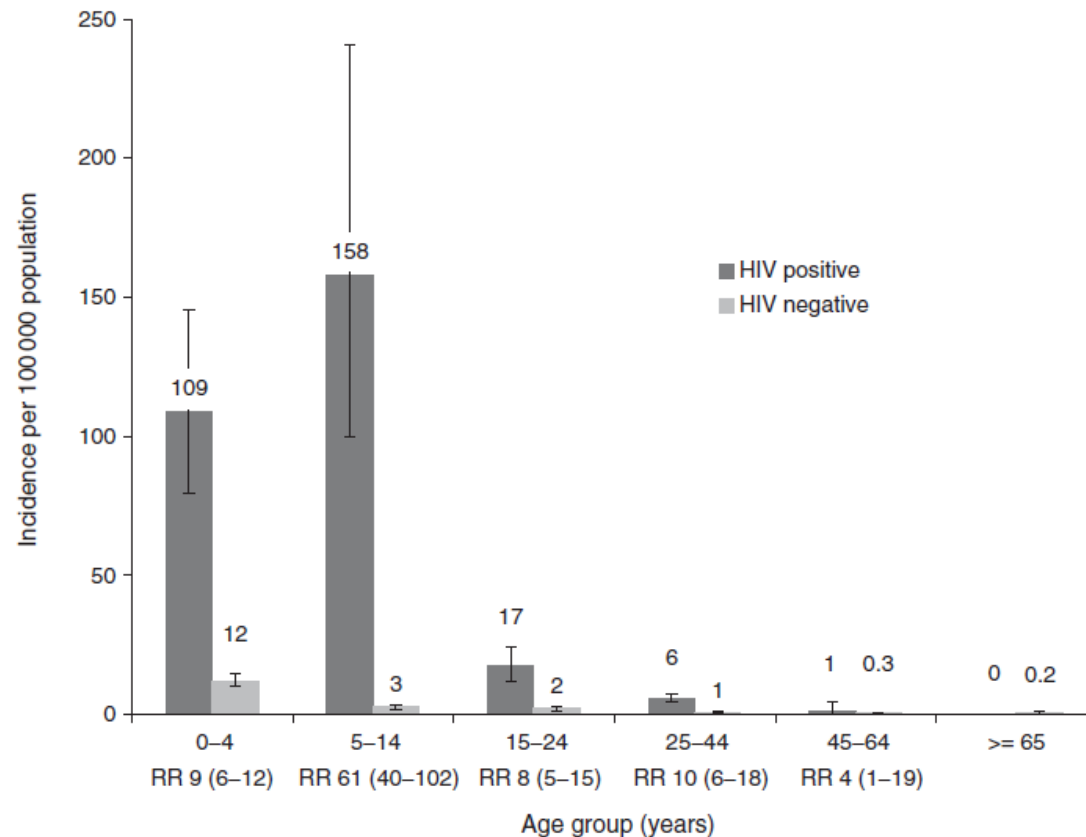
Uncommon:

Gram-negative enteric bacterial – *Salmonella* species

Gram-negative non-fermenters – *Pseudomonas* species



# A note on epidemiology

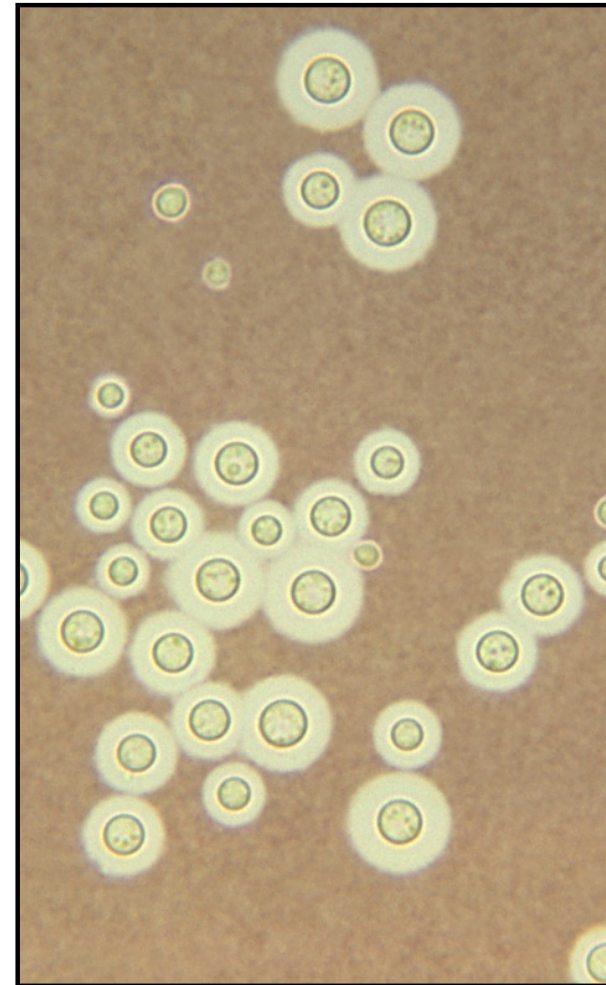


**Fig. 2. Estimated incidence of meningococcal disease by age group and HIV status, Gauteng Province, 2005.** Numbers above bars indicate point estimates of incidence and error bars indicate 95% confidence limits around incidence estimates. RR, relative risk HIV-positive vs. HIV-negative (95% confidence interval).

Cohen et al. AIDS AIDS 2010, 24:1351–1360

# The differential diagnosis - working within the HIV epidemic

- Could this be a cryptococcal meningitis / meningo-encephalitis
- Suggestive si/sy
  - CD4 < 200 cells/mm<sup>3</sup>, but often < 50;
  - Diplopia / 6<sup>th</sup> CN palsy
  - Subtle changes – memory loss, mood changes
  - Skin lesions





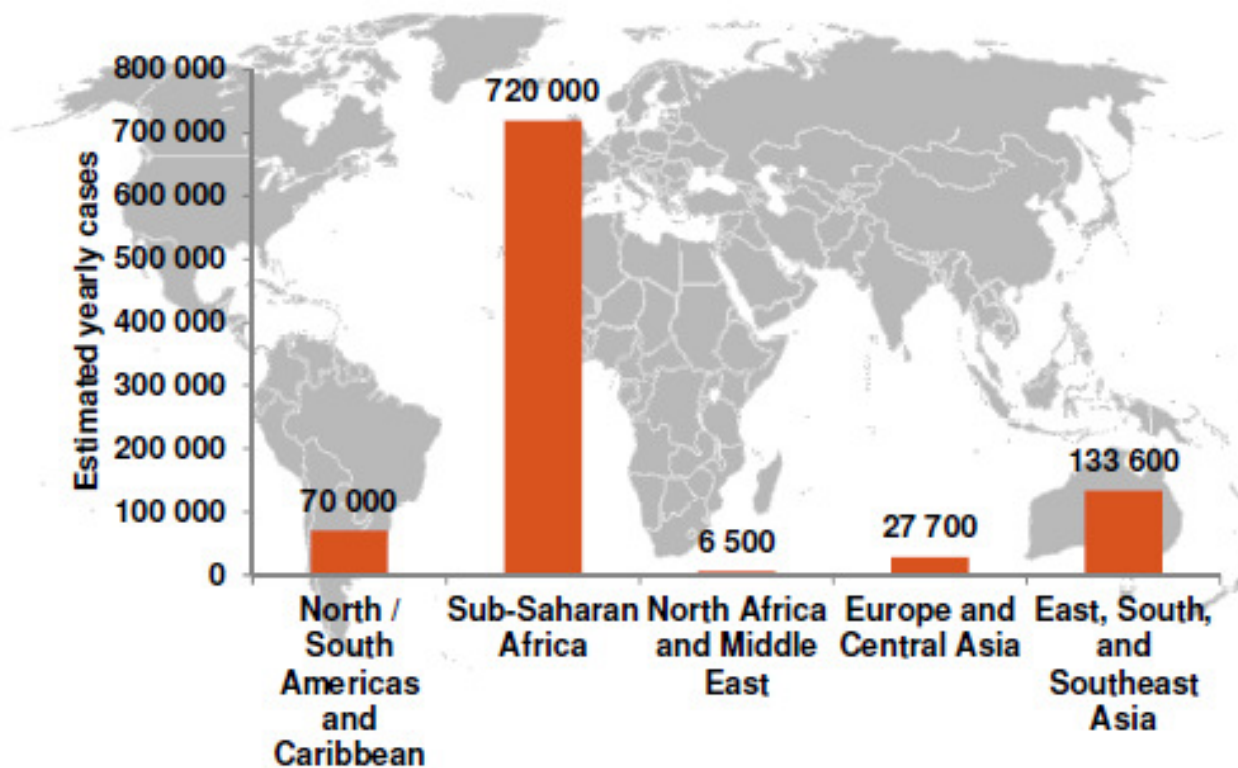
Cutaneous cryptococcal infection—



VI CN palsy

# A note on epidemiology

- Cryptococcal meningitis across the globe

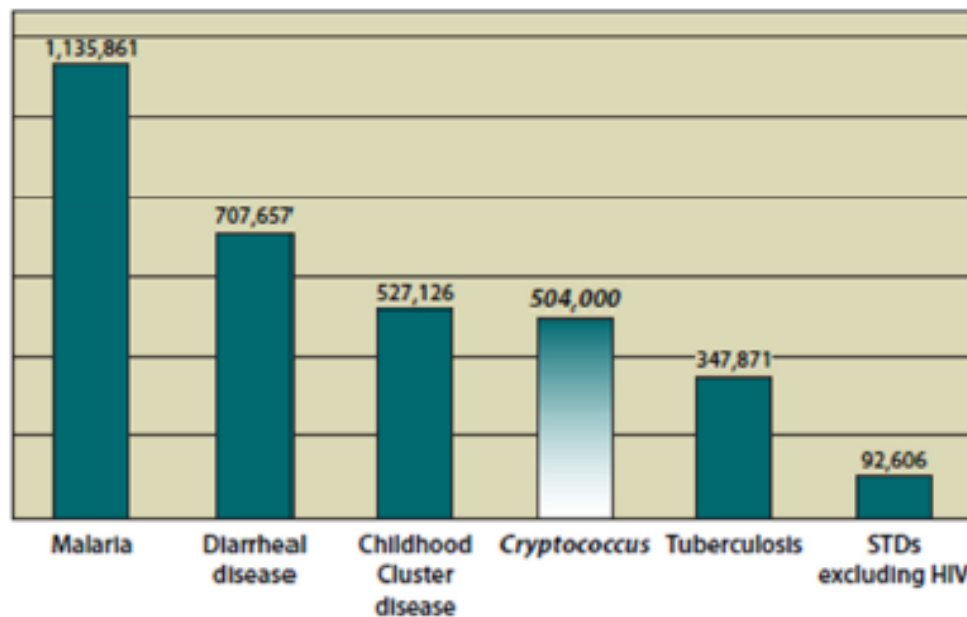


Images adapted from B.J. Park et al. AIDS 2009; 23: 525-30.

