Cryptococcal meningitis
TREATMENT AND DIAGNOSIS

Joe Jarvis
NIHR Global Health Professor
London School of Hygiene and Tropical Medicine & Botswana Harvard AIDS Institute Partnership
Outline

Epidemiology

Treatment
- current treatment outcomes
- findings from recent trials
- new short-course treatments
- potential adjunctive therapies
- novel drugs

Diagnostics

Challenges and opportunities
“We are threatened with extinction, People are dying in chillingly high numbers.”

“One more day of delayed action is a day too late for our people. Our people are crying out for help. Let us respond while there is time.”
Botswana’s progress toward achieving the 2020 UNAIDS 90-90-90 antiretroviral therapy and virological suppression goals: a population-based survey


Findings 81% of enumerated eligible household members took part in the survey (10% refused and 9% were absent). Among 12,610 participants surveyed, 3,596 (29%) were infected with HIV, and 2,995 (83.3%, 95% CI 81.4–85.2) of these individuals already knew their HIV status. Among those who knew their HIV status, 2,617 (87.4%, 95% CI 85.8–89.0) were receiving ART (95% of those eligible by national guidelines, and 73% of all infected people). Of the 2,609 individuals receiving ART with a viral load measurement, 2,517 (96.5%, 95% CI 96.0–97.0) had viral load of 400 copies per mL or less. Overall, 70.2% (95% CI 67.5–73.0) of HIV-infected people had virological suppression, close to the UNAIDS target of 73%.
People living with HIV (all ages)

New HIV infections (all ages)

Source: UNAIDS Estimates 2018
Advanced Human Immunodeficiency Virus Disease in Botswana Following Successful Antiretroviral Therapy Rollout: Incidence of and Temporal Trends in Cryptococcal Meningitis

Mark W. Tenforde,1,2 Margaret Mokosane,1 Tohoko Leena,1 Raje K. K. Patel,1 N samoleti Lekwane,3 Chedepiro Rama damaged,1 Bomo Dube,1
Elizabeth A. Williams,1 Kelebeletse O. Mokoliledi,1 Ephraim Twanana,1 Tlhaginye Pilane,1 William J. Hurt,1 Hannah Mitchell,1
Doreen L. Banda,1 Hunter Stue,2 Mocketzitso Mothi,1 Kabelo Mokhach,1 Henton Phillips,1 Paul C. Mullen,1 Andrew P. Steenhoff,1
Yohane Morshafi,1 Medico Mine,1 and Joseph N. Jacobs1,2,4,5

The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa

Meg Otieno,1 Katherine Hilderbrandt,1,5 Eric Gooszen,1,6 Nathan Ford,1,6 Mariette Smith,1,6 Gwenevere Menvija,6 Jannes Kruger,1 Neleth P. Gwendera,1 and Andrew South1,6,9

Clinical Infectious Diseases® 2017;00(00):1–8

Clinical Infectious Diseases® 2018;66(52):S118–25
Advanced Human Immunodeficiency Virus Disease in Botswana Following Successful Antiretroviral Therapy Rollout: Incidence of and Temporal Trends in Cryptococcal Meningitis

The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa

ART experienced

ART naive
Background

- 36% acute mortality in Vietnam
  *Day et al. NEJM 2013;368:1291-302*
- 41% acute mortality in Africa and Asia
  *Beardsley et al. NEJM 2016;374:542-54*
- 15% of all HIV-related mortality
  *Rajasingham et al. Lancet ID 2017; pii: S1473-3099(17)30243-8*
Mortality rates with current antifungal therapy are unacceptably high

Princess Marina Hospital, Gaborone
Amphotericin B 1mg/kg plus Fluconazole 800mg daily for 14 days
Universal ART access

Tshepo Leeme et al. Mortality due to HIV-associated Cryptococcal Meningitis in Botswana in the ART Era. CROI 2017, Seattle WA.
Background

- 36% acute mortality in Vietnam
  
  Day et al. NEJM 2013;368:1291-302

- 41% acute mortality in Africa and Asia
  
  Beardsley et al. NEJM 2016;374:542-54

- 15% of all HIV-related mortality
  
  Rajasingham et al. Lancet ID 2017; pii: S1473-3099(17)30243-8
Amphotericin B deoxycholate is toxic and difficult to administer in resource-limited settings

- Thrombophlebitis
- Nosocomial sepsis (15%)
  

- Infusion reactions
- Anaemia (mean 2.3g/dL drop over 14 days)
  
  Bicanic et al AAC 2015

- Renal impairment

- Potassium and magnesium wasting
Efficacy of an Abbreviated Induction Regimen of Amphotericin B Deoxycholate for Cryptococcal Meningoencephalitis: 3 Days of Therapy Is Equivalent to 14 Days


(experimental cryptococcal meningoencephalitis in rabbits)

Abbreviated Amphotericin B Deoxycholate regimens have been tested in humans in the recently completed ACTA randomized controlled trial

