Tackling Public Enemy #2: Screening to Prevent Cryptococcal Deaths

Fighting a deadly fungus
A common, deadly and costly disease
Weighing up strategies to prevent deaths
Screening to prevent deaths in South Africa
Case studies

Fighting a deadly fungus

Global burden of HIV-associated cryptococcal meningitis

High burden of cryptococcosis in South Africa
Incidence of cryptococcosis (n=17,065*) vs. number of persons on antiretroviral treatment (ART)** by year, Gauteng Province, 2002-2010

High, early mortality amongst adults accessing ART in sub-Saharan Africa

*Complete surveillance audits were conducted throughout. **ASSA-2003 model

Lawn S, et al. AIDS. 2008
3-pillared strategy to reduce early mortality

Early HIV diagnosis
Strong links to ART
Prevent, screen 
& treat OIs

Lisen S, et al. AIDS. 2008

Death from Cryptococcus in sub-Saharan Africa

Estimated causes of death in sub-Saharan Africa, excluding HIV, 2009

Early HIV diagnosis
Prevent, screen & treat OIs
Strong links to ART

Post-discharge survival in the pre-ART era
- Eight hospitals in Gauteng
- Follow-up post-discharge
  - Pharmacy records
  - Outpatient records
  - Interviews

Post-discharge survival in the post-ART era
- One hospital in Gauteng
- Follow-up post-discharge
  - Pharmacy records
  - Outpatient records
  - Interviews

What does it cost annually to treat patients in hospital?

Number of cases of cryptococcal meningitis per year
8,330
Cost of hospitalisation
R 20,080

Estimated annual cost
R 167,266,400

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Screening to prevent deaths

Case studies

Preventing deaths amongst patients with CD4 <100

Why is screening an attractive option?

1 - Cryptococcal Antigen

- Detectable in serum, plasma (& urine) before symptoms of meningitis develop
  - Average of 22 days prior to symptom onset
- Highly predictive of who is at risk for developing cryptococcal disease
  - In Cape Town, 13/46 CrAg+ and 0/661 CrAg- patients developed meningitis
- Prevalence of cryptococcal antigenemia ranges from 3% to 21%
  - Highest amongst patients with CD4 <100

2 - Missed opportunities for screening

- Antiretroviral treatment at time of diagnosis for cases of incident lab-confirmed cryptococcosis (n=7,397) diagnosed at GEMS-SA enhanced surveillance sites, South Africa, 2005-2010

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Setting</th>
<th>Serum CrAg Prevalence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire (Congo)</td>
<td>1989</td>
<td>Newly diagnosed HIV+</td>
<td>12.3% (160)</td>
<td>Includes asymptomatic</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1990</td>
<td>Laboratory serum tested</td>
<td>4.5% (313)</td>
<td></td>
</tr>
<tr>
<td>South Africa (Soweto)</td>
<td>2011</td>
<td>ART enrolment hospital clinic</td>
<td>3.0% (1830)</td>
<td>No history of CM CD4 &lt;100</td>
</tr>
<tr>
<td>South Africa (Cape Town)</td>
<td>2002-2005</td>
<td>Community clinic Retrospective</td>
<td>7.6% (707)</td>
<td>No history of CM CD4 &lt;100</td>
</tr>
<tr>
<td>Uganda</td>
<td>2000-2004</td>
<td>ART clinic Retrospective</td>
<td>9.6% (377)</td>
<td>CD4 &lt; 100</td>
</tr>
<tr>
<td>Uganda</td>
<td>2000-2004</td>
<td>ART enrolment Prospective</td>
<td>8.2% (604)</td>
<td>CD4 &lt; 100</td>
</tr>
<tr>
<td>Uganda</td>
<td>2000</td>
<td>ART enrolment Prospective</td>
<td>16.7% (147)</td>
<td>Stage III-IV</td>
</tr>
<tr>
<td>Cambodia</td>
<td>1996-1999</td>
<td>Community clinic Cohort</td>
<td>5.4% (1470)</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>2006</td>
<td>ART enrolment Cross-sectional</td>
<td>18.0% (327)</td>
<td>Includes asymptomatic CD4 &lt;100</td>
</tr>
<tr>
<td>Thailand</td>
<td>2006</td>
<td>Retrospective</td>
<td>9.2% (1351)</td>
<td>CD4 &lt;100</td>
</tr>
</tbody>
</table>

1 2

Missed opportunities for screening

- Prior diagnosis of HIV infection
- Prior initiation of antiretroviral treatment
- Admission to hospital with cryptococcal meningitis (n=1,468)
- Death in hospital
- Death post-discharge

Timeline

- 1,075/1,468 (73%)
- 313/1,468 (21%)
- 503/1,468 (35%)