# A note on epidemiology

- Cryptococcal meningitis across the globe
  - It's a killer.....

Leading causes of death in sub-Saharan Africa, excluding HIV



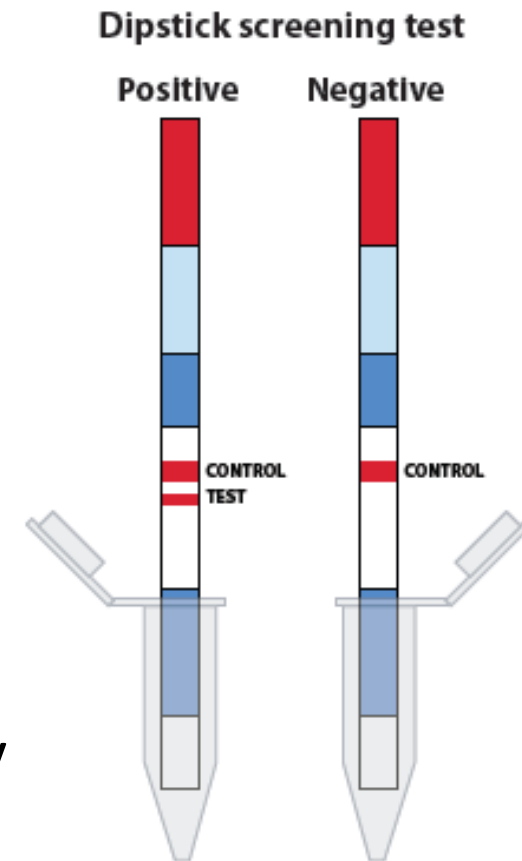
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# LP and laboratory tests to facilitate diagnosis of cause of meningitis

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Fungal (cryptococcal)	PMNs ↑ Lymphs ↑↑↑	Protein ↑↑↑	India ink Result due 14 days	LA or Lateral flow assay (new)

# A note on newer diagnostics

- Lateral flow assay for *C neoformans* in CSF
  - **Simple and quick:** Results available in 10 minutes
  - **Accessible:** can be done at the bedside
  - **Effective:** Highly sensitive and accurate (>95%)
  - **Affordable:** costs approximately 16 rand per test

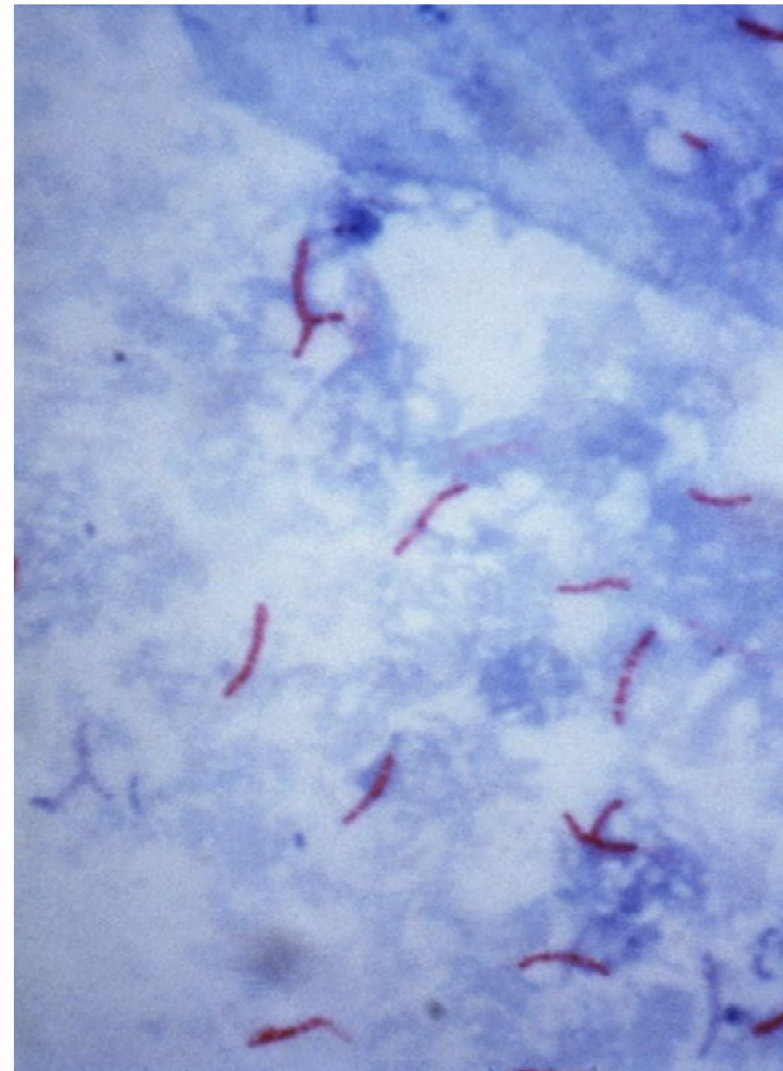


Slide courtesy N Govender. NICD



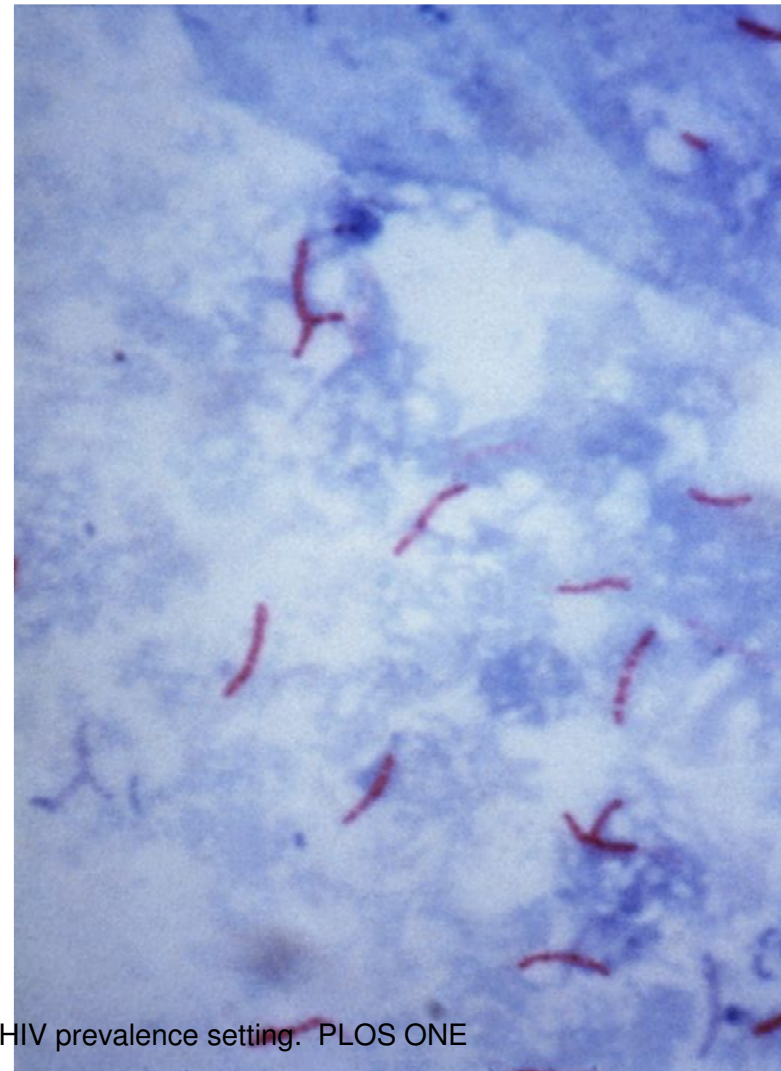
# The differential diagnosis - working within the HIV epidemic

- Could this be a tuberculous meningitis?
- Suggestive si/sy
  - Chronicity with progressive worsening of headache over weeks
  - Loss of weight, night sweats
  - Focus of TB infection elsewhere
    - LNs, lungs;
    - disseminated infection with pancytopenia



# The differential diagnosis - working within the HIV epidemic

- TB meningitis
  - Definite –culture or ZN positive (47/109 cases)
  - Probable
    - Clinical features of meningitis
    - Suggestive CSF findings
    - 1 of the following
      - CXR consistent with PTB
      - Extrameningeal TB (e.g. LNs or splenic microabscesses on abd u/s)
      - CT brain evidence of TB such as basal meningeal enhancement, hydrocephalus or enhancement



# LP and laboratory tests to facilitate diagnosis of cause of meningitis

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Tuberculous	PMNs ↑ Lymphs ↑↑↑	Protein ↑↑↑	ZN rarely positive Result due 6 weeks; uncommonly positive	GeneXpert not more helpful than culture

# A note on newer diagnostics

- GeneXpert for *M. tuberculosis* in CSF
- Not validated for non-sputum specimens
- Limited use with CSF,
  - Cultures are uncommonly positive
  - Xpert sensitivity is 75% of culture positive cases



# The differential diagnosis - working within the HIV epidemic

- Could this be a viral encephalitis?
  - HSV, VZV, enterovirus
- Suggestive si/sy
  - High red cell count
  - Focal temporal lobe signs
  - Occasionally oral HSV or disseminated VZV skin rash
  - Large vessel involvement with haemorrhagic CVA



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# LP and laboratory tests to facilitate diagnosis of cause of meningitis

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Viral	PMNs ↑ Lymphs ↑↑↑	Protein ↑↑↑	Not helpful routinely	PCR

# A note on epidemiology....

*Common things occur commonly*

Hospital	Country	Sample size	HIV infected	Bacterial/pyogenic	Tuberculosis	Cryptococcal	Aseptic/viral
Mulago and Mbarana <sup>1</sup>	Uganda	416	90%	4%	8%	59%	29%
GF Jooste <sup>2</sup>	South Africa	1737	96%	19%	13%	30%	38%
Queen Elizabeth <sup>3</sup>	Malawi	263	77%	20%	17%	43%	20%
Harare <sup>4</sup>	Zimbabwe	200	90%	16%	12%	45%	28%
<b>Average</b>		<b>2616</b>	<b>93%</b>	<b>9.3%</b>	<b>12.7%</b>	<b>37%</b>	<b>41%</b>

<sup>1</sup> Durski K et al. *JAIDS* 2013, *In Press*

<sup>2</sup> Jarvis JN, et al. *BMC Infect Dis.* 2010; 10: 67.

