Cryptococcal disease screen & treat intervention:
Phase 1 implementation update

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Outline

1. Background
2. Cryptococcal screen-and-treat intervention
3. Screen-and-treat approaches
4. Timeline for screen and treat in SA
5. Update from phase 1: GA, FS, KZN and WC
6. Conclusions
7. Next steps
Cryptococcal meningitis is common and deadly

• caused by a ubiquitous fungal pathogen, *Cryptococcus* spp.

• is a common opportunistic infection among individuals with HIV/AIDS

• leading cause of death and continues to be associated with high mortality rates (20%-70%), despite increased availability of antiretroviral treatment (ART) and anti-fungal therapy

• Sub-Saharan Africa has the largest burden of disease

• > 6000 cases of incident CM were diagnosed in SA in 2013
Cryptococcal meningitis can be prevented

- Early targeted screening and treatment is likely to be a cost-effective and successful means of reducing CM-related mortality.
- Cryptococcal antigen (CrAg) is detectable in human serum weeks to months prior to development of meningitis.
- Patients with CD4+ T-cell counts < 100 cells/μl are at highest risk for developing antigenaemia and cryptococcal disease.
Cryptococcal meningitis can be prevented

- The lateral flow assay (LFA) provides a sensitive, specific, and affordable means to diagnose cryptococcal antigenaemia using remnant CD4 blood samples
Screen & treat saves lives

28% ↓ in all-cause mortality

Screen & treat approaches

1: Reflex lab

- HIV-infected person
- Blood for CD4 count
- Lab tests for CrAg if CD4 count <100

2: Clinician-initiated lab

- HIV-infected person
- Blood for CD4 count
- Clinician requests a CrAg test if CD4 count <100
Screen & treat approaches

3: Clinician-initiated point-of-care

HIV-infected person → Blood for POC CD4 count → Clinician tests for CrAg if CD4 count <100

HIV-infected person → Blood to the lab for CD4 count → Clinician tests for CrAg if CD4 count <100
Timeline for screen & treat in SA

2011: Recommended by the World Health Organization in Rapid Advice Guidelines

2012: Included in SA’s National Strategic Plan on HIV/AIDS, STIs and TB

2012: Recommended for implementation by National Department of Health

Sept 2012: Phase 1 implementation of crypto screen-and-treat programme began

2014: Included in National Consolidated HIV Guidelines

2015: Included in Primary Healthcare Level Standard Treatment Guidelines and EML
Phase 1: Reflex lab screen & treat in Gauteng and Free State

1. Set up stakeholder meetings
2. Set up reflex CrAg testing at a NHLS CD4 laboratory
3. Ensure fluconazole is available at facility level
4. Conduct intensive healthcare worker training
5. Start reflex CrAg screening
6. Conduct refresher training workshops
7. Monitor and evaluate the intervention → cascade of care for those who screened CrAg+
Phase 1: *Reflex CD4 laboratory screen-and-treat*

<table>
<thead>
<tr>
<th>Johannesburg Metro</th>
<th>Ekurhuleni Metro</th>
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</thead>
</table>

**Gauteng**  
(Sept 2012)

- CD4

**Free State**  
(Oct 2014)

- CD4

CD4<100 → Test for CrAg
Phase 1: Reflex CD4 laboratory screen-and-treat

KwaZulu-Natal (June 2015)

3501 CrAg tests done
154 (4.4%) positive

Prince Mshiyeni Memorial Hospital
Cryptococcal antigen screening when CD4+ T-lymphocyte count <100 cells/μl

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

Symptomatic

Start fluconazole 1200 mg daily and refer immediately for lumbar puncture

Lumbar puncture (+)  
Lumbar puncture (-)

Asymptomatic§

Fluconazole 800 mg daily for 2 weeks as outpatient

Amphotericin B plus fluconazole 800 mg daily for 2 weeks in hospital

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

Start ART after 4-6 weeks of antifungal therapy  
Start ART after 2 weeks of antifungal therapy

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.