>50% of persons who survive admission

2005 (n=954) 2006 (n=1,034) 2007 (n=1,247) 2008 (n=1,651) 2009 (n=1,647) 2010 (n=1,075)
3 – development of a new test for Cryptococcus

The new test (lateral flow assay) is:

Simple and quick
Results available in 10 minutes

Available and effective
Highly sensitive and accurate (>95%)

Affordable
$2/test

Lateral flow assay format

LFA can detect tiny amounts of antigen in body fluids

<table>
<thead>
<tr>
<th>Immunoassay</th>
<th>Format</th>
<th>Serotype sensitivity (ng Crag/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMY</td>
<td>LA</td>
<td>A 28 B 47 C 380 D 62</td>
</tr>
<tr>
<td>Meridian CALAS</td>
<td>LA</td>
<td>A 19 B 37 C 940 D 54</td>
</tr>
<tr>
<td>Inverness</td>
<td>LA</td>
<td>A 38 B 64 C 1600 D 50</td>
</tr>
<tr>
<td>Meridian Premier</td>
<td>ELISA</td>
<td>A 28 B 23 C &gt;2000 D 770</td>
</tr>
<tr>
<td>mAbs F12D2 + 339</td>
<td>ELISA</td>
<td>A 0.6 B 0.8 C 5.0 D 0.6</td>
</tr>
<tr>
<td>IMMY</td>
<td>LFA</td>
<td>A 1 B 1 C 9 D 8</td>
</tr>
</tbody>
</table>

Comparison of LFA vs. EIA

- Sets of samples from 62 patients with culture-proven cryptococcosis
- Samples assayed by quantitative EIA and by LFA

<table>
<thead>
<tr>
<th>Sample</th>
<th>Patients</th>
<th>LFA Positive</th>
<th>EIA Positive</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>94-100%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>95%</td>
<td>94-100%</td>
<td>94-100%</td>
<td>91-100%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>95%</td>
<td>94-100%</td>
<td>94-100%</td>
<td>91-100%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Correlation = 0.93, P < 0.001
Correlation = 0.94, P < 0.001
Correlation = 0.94, P < 0.001

4 - An intervention exists...
Screening costs vs. cost of amphotericin B (based on prevalence of cryptococcal antigenemia)


Preventing deaths amongst patients with CD4 <100

Cryptococcal Screening Programme Objectives

1. Identify patients at risk (CD4 <100)
2. Test for cryptococcal antigen
3. Treat with oral fluconazole
4. Prevent cryptococcal meningitis deaths
Proposed Cryptococcal Screening Algorithm for HIV+ Patients

† A lumbar puncture may considered in asymptomatic patients. Pregnant women, children, and those with liver failure may require special attention.

* Initiate ART if not already started

Screening Fits into Routine HIV Care

Role of lumbar puncture

- Three options for asymptomatic patients
  - Offer lumbar puncture to all CrAg+ patients
  - Offer lumbar puncture if CrAg titre greater than cutoff value
  - Treat empirically with fluconazole, no lumbar puncture

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Timing of ART initiation

- SA HIV Clinicians’ Society Guidelines: 2 to 4 weeks post-diagnosis
- IDSA Guidelines: 2 to 10 weeks post-diagnosis
- Zolopa\(^1\): supportive of 2 weeks
- Makadzange\(^2\): <3 days not recommended
- Boulware: ongoing, NIH-funded, multicentre RCT

\(^1\) Zolopa et al. ACTG A5164 PLOS One; \(^2\) Makadzange et al. Clin Infect Dis 2010
Screening in the real world: Soweto, 2009-2010

Patient referred after hospital discharge (with AIDS-defining illness) or from outpatient provider

Intake visit by clinic nurse: reviewed CD4 count and clinical history to determine ARV eligibility (CD4 <250 or WHO Stage IV)

Patient sent for baseline labs (including CrAg) and given clinic appointment in 2 weeks

Some patients lost to follow up

CrAg results available to clinician

Patient scheduled for earlier visit

Patient keeps regularly scheduled appointment

Patient came to ART initiation clinic visit

Needs LP or is ill

No LP and is well

Assessed by physician

Patient came to ART initiation clinic visit

How did screening work in practice?

- CrAg results provided to clinicians within 1 week
- Prevalence of incident antigenaemia = 3%
- Approximately half of CrAg+ patients had previous history of CM
- Median CD4 count of patients with incident CrAg+ was extremely low (19)

Programme Implementation

- Three initial implementation sites, 2011
  - 3 NHLS CD4 testing labs in Gauteng and Free State
  - Chosen for convenience
- Intensive laboratory and clinician training
- Monitoring and programme evaluation
  - Identify operational issues
  - Define magnitude of benefit of screening strategy
- Long-term goal: Nationwide implementation

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How did screening work in practice?