<sup>3</sup> Cohen DB, et al. *Trop Med Int Health.* 2010; 15: 910-917.

<sup>4</sup> Hakim JG et al. *AIDS.* 2000; 14: 1401-1407.

Slide courtesy D Boulware, CROI 2013



**THE AURUM  
INSTITUTE**

## Other uncommon causes of a lymphocytic meningitis...

- Or perhaps syphilitic meningo-encephalitis due to *Treponema pallidum*?





# Outliers in the differential of a sub-acute meningo-encephalitis

- HIV dementia?
- Metabolic derangements?
- Intra-cranial bleed?
- Trauma?
- Space occupying lesions
  - Tuberculoma
  - Cryptococcoma
  - Abscess
  - CNS lymphoma
- Or is this merely sepsis with delirium?

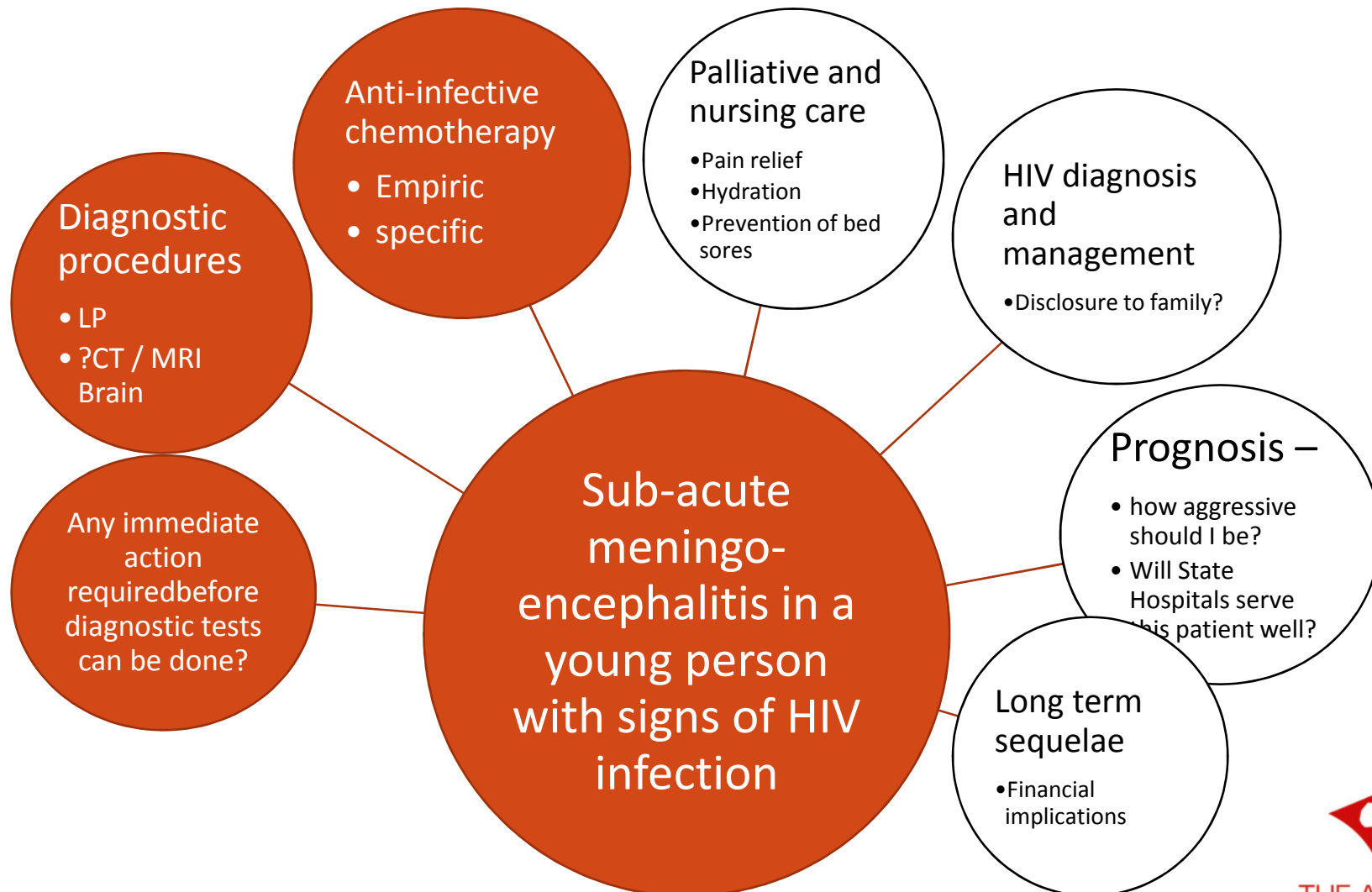


# The differential diagnosis – a summary

- Infectious causes of meningo-encephalitis
  - Bacterial causes
    - *Streptococcus pneumoniae*
    - *Haemophilus influenzae*
    - *Listeria monocytogenes*
    - Gram-negative bacteria
  - Fungal causes
    - *Cryptococcus neoformans*
  - Mycobacterial and treponemal causes
    - *Mycobacterium tuberculosis*
    - Syphilitic meningitis
  - Viral encephalitis
    - Herpes simplex
    - Herpes Zoster
    - Enterovirus
- Space-occupying lesions
  - *Toxoplasma gondii* (and other parasitic organisms)
  - Abscess
  - Tuberculoma, Cryptococcoma
- Non-infectious causes
  - HIV encephalopathy
  - Intra-cranial bleed
  - Lymphoma (and other neoplasms)
  - Toxic, metabolic, auto-immune, etc



# Going through our minds.....



# Anti-infective chemotherapy

- Bacterial meningitis
  - Empiric treatment (following Gram's stain)
    - Ceftriaxone +/- vancomycin
      - Depends on local susceptibility profile of *S. pneumoniae*
    - Consider amoxicillin ivi if not using vancomycin (*Listeria* is resistant to cephalosporins)
  - Specific therapy
    - 3<sup>rd</sup> generation cephalosporin adequate for GPC, GNB including *Haemophilus influenzae*
    - Ask for pneumococcal MICs to penicillin and ceftriaxone
    - Amoxicillin for *Listeria*



# Anti-infective chemotherapy

- Bacterial meningitis – empiric therapy

Community-acquired meningitis		
Age <1 month	<i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i>	Amoxicillin/ampicillin plus cefotaxime, or amoxicillin/ ampicillin plus an aminoglycoside
Age 1–23 months	<i>S agalactiae</i> , <i>E coli</i> , <i>S pneumoniae</i> , <i>Neisseria meningitidis</i>	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)*
Age 2–50 years	<i>S pneumoniae</i> , <i>N meningitidis</i>	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)*
Age >50 years	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , aerobic Gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)
Immunocompromised state	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , <i>Staphylococcus aureus</i> , <i>Salmonella spp</i> , aerobic Gram-negative bacilli (including <i>Pseudomonas aeruginosa</i> )	Vancomycin plus ampicillin plus either cefepime or meropenem

Van der Beek. Advances in the treatment of meningitis. Lancet 390: 1690. 2012

# Anti-infective chemotherapy

- Bacterial meningitis – empiric therapy
  - Alter based on Gram's stain result

	Antibiotic therapy
Gram-positive cocci in pairs	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)
Gram-negative cocci in pairs	Third-generation cephalosporin (either cefotaxime or ceftriaxone)
Gram-positive bacilli	Amoxicillin/ampicillin* or penicillin G*
Gram-positive cocci in chains	Amoxicillin/ampicillin or penicillin G*
Gram-negative bacilli	Third-generation cephalosporin

\*Consider the addition of an aminoglycoside.

Table 3: Recommended antibiotics in patients with community-acquired meningitis by result of cerebrospinal fluid Gram stain

