Meningitis
in the context of the
HIV epidemic

14th March 2013
Kerrigan McCarthy
MBBCh, DTM+H, FCPath (Micro)
KZN is the epicentre of the epidemic
A note on our context.....
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

- Malaria: 1,135,861
- Diarrheal disease: 707,657
- Childhood Cluster disease: 527,126
- Cryptococcus: 504,000
- Tuberculosis: 347,871
- STDs excluding HIV: 92,606

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......

**Sub-acute meningoencephalitis in a young person with signs of HIV infection**

**Diagnostic procedures**
- LP
- CT / MRI Brain

**Anti-infective chemotherapy**
- Empiric
- Specific

**Palliative and nursing care**
- Pain relief
- Hydration
- Prevention of bed sores

**HIV diagnosis and management**
- Disclosure to family?

**Palliative and nursing care**
- Pain relief
- Hydration
- Prevention of bed sores

**Prognosis**
- how aggressive should I be?
- Will State Hospitals serve this patient well?

**Long term sequelae**
- Financial implications

**Any immediate action required before diagnostic tests can be done?**
Going through our minds......

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Any immediate action required before diagnostic tests can be done?
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......

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Long term sequelae
- Financial implications
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, yet CT equipment can be scarce in these settings. 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.

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

<table>
<thead>
<tr>
<th>Aetiology</th>
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<th>Specific tests</th>
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<tr>
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<td>Protein ↑</td>
<td>Gram’s stain helpful</td>
<td>Bacterial latex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Result due 24-48 hrs</td>
<td>agglutination</td>
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</table>

**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).

The differential diagnosis - working within the HIV epidemic

• Could this be a cryptococcal meningitis / meningo-encephalitis

• Suggestive si/sy
  • CD4<200 cells/mm3, but often <50;
  • Diplopia / 6th CN palsy
  • Subtle changes – memory loss, mood changes
  • Skin lesions
Cutaneous cryptococcal infection–
A note on epidemiology

- Cryptococcal meningitis across the globe

A note on epidemiology

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- It’s a killer.....
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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

Marais et al. Presentation and outcome of TB meningitis in a high HIV prevalence setting. PLOS ONE 6(5):e20077)
LP and laboratory tests to facilitate diagnosis of cause of meningitis

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<td></td>
<td>Result due 6 weeks; uncommonly positive</td>
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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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<td>GeneXpert not more helpful than culture</td>
</tr>
<tr>
<td>Viral</td>
<td>PMNs ↑↑↑↑↑</td>
<td>Protein ↑↑↑↑</td>
<td>Not helpful routinely</td>
<td>PCR</td>
</tr>
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A note on epidemiology....

*Common things occur commonly*

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Country</th>
<th>Sample size</th>
<th>HIV infected</th>
<th>Bacterial/pyogenic</th>
<th>Tuberculosis</th>
<th>Crypto-coccal</th>
<th>Aseptic/viral</th>
</tr>
</thead>
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<tr>
<td>Mulago and Mbarana(^1)</td>
<td>Uganda</td>
<td>416</td>
<td>90%</td>
<td>4%</td>
<td>8%</td>
<td>59%</td>
<td>29%</td>
</tr>
<tr>
<td>GF Jooste(^2)</td>
<td>South Africa</td>
<td>1737</td>
<td>96%</td>
<td>19%</td>
<td>13%</td>
<td>30%</td>
<td>38%</td>
</tr>
<tr>
<td>Queen Elizabeth(^3)</td>
<td>Malawi</td>
<td>263</td>
<td>77%</td>
<td>20%</td>
<td>17%</td>
<td>43%</td>
<td>20%</td>
</tr>
<tr>
<td>Harare(^4)</td>
<td>Zimbabwe</td>
<td>200</td>
<td>90%</td>
<td>16%</td>
<td>12%</td>
<td>45%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td><strong>2616</strong></td>
<td><strong>93%</strong></td>
<td><strong>9.3%</strong></td>
<td><strong>12.7%</strong></td>
<td><strong>37%</strong></td>
<td><strong>41%</strong></td>
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1 Durski K et al. J AIDS 2013, In Press.

Slide courtesy D Boulware, CROI 2013
Other uncommon causes of a lymphocytic meningitis...

- Or perhaps syphilitic meningoencephalitis 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......

Sub-acute meningo-encephalitis in a young person with signs of HIV infection

Diagnostic procedures
• LP
• CT/MRI Brain

Any immediate action required before diagnostic tests can be done?

Anti-infective chemotherapy
• Empiric
• Specific

Palliative and nursing care
• Pain relief
• Hydration
• Prevention of bed sores

HIV diagnosis and management
• Disclosure to family?