Toxicity of abbreviated regimes is significantly less than with standard 14-day regimens

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Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

S.F. Molloy, C. Kanyama, R.S. Heyderman, A. Loyse, C. Kouanfack, D. Chanda,

1 week AmB + 5FC vs 2 weeks AmB + 5FC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 week mortality</th>
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<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
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<tr>
<td>1 week AmB + 5FC</td>
<td>0.56 (0.35 to 0.91)</td>
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Probability of death by 10 wks % (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oral</th>
<th>1 week AmB + FLU</th>
<th>1 week AmB + 5FC</th>
<th>2 weeks AmB + FLU</th>
<th>2 weeks AmB + 5FC</th>
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<tr>
<td></td>
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<td>Probability</td>
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<td>of death by 10 wks % (95% CI)</td>
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<td>of death by 10 wks % (95% CI)</td>
</tr>
<tr>
<td>1 week AmB + FLU</td>
<td></td>
<td>35% (29 - 41)</td>
<td>24% (16 - 32)</td>
<td>41% (32 - 50)</td>
<td>38% (29 - 47)</td>
</tr>
<tr>
<td>1 week AmB + 5FC</td>
<td></td>
<td>49% (39 - 58)</td>
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<tr>
<td>2 weeks AmB + FLU</td>
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<tr>
<td>2 weeks AmB + 5FC</td>
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79/225  54/111  27/113  47/114  44/115
Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

S.F. Molloy, C. Kanyama, R.S. Heyderman, A. Loyse, C. Kouanfack, D. Chanda,

Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>AmB + 5FC vs AmB + FLU</th>
<th>p-value (log-rank test)</th>
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<tbody>
<tr>
<td>10 week mortality</td>
<td>0.62 (0.45 to 0.84)</td>
<td>0.002</td>
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</table>

10 week mortality:

FLU: 45% (101/225)

5FC: 31% (71/228)
Combination Antifungal Therapy for Cryptococcal Meningitis

Jeremy N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D.,

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013

A

- Amphotericin B plus fluconazole
- Amphotericin B plus flucytosine
- Amphotericin B alone

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td></td>
<td>Amphotericin B alone</td>
</tr>
<tr>
<td></td>
<td>99 74</td>
</tr>
<tr>
<td></td>
<td>74 59</td>
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<td>59 54</td>
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<td>49 46</td>
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<td>46 30</td>
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What about liposomal amphotericin B?

Less nephrotoxic
- higher doses can be given safely

Excellent tissue penetration and long tissue half life
- should be possible to deliver highly effective induction therapy with very few (1, 2, or 3) doses

Effective long-lasting therapy with just one dose of high dose liposomal amphotericin B has been established in the treatment of visceral leishmaniasis

Use in CM previously limited by cost, but short courses and reduced pricing could make it a cost-effective option

Need to define the most effective and most cost-effective schedules
The pharmacokinetics of liposomal amphotericin B in murine plasma (red) and cerebrum (black) in cohorts of mice infected with *Cryptococcus neoformans* receiving LAmB 20 mg/kg SINGLE DOSE i.v.

The terminal half-life in the plasma and cerebrum is circa 133 hours.

The Ambition Phase 2 Study: Primary Endpoint EFA (Jarvis et al. CID 2018)

- **CONTROL**
  - Ambisome 3mg/kg/day
  - Fluconazole 1200mg/day for 14 days

- **SINGLE DOSE**
  - Ambisome 10mg/kg (day 1 only)
  - Fluconazole 1200mg/day for 14 days

- **TWO DOSES**
  - Ambisome 10mg/kg (day 1)
  - Ambisome 5mg/kg (day 3)
  - Fluconazole 1200mg/day for 14 days

- **THREE DOSES**
  - Ambisome 10mg/kg (day 1)
  - Ambisome 5mg/kg (day 3 & 7)
  - Fluconazole 1200mg/day for 14 days

**Graphs**

- **14 Days**
  - Mean -0.41 SD 0.11 cfu/ml/d
  - Mortality 29% (6/21)

- **Single dose**
  - Mean -0.52 SD 0.35 cfu/ml/d
  - Mortality 22% (4/18)

- **Two doses**
  - Mean -0.47 SD 0.29 cfu/ml/d
  - Mortality 15% (3/20)

- **Three doses**
  - Mean -0.54 SD 0.44 cfu/ml/d
  - Mortality 50% (10/20)
All 3 short course Liposomal Amphotericin B treatment arms were non-inferior to control
L-AmB 10 mg/kg day 1 (single dose) vs Amphotericin B deoxycholate 1.0 mg/kg/d 7 days ("control arm")

Hypothesis: Short-course high-dose L-AmB given with high dose fluconazole and flucytosine will be non-inferior to standard daily-dosed amphotericin B deoxycholate with flucytosine induction therapy for the treatment of HIV-associated cryptococcal meningitis in averting all-cause mortality.