# Anti-infective chemotherapy

- Specific therapy for *S pneumoniae* meningitis

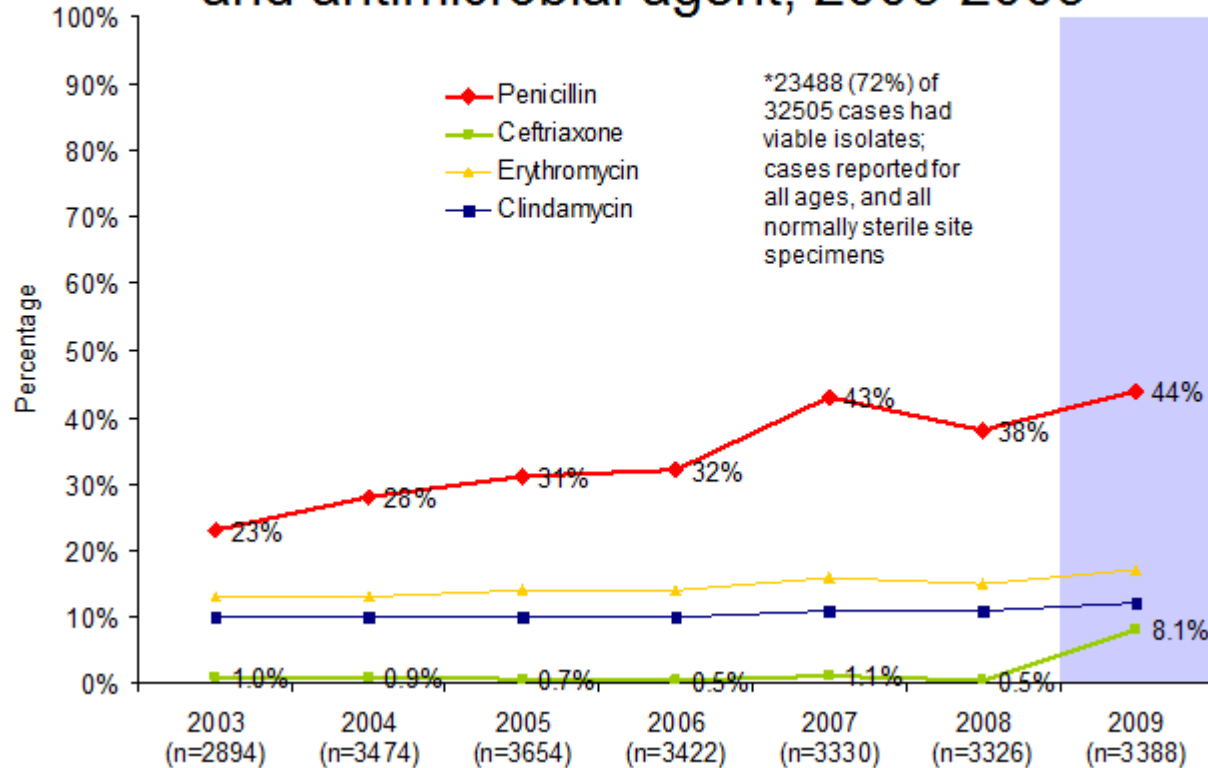
Comparison of former and new **penicillin** breakpoints (minimum inhibitory concentrations [MIC]) for *Streptococcus pneumoniae*, by susceptibility category – Clinical and Laboratory Standards Institute [CLSI], 2008

Standard	Susceptibility category (µg/mL)		
	Susceptible	Intermediate	Resistant
<b>Former (all clinical syndromes and penicillin routes)</b>	≤0.06	0.12-1	≥2
<b>New (by clinical syndrome and penicillin route)</b>			
Meningitis, intravenous penicillin	≤0.06	-*	≥0.12
Non-meningitis, intravenous penicillin	≤2	4	≥8
Non-meningitis, oral penicillin	≤0.06	0.12-1	≥2

Slide courtesy Anne von Gottberg, NICD

# Anti-infective chemotherapy

Percentage of non-susceptible pneumococcal isolates causing invasive disease\* by year and antimicrobial agent, 2003-2009

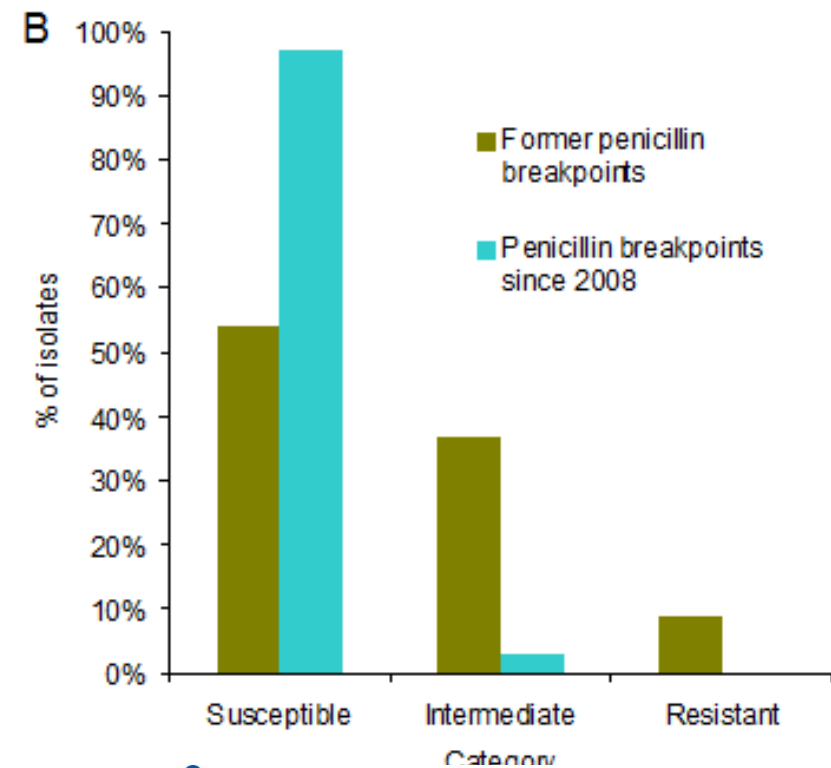
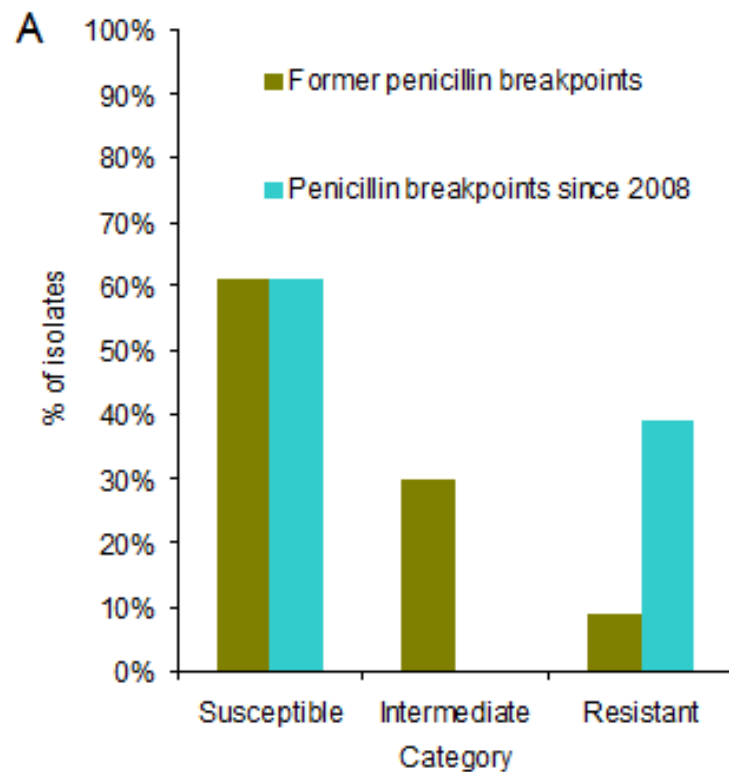


Slide courtesy Anne von Gottberg, NICD



# Anti-infective chemotherapy

Percentage of pneumococcal isolates from (A) cerebrospinal fluid (n=1245) and (B) other invasive specimens (n=2143) by former and new **penicillin** breakpoints, South Africa, 2009



# Anti-infective chemotherapy

- Adjunctive steroids for bacterial meningitis
  - Studies are confusing
    - In adults, in high socio-economic countries, dexamethasone improves outcome, reduces adverse effects, but not in low income countries
    - Children – definite benefit if given on or with the first dose of antibiotics
  - Dose of dexamethasone
    - Kids – 0.6mg/kg
    - Adults 10mg every 6 hrly

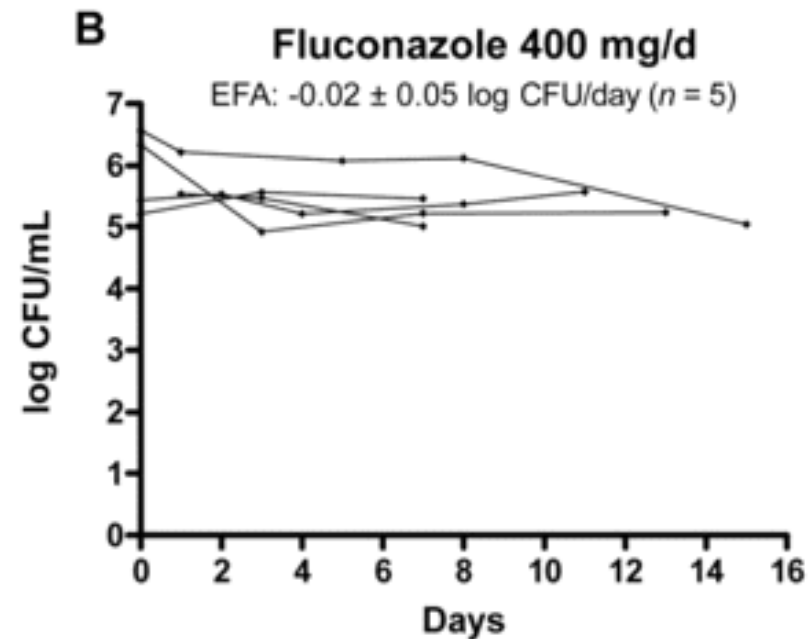
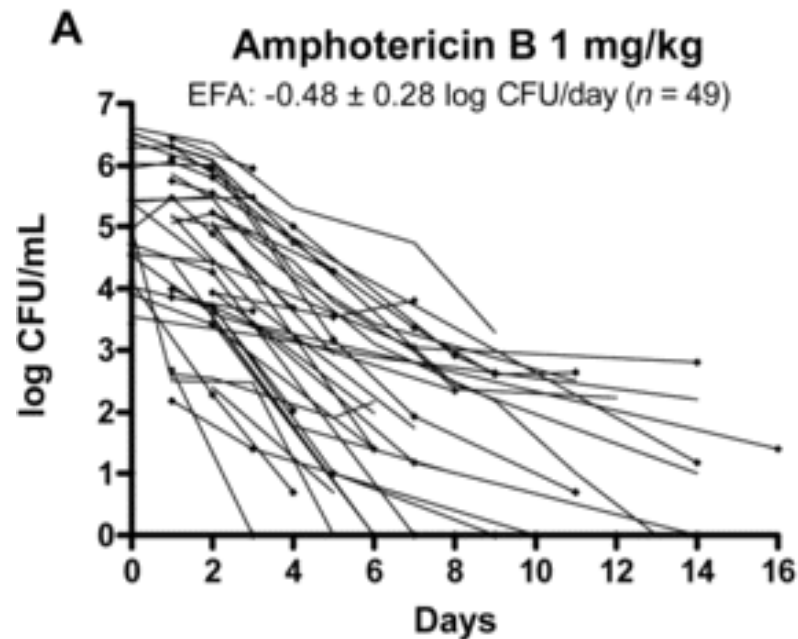
# Anti-infective chemotherapy