- Almost one-third (30%) of incident CrAg+ patients never returned to ART clinic for follow-up
- Almost half (45%) refused an LP when offered
- Only three-quarters (73%) were prescribed an antifungal drug
- Three incident antigenaemic patients developed meningitis post-screening (no fluconazole)

Case 1

- 40-year old man was seen at primary health care clinic in Cape Town
  - New diagnosis of HIV infection, CD4 count = 9
  - Diarrhoea for 1 month and significant weight loss
  - No headache, fever, photophobia or vomiting
- Unkempt, lived alone in an informal settlement
- Significant alcohol history

All cases courtesy of Nicky Longley, Cape Town
Case 1
- CRAG screening test was performed
- Urgently worked up for initiation of ARVs and asked to return for ARVs in 2 weeks
- Patient defaulted - did not return to clinic and could not be contacted
- CrAg screening test done at clinic was positive

3 months later
- Admitted to GF Jooste Hospital with a 2-week history of headache, neck stiffness and confusion
- Still not on ARVs
- LP: India ink positive, serum CrAg positive, opening pressure 45cm water
- Had therapeutic tap and subsequent daily LPs
- Started on amphotericin B 1 mg/kg/day

Patient died on day 5 post-admission

Discussion points
- Delay in presentation → severe disease
- Early detection of antigenaemia and preemptive treatment could have averted fatal disease
- Role of point-of-care testing

Case 2
- 40-year old man
- Referred to primary health care clinic for ARVs from GF Jooste Hospital
  - New HIV diagnosis, CD4 count = 11
  - Recent admission with PCP: treated with cotrimoxazole & steroids → good recovery
- At clinic
  - Well-looking man
  - No headache, fever, confusion or neck stiffness
  - Severe oral candidiasis
  - Single KS lesion on back
  - Peripheral neuropathy
- Urgently worked up for ART

CrAg test positive
- Patient called back to clinic
  - Still well, no CNS symptoms
  - Agreed to have an LP
    - 3 attempts at LP failed - very large man (98kg)
    - As patient apparently well, did not persist.
    - Blood culture sent instead
  - Patient started on fluconazole 800 mg per day
  - Plan to follow up in 2 weeks to start ART
  - Given phone numbers if problems

Day 10 of fluconazole (Thursday)
- Lab called - Cryptococcus neoformans cultured from blood.
- Spoke to patient - still felt well, taking fluconazole, no headache,
- Did not want to come to hospital until next Monday but was convinced to go to GF Jooste the next day

GF Jooste
- New small umbilicated lesion on left forearm - cutaneous cryptococcosis
- LP: CrAg positive, India ink positive, opening pressure 21 cm H2O
- Patient started on amphotericin B 1 mg/kg/day with pre-hydration
Case 2

- GF Jooste
  - Day 4 amphotericin B - creatinine increased from 84 to 176
  - Fluids increased and amphotericin B dose reduced to 0.7 mg/kg
  - Completed 16 days amphotericin B
  - Had one subsequent LP with normal opening pressure
  - Developed amphotericin B-induced thrombophlebitis

- Post-discharge follow-up at clinic
  - Fluconazole 400 mg/day, doing well
  - Started on ART (AZT, 3TC, EFZ) in view of high creatinine and peripheral neuropathy, Hb = 9.6

Case 3

- 35-year old man
- Referred for ARVs from TB clinic
  - Diagnosed with sputum smear-positive TB 4 weeks prior to clinic appointment
  - Started on regimen 1
  - Pulmonary symptoms improving
  - Patient felt well otherwise, no headache, fever and neck stiffness
  - CD4 count = 50; other screening bloods normal.

- CrAg positive
- Started on fluconazole 1200 mg per day for 2 weeks
- Reviewed at 2 weeks to start ART: EFZ, 3TC, TDF

Discussion points

- If patient had been screened when diagnosed with PCP at GF Jooste, he may have been diagnosed before developing meningitis and been successfully treated with fluconazole
- Insidious onset of cryptococcosis - if he had not been screened, he would not have presented to hospital for some time
- Toxicity of amphotericin B and benefits of detecting cryptococcal disease early
- Late-stage patients often have multiple pathologies – need high index of suspicion

Discussion points

- 30% of patients with CD4 count <100 will have concomitant TB
- Rifampin induces cytochrome p450 enzymes — need to increase dose of fluconazole by 50%
- Fluconazole and rifampin are both hepatotoxic — watch out for signs of liver toxicity
- High-dose fluconazole & TB meds can often cause nausea/GI disturbance
  - May help to split fluconazole dose to twice daily
  - If severe nausea, give antiemetic 30 minutes before

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