CRYPTOCOCCOSIS MASKING AS FULMINANT BACTERIAL SEPSIS: A MANIFESTATION OF UNMASKING IRIS?

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Disclosures

- Nothing to disclose

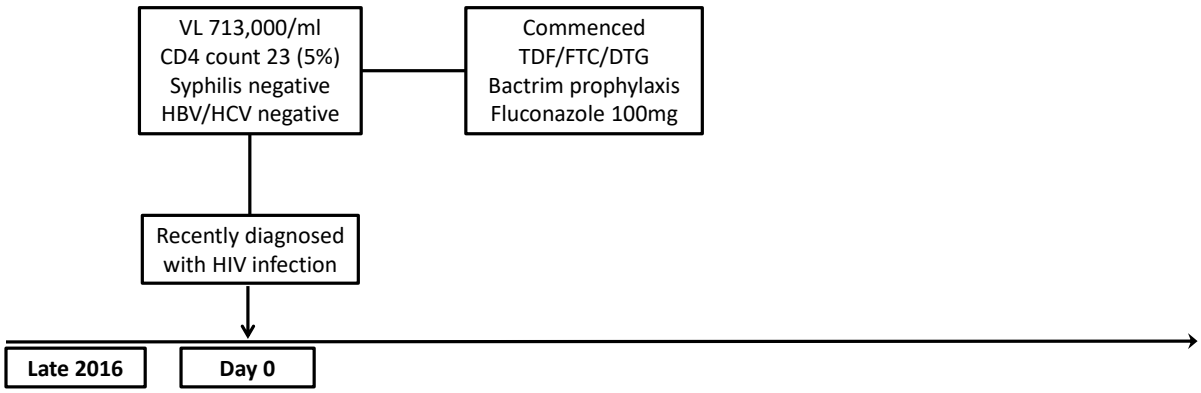
The Royal Melbourne Hospital

VIDS Victorian Infectious Diseases Service

Mr S

- 54 yo admin worker
- MSM- home with partner 15yrs
- PMHx:
  - BPH on tamsulosin
- Newly diagnosed advanced HIV infection
  - Chronic diarrhoea, with 6kg weight loss
  - Recent gastroscopy – oesophageal candidiasis
  - Commenced on 100mg fluconazole daily

Introduction to care



Admission

48 hrs
Headache, fever and subjective unsteadiness on feet

Presentation to RMH

Examination:

Flushed
Febrile 39.8 C,
HR 130, ST
Normotensive
SpO2 97% RA

Alert, oriented
no localizing signs

Lactate 1.0 mmol/L
BSL 6.2 mmol/L

Investigations:
Na+ 128, Cre 139
CRP 83
CD4 70 (7.8%)

Blood cultures taken (3 sets)
Stool and urine NAD
CT brain, CXR NAD

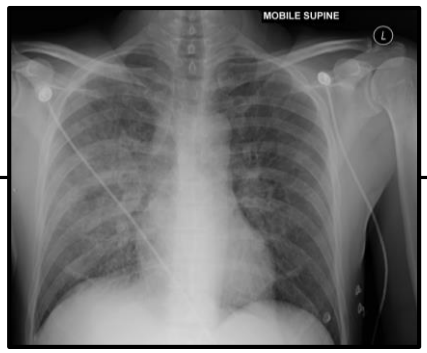
Lumbar puncture:
Opening pressure 7cm H20
CSF protein 0.36, glucose 3.0,
RCC 0, PMN 3, Lymph 3,
Cryptococcal antigen (CrAg) 1: 10
Encapsulated yeast on India ink
Culture: **C. neoformans**