- Cryptococcal meningitis
  - New recommendation – revised guidelines from HIV clinician’s society:

Phase	Induction phase	Consolidation phase	Maintenance phase
Duration	2 weeks	8 weeks	For at least 12 months total treatment and with two CD4 counts >200 6 month apart, on ART
Treatment	Amphotericin B 1 mg/kg/dose IV <b>plus</b> Fluconazole 800 mg PO daily	Fluconazole 400 mg PO daily	Fluconazole 200 mg PO daily

# Anti-infective chemotherapy

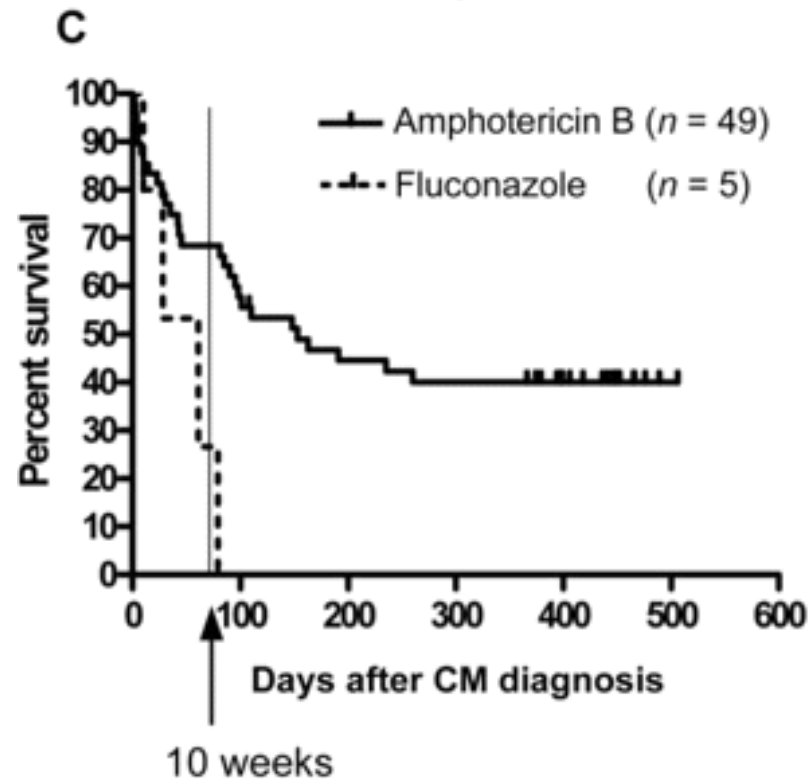
- Cryptococcal meningitis
  - Why not fluconazole alone?



Bicanic T, Meintjes G, et al Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with **amphotericin B** or **fluconazole**. Clin Infect Dis. 2007 Jul 1;45(1):76-80. Epub 2007 May 25.

# Anti-infective chemotherapy

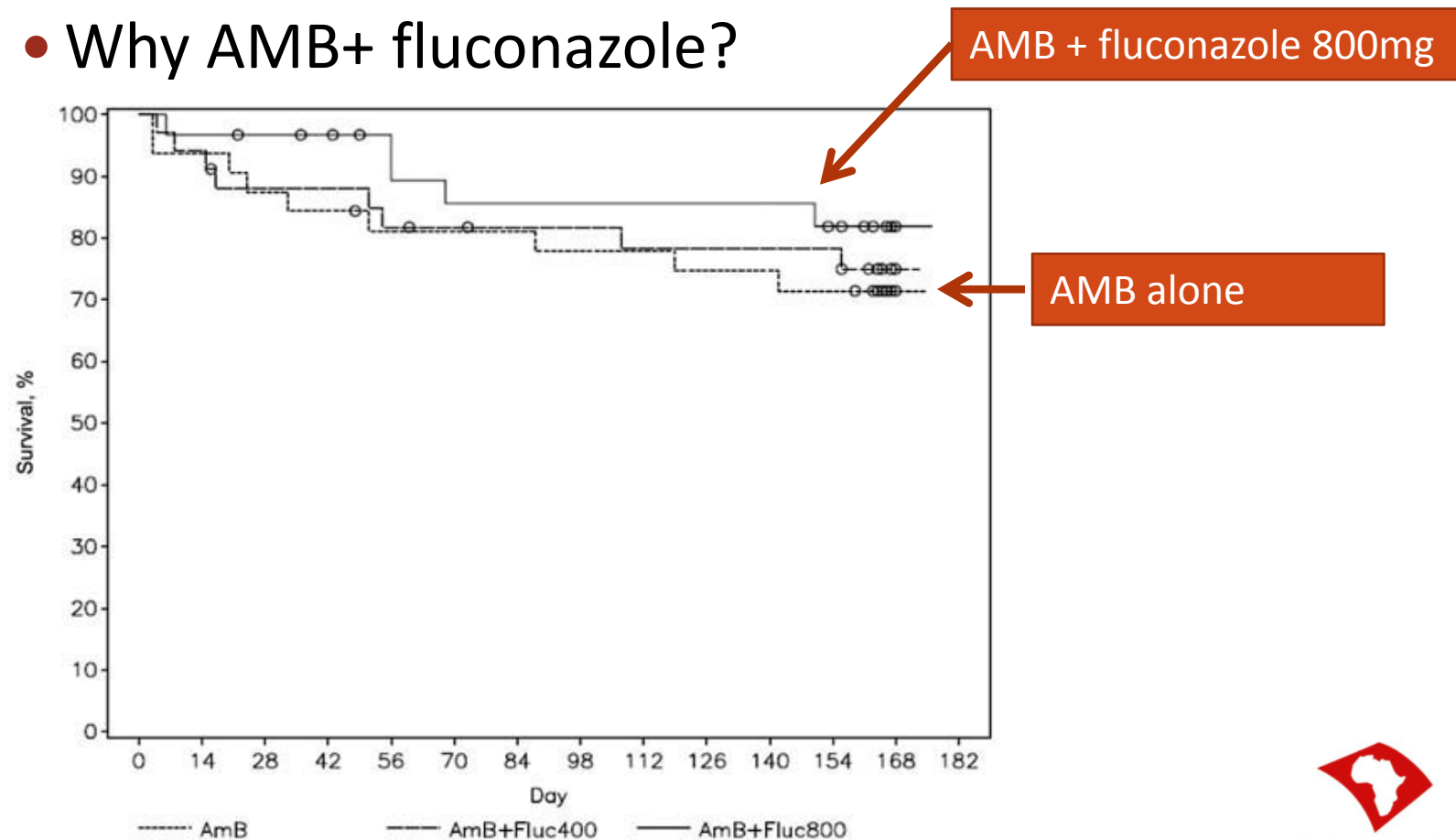
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# Anti-infective chemotherapy

- Cryptococcal meningitis
  - Why AMB+ fluconazole?



# Anti-infective chemotherapy

- Supplementary management for Cryptococcal meningitis
  - Management of raised intracranial pressure
    - Essential to mortality
    - Measure pressure at baseline
    - Tap if symptomatic (worsening headache, LOC, 6<sup>th</sup> CN palsy)



# Anti-infective chemotherapy

- Supplementary management for Cryptococcal meningitis:
  - Prehydration and K<sup>+</sup> supplementation to prevent renal decompensation/failure 2<sup>o</sup> to amphotericin B