Endpoints:
**Primary:** All-cause mortality within the first 10 weeks

**Secondary:** Early Fungicidal Activity (EFA); 2-week mortality; tolerability and adverse events; cost-effectiveness

850 patients total (425 per arm) (10% NI margin)
We are studying a form triple therapy chosen as best possible challenger to the new standard of care established by ACTA, on the basis that:

1. AMBITION phase II: single high dose is best way to deliver Ambisome

2. ACTA data showing 5FC essential component and best partner drug with AmB

3. Concern if ONLY single dose Ambisome + 5FC were used a risk of 5FC monotherapy in second week leading possible 5FC resistance, and no phase 2 data for this approach

4. With oral combination Fluconazole / 5FC backbone: includes the AMBITION phase II combination, phase 3 ACTA supported oral combination (which was just lacking a non toxic EFA kick?), no downside to including fluconazole (cost, availability), and ........some evidence 3 drugs may actually be superior
Can we lower mortality with adjunct therapies?
Can we lower mortality with adjunct therapies?

Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial

Joshua Rhine, Kathy-Hepppler Hufnagel, Lillian Siegume, Edwin Nwagama, Edward Mtizane, Emily E Evans, Rebecca Kiggundu, Katelyn A Postick, Kenneth Ssesembubule, Andrew Akampimpa, Darlsha A Williams, Ananta S Bangdiwala, Mahsa Abassi, Abdu K Mosube, Melanie R Nicol, Carvid Muzoora, David B Meya, David R Boulware, on behalf of ASTRO-CM team

Lancet Infect Dis 2019; 19: 843-51

No mortality benefit of adding sertraline to amphotericin B and fluconazol

52% 18-week mortality in the sertraline group,

vs

46% in the control group.
Can we lower mortality with adjunct therapies?

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc,
Can we lower mortality with adjunct therapies?

Interferon-γ (IFNγ) plays a key role in host defense.
Can we lower mortality with adjunct therapies?

IFN\(_\gamma\) therapy led to significantly increased rates of clearance of cryptococcal infection from the CSF.
Novel drugs for cryptococcal meningitis

Novel azole type drugs – (Mycovia) VT-1598.

Amplyx APX001. First in a new class of broad-spectrum antifungal agents that inhibit Gwt1, an enzyme which is required for cell wall localization of glycosylphosphatidylinositol (GPI)-anchored mannoproteins in fungi.

Oral formulations of Amphotericin B.
Novel drugs for cryptococcal meningitis

Novel azole type drugs – (Mycovia) VT-1598.


Oral formulations of Amphotericin B.
Diagnosis

Lumbar puncture and India ink staining +/- culture

Immunodiagnosis (CRAG)
Diagnosis

Lumbar puncture and India ink staining +/- culture

Immunodiagnosis (CRAG)

A point of care test?

Earlier diagnosis

Antigen screening

Serum, Plasma, and fingerprick
IMMY CrAg LFA


Sensitivity 99.3%, Specificity 99.1%

Cryptococcal antigen screening

“Screening for cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying risk of progression to disease when managing people presenting with advanced HIV disease.”

Recommendations

• Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm$^3$ (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of <200 cells/mm$^3$ (conditional recommendation; moderate-certainty evidence).
Cryptococcal antigen screening

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TOP 5 POSTER session later today:
Cryptococcal Meningitis is a Cause of Death Among HIV-Infected Adults Despite Cryptococcal Antigen Screening and Pre-emptive Fluconazole Treatment
Dr Rachel Wake, St George’s University of London
A novel semi-quantitative CrAg dipstick may enable stratified treatment

220 CrAg+ plasma samples from patients in Botswana

To be presented at CROI 2020
Boston, MA, USA

*Kwana Lechiile et al*
Challenges and opportunities

**Challenges**
Flucytosine access
Liposomal amphotericin B pricing and availability

**Progress**
WHO prequalification of liposomal amphotericin B (AmBisome) in June, 2018;

Addition of cryptococcal meningitis to the US Food and Drug Administration’s priority review voucher scheme in August, 2018;

Expansion of Gilead’s preferential AmBisome pricing programme for visceral leishmaniasis to include cryptococcal meningitis in September, 2018;

Announcement of substantial UNITAID funding for cryptococcal meningitis treatment in high-burden African countries in January, 2019
Summary

Cryptococcal meningitis remains the commonest cause of adult meningitis in east, central, and southern Africa despite expanded access to ART.

Mortality rates are unacceptably high with current treatments, which are toxic and difficult to administer in low-resource settings.

A novel short-course highly effective and safer L-AmB treatment regimen for CM could transform the management of late-stage HIV and markedly improve outcomes in HIV programmes in Africa.

Screening HIV-positive individuals with low CD4 counts for sub-clinical cryptococcal infection using CrAg tests and giving early treatment is recommended to reduce the burden of cryptococcal meningitis.