Cascade of Care with Cryptococcal Disease Screen-and-Treat

- **CrAg Testing**: CD4<100
  - N=

- **CrAg+**
  - N= (%)  
  - Prior CM vs. incident CrAg+

- **Fluconazole**
  - N= (%)  
  - Lost, N=  
  - Symptoms, N=  
  - Pregnant, N=

- **Started ART**
  - N= (%)  
  - ART-naïve vs. ART-experienced

- **Survived 6 months**
  - N = (％)
Phase 1: CD4 *Lab-initiated* reflex screening

**Gauteng and Free State**

<table>
<thead>
<tr>
<th>Province</th>
<th>District</th>
<th>NHL6 CD4 laboratory</th>
<th>Number of health care facilities (Enhanced sites i.e M&amp;E conducted)</th>
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<tbody>
<tr>
<td>Gauteng</td>
<td>City of Johannesburg Metro</td>
<td>Charlotte Maxeke Johannesburg Academic Hospital (CMUAH)</td>
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<tr>
<td></td>
<td>Ekurhuleni</td>
<td>Tambo Memorial Hospital</td>
<td>84 (25)</td>
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<tr>
<td>Free State</td>
<td>Lejweleputswa</td>
<td>Bongani Hospital</td>
<td>46 (34)</td>
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<tr>
<td></td>
<td>Fezile Dabi</td>
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<td>48 (34)</td>
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</table>
Phase 1: Gauteng and Free State

- Laboratory and clinical training was provided prior to initiation of the screening programme by NHLS and PEPFAR partners (RTC, Anova, Aurum, HST)
  > 4 200 HCWs trained

- PEPFAR-funded CrAg LFA lab tests were distributed by the NICD:
  > 65 000 LFA tests distributed

- 289 772 x 200 mg fluconazole pills were provided through PEPFAR partner USAID, procured and distributed by SCMS
Screen & treat operational at 3 laboratories in 4 districts (GA,FS)

- 50 327 samples from 42 666 patients with a CD4 count <100 were tested for CrAg
  - Approx. 15% duplicate testing (testing on same patient)
  - **41,999**/42,666 (98%) with no prior CM
Case detection from 3 NHLS CD4 laboratories, Sep 2012-Aug 2015

↑

CrAg-positive cases

1 271 (3%)

↑

Diagnosed at an enhanced M&E facility (n=114)

688 (54%)

↑

Case report form

550 (80%)

No follow-up data

138 (20%)
**Incident antigenaemia**

550

Symptoms not recorded n=11

Symptomatic: 316 (59%)
- LP performed: 120 (38%)
  - CSF cryptococcal test+: 68 (74%)
  - Amphotericin B: 59 (87%)
- No LP: 196 (62%)

Asymptomatic: 223 (41%)
- LP performed: 63 (28%)
  - CSF cryptococcal test+: 11 (17%)
  - Amphotericin B: 10 (99%)
- No LP: 160 (72%)
Fluconazole

- Fluconazole initiated among those with a new CrAg positive test at ES facilities 332/378 (88%), unknown 172

- **Fluconazole also prescribed for**
  - 21/24 (88%) symptomatic and CSF CrAg negative patients
  - 31/32 (99%) asymptomatic and CSF CrAg negative patients
**Clinician-initiated screen-and-treat: Western Cape**

Proportion of eligible patients with screening CLAT test by month, September 2012-August 2013

Vallabhaneni S, et al. Manuscript in progress
Conclusions

• Screen & treat is a life-saving intervention
• Reflex laboratory screen & treat was feasibly integrated into the HIV cascade of care at a district-level
• Challenges include:
  – Integration of a manual CrAg test into high-volume laboratories and duplicate CrAg testing → consider a tiered lab testing model and use of unique patient identifier
  – Immediate loss to follow-up among those with a CrAg+ result → consider enhanced patient tracing
  – Non-adherence to clinical algorithm → healthcare worker training is essential
Next steps

With national expansion, the NICD will provide technical support in the following key areas:

- implementation of reflex CrAg screening at 64 NHLS CD4 laboratories and development of a proficiency testing scheme for CrAg testing
- integration of clinical training for CM into NIMART program
- monitoring the impact of screening and treatment at facility-level by intensive M&E in selected districts in each province
- measuring the cost-effectiveness of screening and treatment
- comparing reflex to point-of-care screening at selected facilities
- advocating for improved access to antifungal medicines and diagnostics
Acknowledgements

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• National Health Laboratory Service
• CDC-South Africa and CDC-Atlanta
• USAID-South Africa
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• Southern African HIV Clinicians’ Society