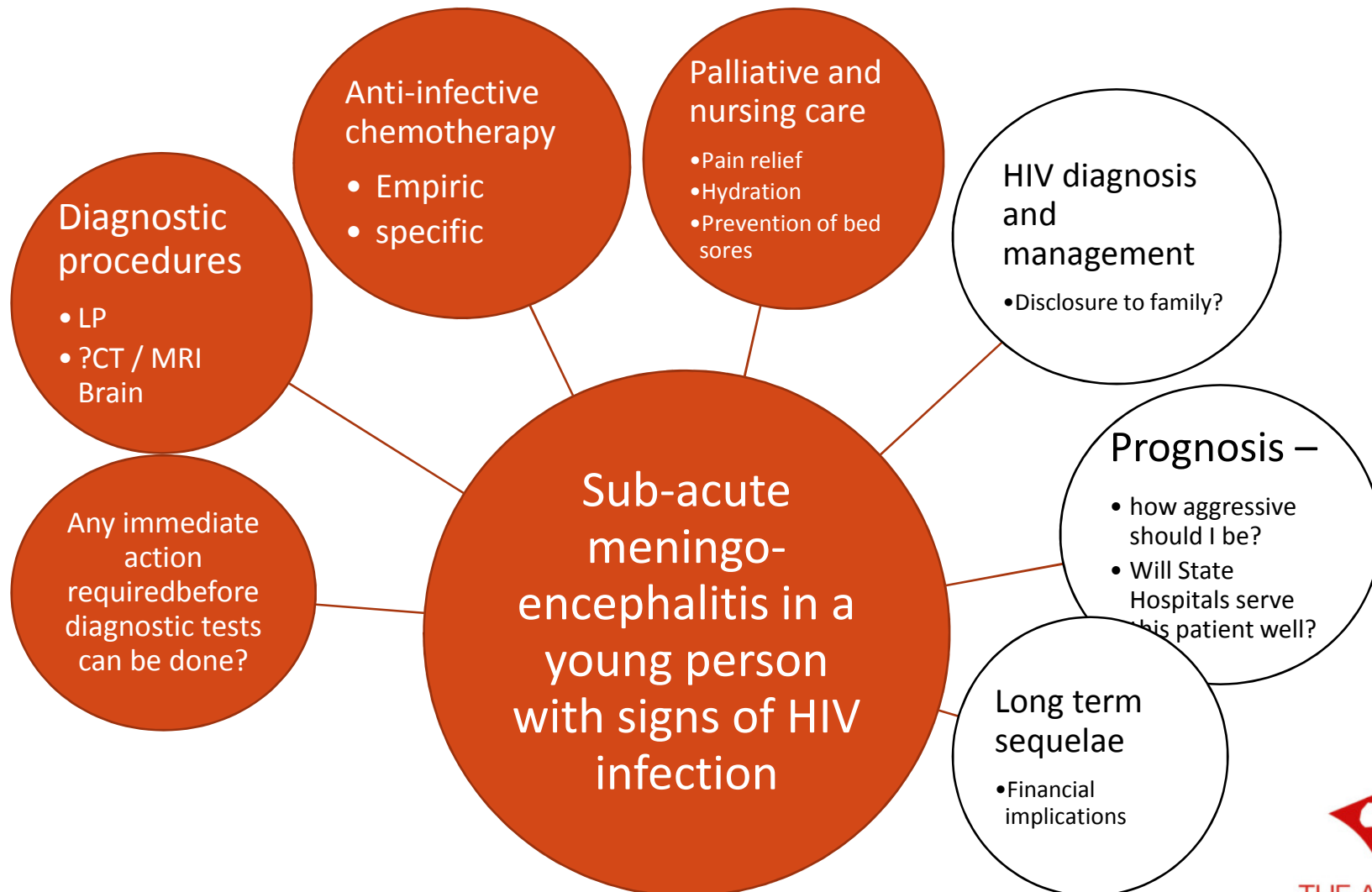
# Anti-infective chemotherapy

- TB meningitis
  - Practically this is a diagnosis of exclusion
  - CSF cultures often negative for TB
  - Prednisone essential

If these tests remain negative or are unavailable, and the patient has no response to the initiated therapy, diagnostic uncertainty continues, particularly in patients in resource-poor settings. In these patients, cryptococcal, tuberculous, and partly treated acute bacterial meningitis are difficult to distinguish apart, and physicians often start empirical treatments for tuberculous and acute bacterial meningitis simultaneously.<sup>38</sup>

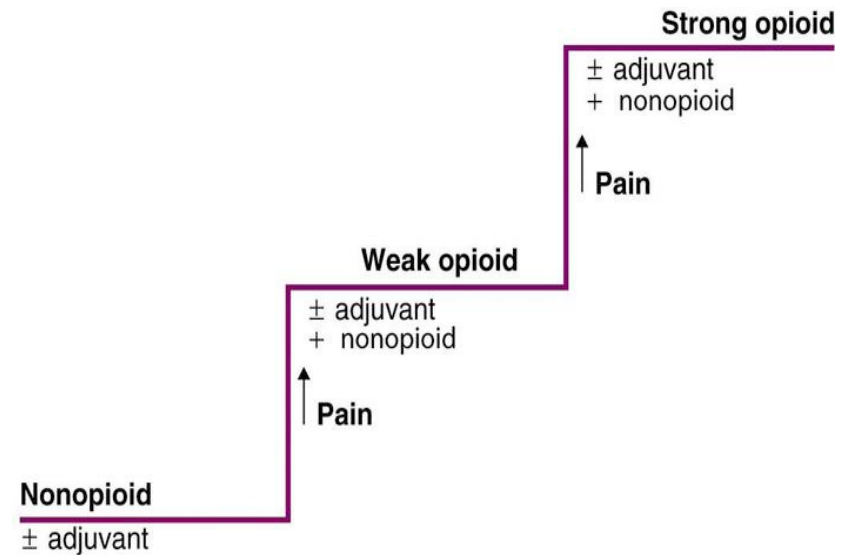
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# Going through our minds.....

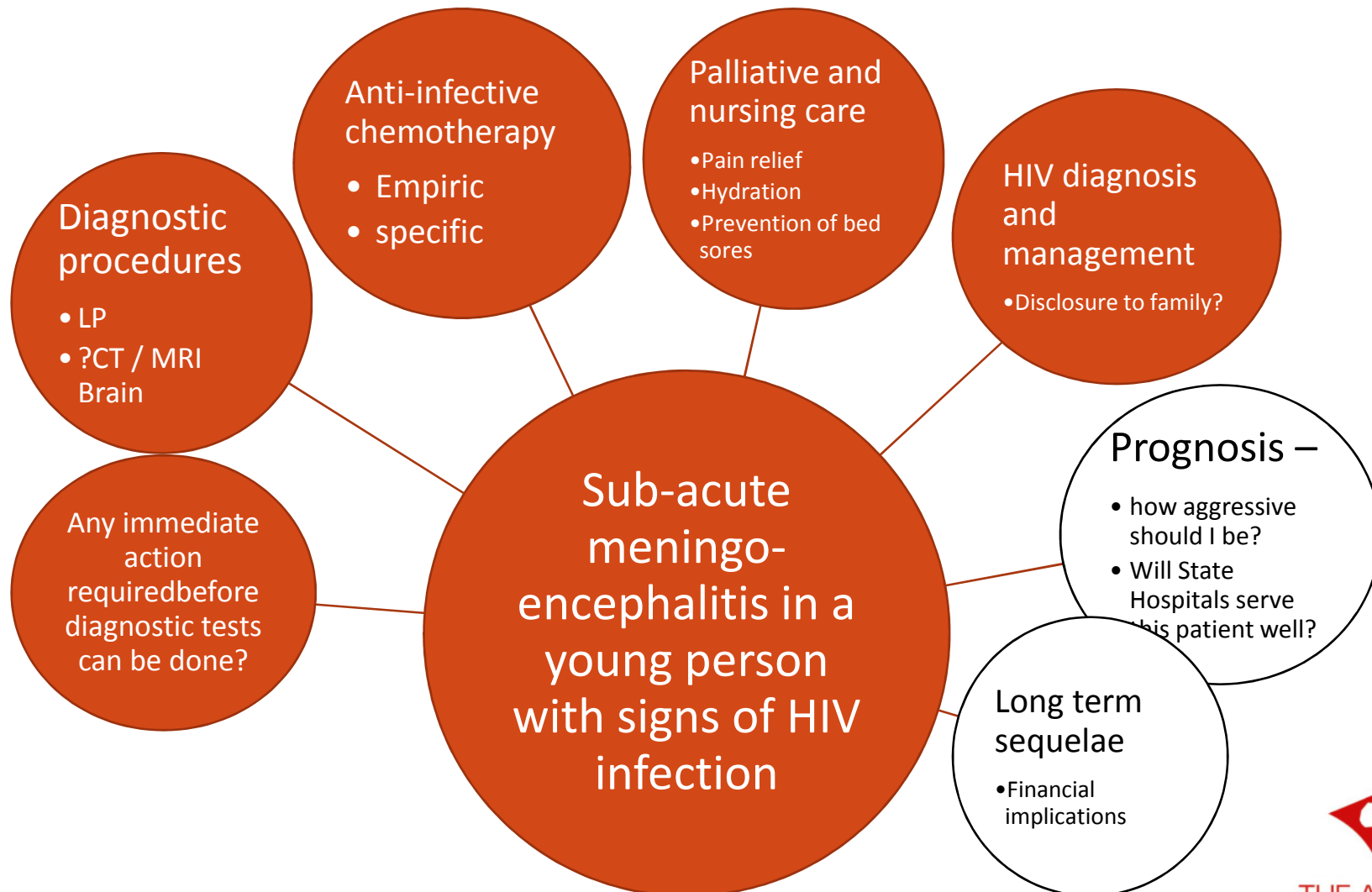


# Palliative and nursing care

- Pain relief
  - WHO analgesic ladder
- Hydration
  - Watch meticulously, and esp if giving AMB
  - Enlist family if nursing care sub-optimal
- Prevention of bed sores
  - Crucial
  - Enlist family if nursing care is suboptimal



# Going through our minds.....



# HIV diagnosis and management in patients with meningitis

- Often tricky to handle when patient is confused and brought in by family
- HIV diagnosis and management is ultimately lifesaving
- Options:
  - Wait and offer HIV test when confusion abates
  - Discuss with the family and obtain consent to test while patient confused



# HIV diagnosis and management in patients with meningitis

- Timing of ART is critical
  - Early ART improves prognosis in PTB – (STRIDE, SAPIT, CAMELIA studies) esp CD4 <50 cells/mm<sup>3</sup>,
- BUT.....timing of ART initiation in pts with meningitis is complicated by potential for IRIS, and ICP
  - 47% of 34 patients with TB meningitis developed TB IRIS