Serum CrAg 1:640

Day 7

L- Amphotericin
5-Flucytosine

Deterioration



Transferred to ICU

Pulmonary infiltrates

Cardiac injury

MET call:
Generalised seizure
SpO2 83%

Broad spectrum antibacterial therapy
Vasopressors
Corticosteroids

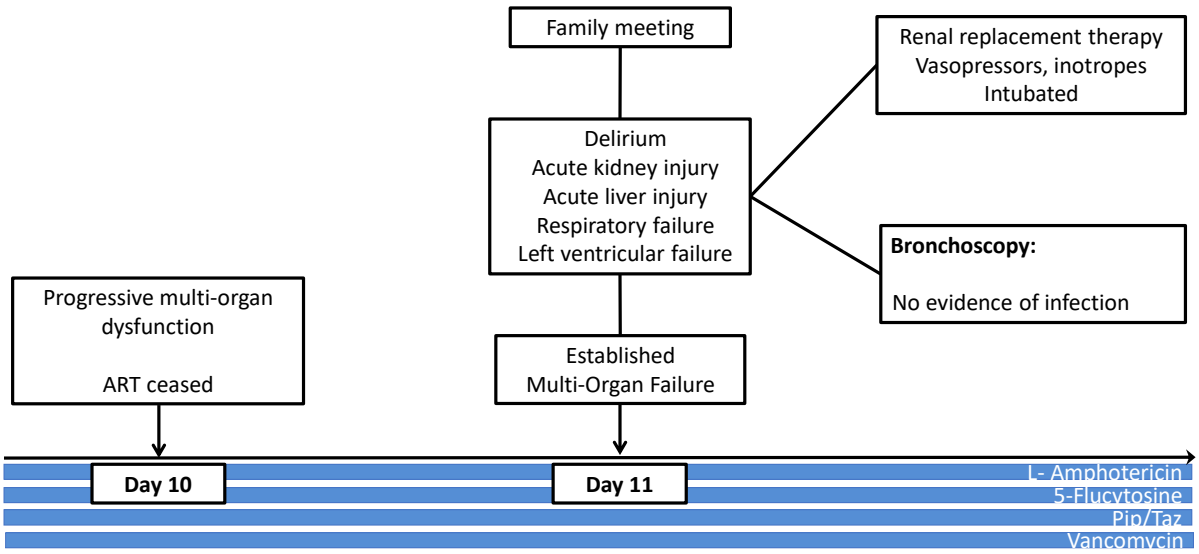
Septic shock

Day 8

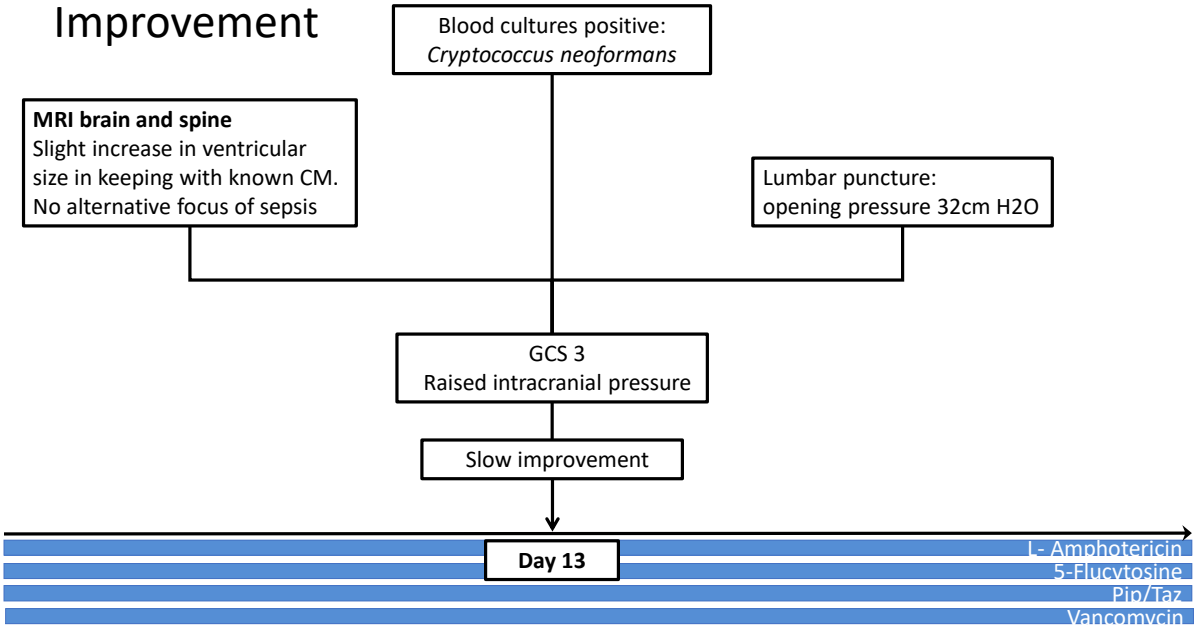
Day 9

L- Amphotericin
5-Flucytosine
Pip/Taz
Vancomycin

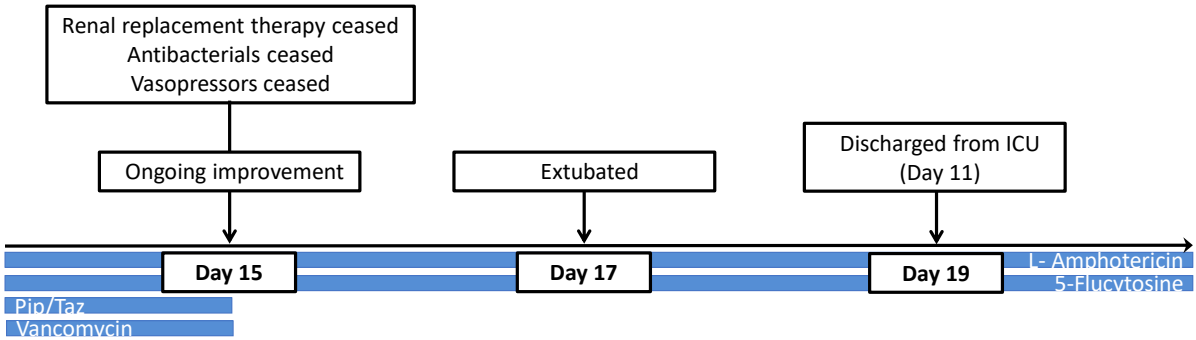
Multiorgan failure



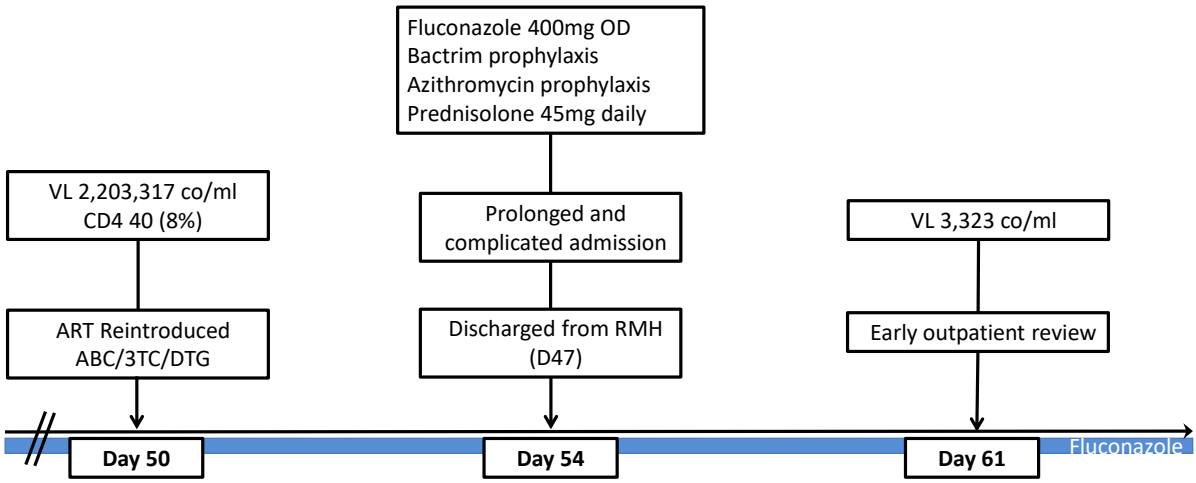
Improvement



Weaning of supports

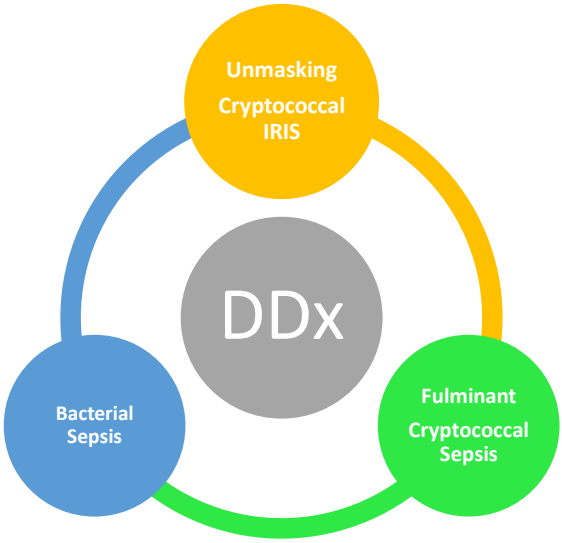


Discharge and linking to care



Summary

54yo man with shock and progressive multiorgan failure in the setting of treatment commencement for late-diagnosed, advanced HIV infection with evidence of disseminated cryptococcosis and cryptococcal meningitis.



Was this bacterial sepsis?

- Patients with HIV infection have increased risk of invasive bacterial sepsis[1]
- HIV infection causes dysregulation of the inflammatory response[1,2]
- Blood cultures are a sensitive means of detecting bacteraemia[3]
- Cultures are frequently negative in septic shock.[4]

- Our patient:
  - Bacterial sepsis can not be entirely excluded in our patient
  - Extensively cultured prior to antimicrobial therapy
  - Empiric antibiotic treatment per local sepsis protocols
  - Better explanation?