Prognosis –
• How aggressive should I be?
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Long term sequelae
• Financial implications

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Anti-infective chemotherapy

- **Bacterial meningitis**
  - **Empiric treatment (following Gram’s stain)**
    - Ceftriaxone +/- vancomycin
      - Depends on local susceptibility profile of *S. pneumoniae*
    - Consider amoxicillin iv if not using vancomycin (*Listeria* is resistant to cephalosporins)
  - **Specific therapy**
    - 3rd 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**

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

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

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<tr>
<td>Gram-positive bacilli</td>
</tr>
<tr>
<td>Amoxicillin/ampicillin* or penicillin G*</td>
</tr>
<tr>
<td>Gram-positive cocci in chains</td>
</tr>
<tr>
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<tr>
<td>Gram-negative bacilli</td>
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<tr>
<td>Third-generation cephalosporin</td>
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*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 |
|---|---|---|---|
| Susceptibility category (µg/mL) | **Standard** | **Former (all clinical syndromes and penicillin routes)** | **New (by clinical syndrome and penicillin route)** |
|  |  | ≤0.06 | 0.12-1 | ≥2 |
| Meningitis, intravenous penicillin |  | ≤0.06 | - | ≥0.12 |
| Non-meningitis, intravenous penicillin |  | ≤2 | 4 | ≥8 |
| Non-meningitis, oral penicillin |  | ≤0.06 | 0.12-1 | ≥2 |

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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

- Penicillin
- Ceftriaxone
- Erythromycin
- Clindamycin

*23488 (72%) of 32505 cases had viable isolates; cases reported for all ages, and all normally sterile site specimens

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:

<table>
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<tr>
<th>Phase</th>
<th>Induction phase</th>
<th>Consolidation phase</th>
<th>Maintenance phase</th>
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<tr>
<td>Duration</td>
<td>2 weeks</td>
<td>8 weeks</td>
<td>For at least 12 months total treatment and with two CD4 counts &gt;200 6 month apart, on ART</td>
</tr>
<tr>
<td>Treatment</td>
<td>Amphotericin B 1 mg/kg/dose IV plus Fluconazole 800 mg PO daily</td>
<td>Fluconazole 400 mg PO daily</td>
<td>Fluconazole 200 mg PO daily</td>
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Anti-infective chemotherapy

- Cryptococcal meningitis
- Why not fluconazole alone?

Anti-infective chemotherapy

- Cryptococcal meningitis
- Why not fluconazole alone?

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\textsuperscript{th} CN palsy)
Anti-infective chemotherapy

• Supplementary management for Cryptococcal meningitis:
  • Prehydration and K+ supplementation to prevent renal decompensation/failure 2° 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.38

Sub-acute meningoencephalitis in a young person with signs of HIV infection

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Long term sequelae
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Any immediate action required before diagnostic tests can be done?
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......

Sub-acute meningitis-encephalitis in a young person with signs of HIV infection

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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/mm³,
  - 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
Randomized Strategy Trial
Cryptococcal Optimal ART Timing (COAT) Trial

HIV-infected, ART-naive persons with Cryptococcal Meningitis
Study Entry at 7-11 days of anti-fungal therapy

Early ART Group
Start ART at <48 hours after study entry
n=250

Standard ART Group
Start ART at >4 weeks after study entry
n=250

Randomization Stratified by Site and by Altered Mental Status

Clinicaltrials.gov NCT01075152

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

**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

- ART >4 weeks after AMB start
- ART 7-11 days after AMB start

![Graph showing overall survival with ART initiation timing](image)
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
Sub-acute meningoencephalitis in a young person with signs of HIV infection

Diagnostic procedures
- LP
- CT / MRI (Brain)

Any immediate action required before diagnostic tests can be done?

Anti-infective chemotherapy
- Empiric
- Specific

Palliative and nursing care
- Pain relief
- Hydration
- Prevention of bed sores

HIV diagnosis and management
- Disclosure to family?

Palliative and nursing care

Prognosis –
- How aggressive should I be?
- Will State Hospitals serve this patient well?

Long term sequelae
- Financial implications
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

Marais et al. Presentation and outcome of TB meningitis in a high HIV prevalence setting. PLOS ONE 6(5):e20077)
Prognosis

- Cryptococcal meningitis

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

Cryptococcal antigen screening when CD4 count <100

- Contact patient for urgent follow-up
- Screen for symptoms of meningitis
- Check for special situations

Symptomatic

- Start fluconazole 800 mg daily and refer immediately for lumbar puncture
- Lumbar puncture (+)
- Amphotericin B plus fluconazole 800 mg daily for 2 weeks in hospital
- Fluconazole 800 mg daily for 2 weeks as outpatient

Asymptomatic

- Fluconazole 400 mg daily for 2 months then 200 mg daily
- Continue fluconazole for minimum of 1 year in total and discontinue when patient has had two CD4 counts >200 taken at least 6 months apart

Initiate ART
No fluconazole

Symptomatic for meningitis if either of the following is present:
1. Headache
2. Confusion

Special situations include:
- Prior cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

A lumbar puncture may be considered if available.
Conclusion

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