Marais et al CID 2013;56 (3):450

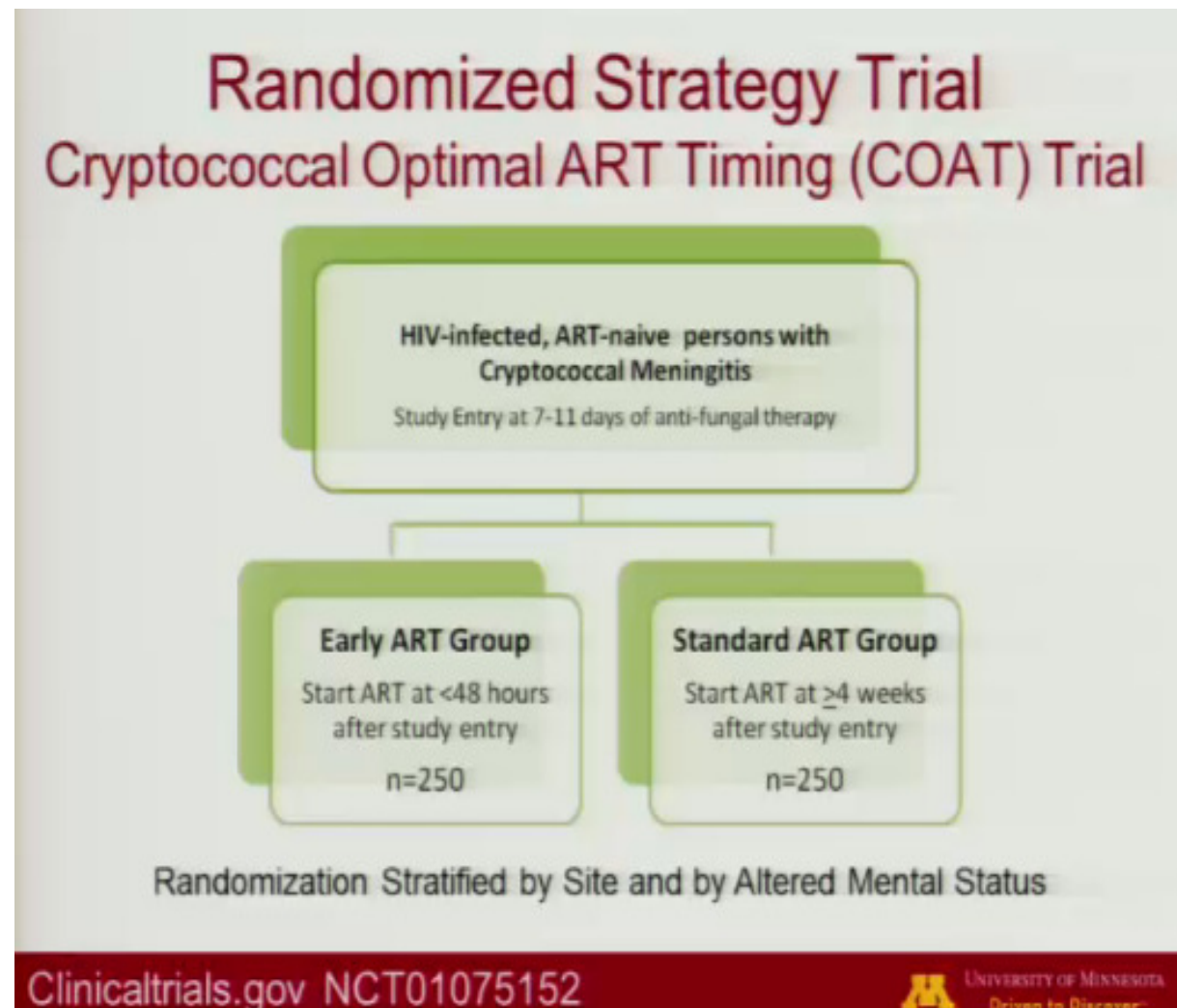


Image courtesy G Meintjies

# HIV diagnosis and management in patients with meningitis

**Boulware et al.**  
ART Initiation  
within the First 2  
Weeks of  
Cryptococcal  
Meningitis Is  
Associated with  
Higher Mortality: A  
Multisite  
Randomized Trial

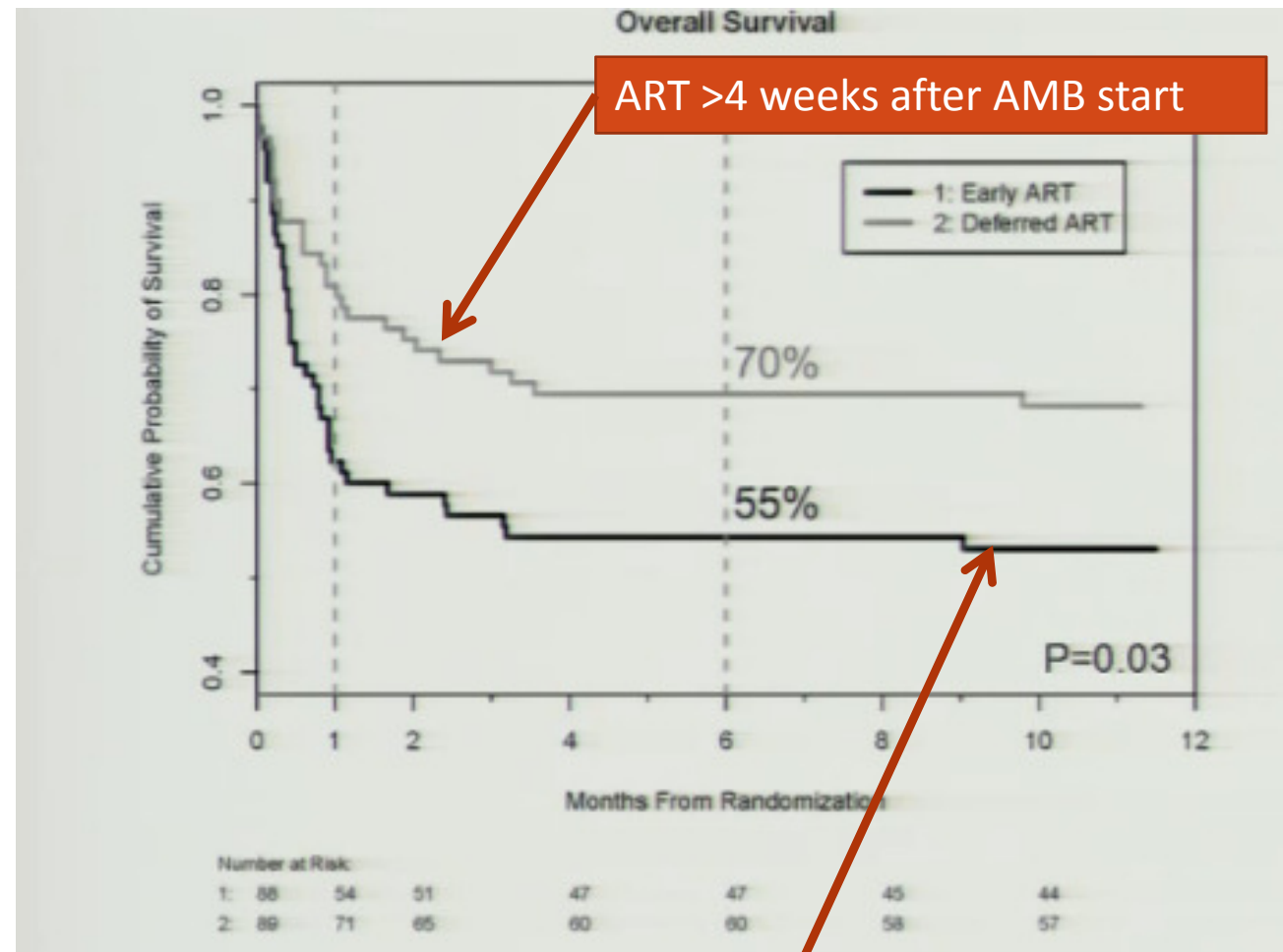
CROI 2013  
LB#144



# HIV diagnosis and management in patients with meningitis

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CROI 2013  
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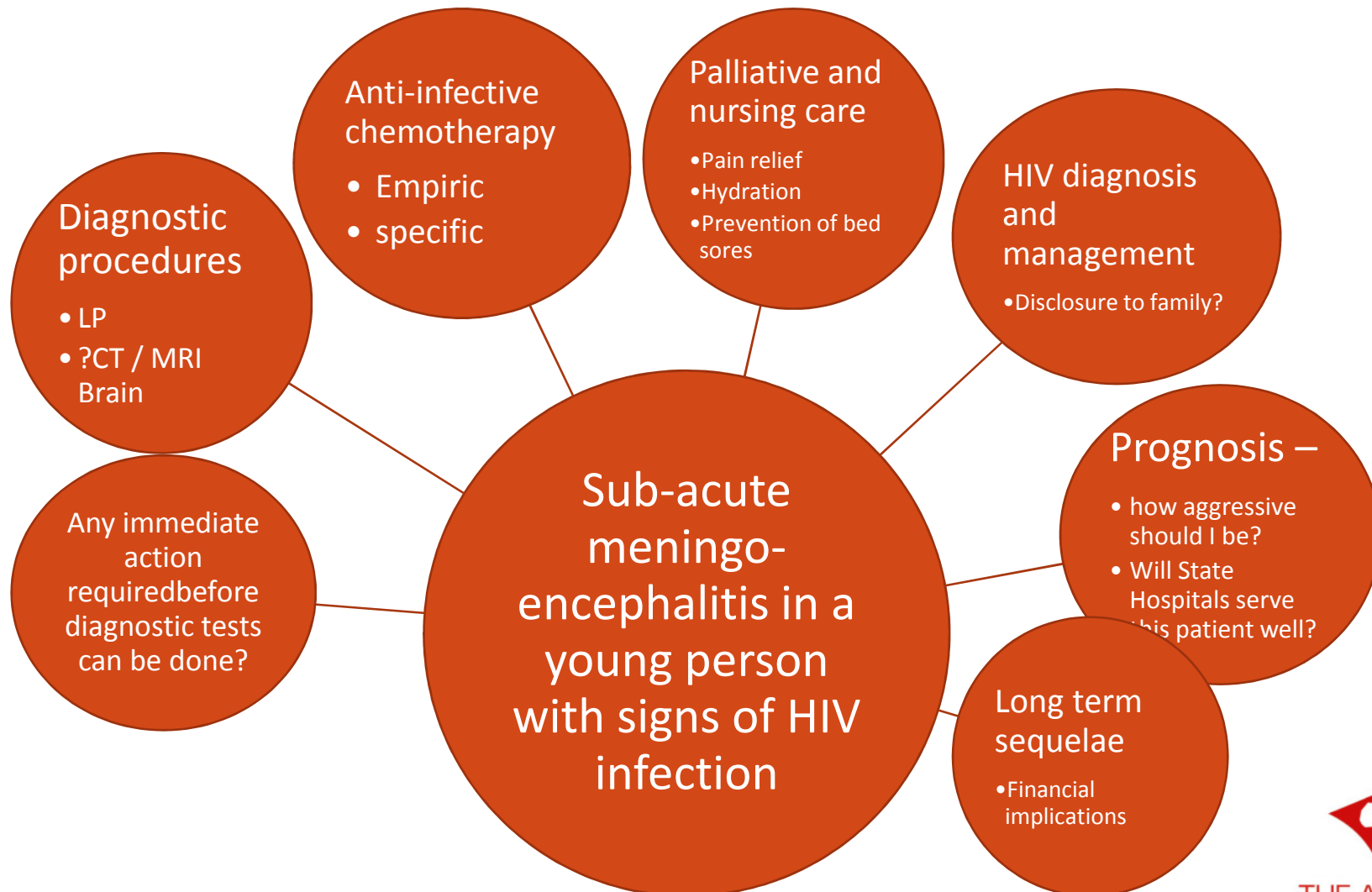


# HIV diagnosis and management in patients with meningitis

- Immune Reconstitution Inflammatory Syndrome (IRIS)
- Recommendation:
  - For proven CC meningitis, ART should not be started until 4 weeks after amphotericin B initiation.
  - For TB meningitis – no evidence for timing of ART start
    - Follow your intuition; do not initiate until symptoms of raised intracranial pressure have abated
    - ALWAYS use prednisone 1.5mg/kg for 2/52, followed by 0.75mg/kg for 2/52, then stop, do not wait for IRIS to occur
- Be careful to use ART regimen that is compatible with TB treatment

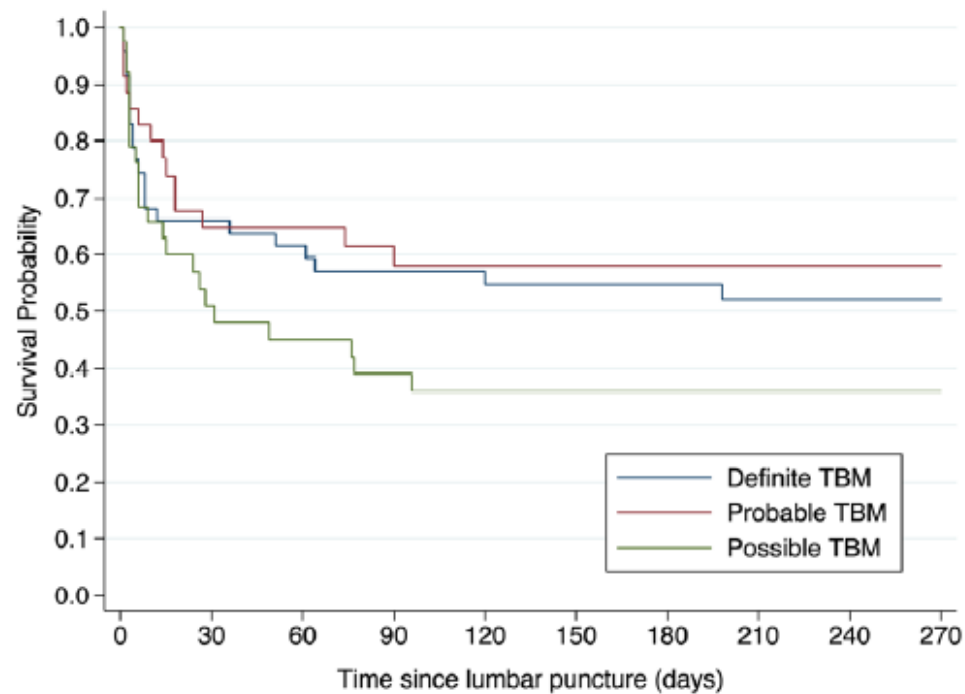
Meintjies and Sonderup, CMEJ October 2011 Vol.29 No.10 **CME 415**

# Going through our minds.....



# Prognosis

- TB meningitis



**Figure 2. Kaplan-Meier survival curves of patients with definite, probable and possible tuberculous meningitis (TBM).** Survival probability at 6-months was similar between patients with definite TBM and those with probable TBM (log-rank test  $p=0.69$ ), and possible TBM (log-rank test  $p=0.15$ ).

doi:10.1371/journal.pone.0020077.g002



# Prognosis

- Cryptococcal meningitis

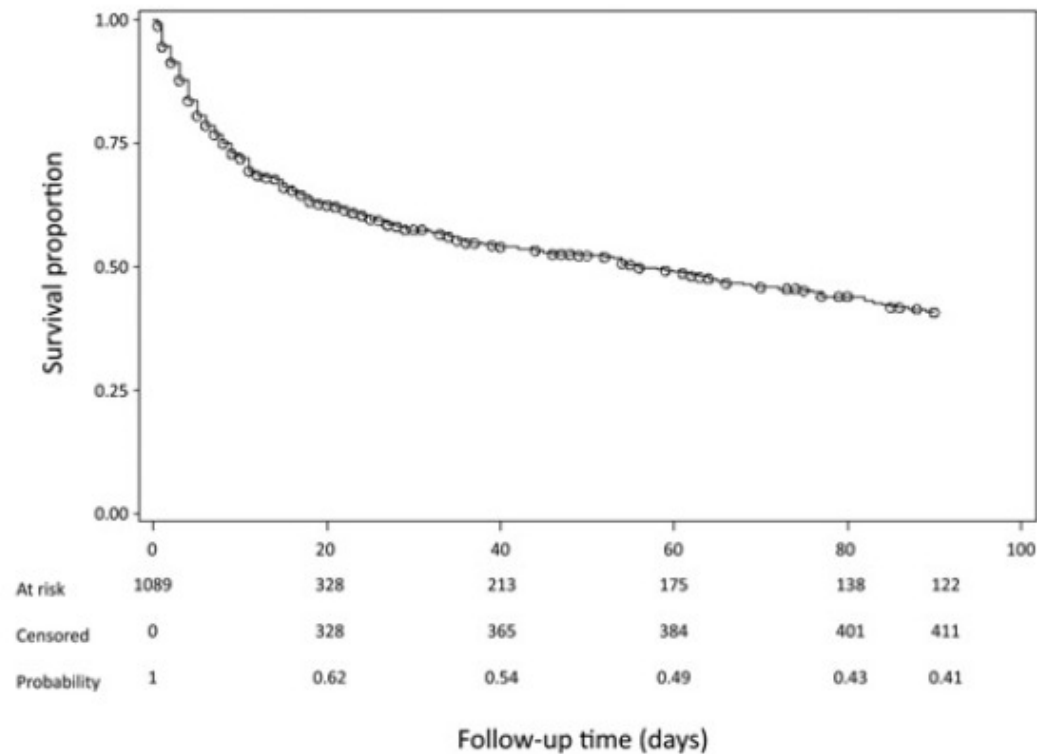


Figure 2 Kaplan-Meier 90-days survival curve after presentation for incident cryptococcal meningitis, Gauteng Province, South Africa

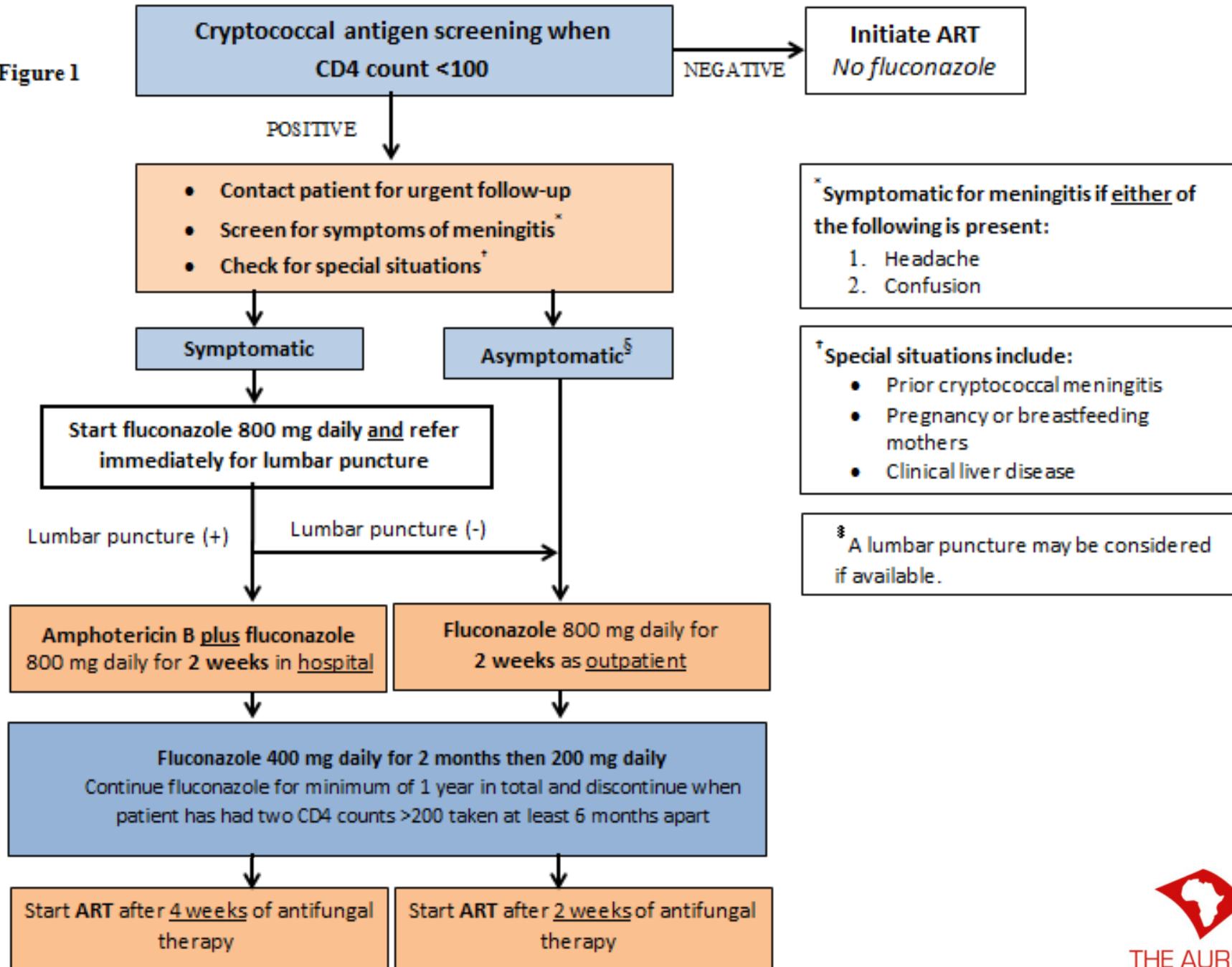
Park et al. Int J  
STD and AIDS.  
2011;22:199

# Prevention is better than cure

- Early HIV diagnosis
- Vaccination when CD4 count high
  - Pneumococcal vaccination
- Early / appropriate ART initiation
- Low CD4 count
  - INH prophylaxis
  - Screening for cryptococcal disease



Figure 1



# Conclusion

- We are in the middle of a devastating epidemic....