Bacterial Sepsis

[1]Huson MA, et al. Lancet ID. 2015;15(1):95-108
[2]Janssen S, et al. CID. 2017;65(1):73-82
[3]Opota O, et al. CMI. 2015;21(4):313-22
[4]Morgenthaler NG, IJM. 2015;2015.

Was this fulminant cryptococcal sepsis?

- Shock in the setting of disseminated cryptococcosis previously reported[1-3]
- Case reports in patients with advanced HIV, esp. CD4 count <100
- High mortality risk, reduced by early antifungal therapy
- Difficult to differentiate from bacterial sepsis and IRIS

- Our patient:
  - Fulminant cryptococcosis possible
  - Fulminant manifestation of cryptococcosis rare
  - Temporal association with ART initiation

Cryptococcal Sepsis

[1]Lozano F, et al. EJCMI. 1999;18(2):151-2
[2]Gariani K, et al. IJID. 2014;22:17-8
[3]Shimoda M, et al. Internal Medicine. 2014;53(15):1641-4
[4]Jean SS, et al. QJM. 2002;95(8):511-8.

Was this unmasking cryptococcal IRIS?

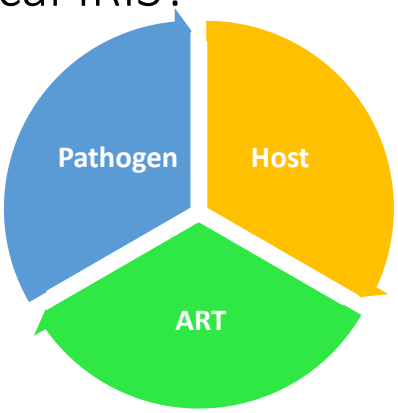
- *Unmasking IRIS*: previously subclinical infection being 'unmasked' by immune restoration resulting in an enhanced immune response.[1]
- Limited data specific to unmasking IRIS
- Heterogeneous definitions, presentation and severity
  - Cryptococcal meningitis and lymphadenitis most frequent[1]
  - Fulminant septic shock unusual
- High morbidity and mortality
- May lead to delays in antiretroviral therapy[3]

Unmasking IRIS

[1]Haddow LJ, et al. Lancet Infect Dis. 2010;10(11):791–802
[2]Rajasingham R, et al. JAIDS. 2012; 59(5):85
[3]Boulware DR, et al. NEJM. 2014;370(26):2487-2498

Was this unmasking cryptococcal IRIS?

- Risk factors for cryptococcal IRIS:
  - Baseline CD4 count of <50/uL[1-5]
  - Paucity of CSF inflammation at the time of initial CM diagnosis[2]
  - Fungal burden[3]
  - Higher baseline and lower on-treatment HIV RNA levels[4]
  - Boosted protease inhibitor regimen[4]
  - Intergrase inhibitor regimen[5]



Unmasking IRIS

[1]French MA, et al. HIV medicine. 2000 Apr 1;1(2):107-15.
[2]Boulware DR, et al. JID 2010 Sep 15;202(6):962-70.
[3]Chang CC, et al.. AIDS. 2013 Aug 24;27(13):2089-99.
[4]Manabe YC, et al. JAIDS. 2007 Dec 1;46(4):456-62.
[5]Dutertre M, et al, Dat'AIDS Study Group. 2017 Sep 1;76(1):e23-6.

Was this unmasking cryptococcal IRIS?

- Criteria for IRIS focus on[1-4]:
  - OI unidentified prior to ART initiation
  - Temporal association with ART initiation
    - Evidence of ART efficacy
  - Exclusion of alternative causes
    - Infection
    - Drug reaction
  - Atypical presentation with heightened inflammatory response
- Our patient:
  - Multiple cryptococcal IRIS risk factors
  - Deterioration in keeping with existing IRIS definitions

Unmasking IRIS

[1]French M, et al AIDS. 2004;18 (12):1615-27
[2]Haddow LJ, et al.. Lancet ID. 2010 Nov 30;10(11):791-802.
[3]Manzardo, et al 2015 Expert Rev. Anti Infect. Ther. 1–17
[4]AIDS clinical Trials Group Network (2009)

Should we screen for Cryptococcus?

- Screening clearly cost effective in high-incidence, low-resource settings[1]
  - Less clear in high income settings
- Screening patients for cryptococcosis is simple, cheap and reliable
- In Australia:
  - Prevalence of cryptococcal infections is significantly reduced with ART[2]
  - Advanced HIV diagnoses still occurring commonly[3]
  - ATSI and recent immigrants overrepresented in late-diagnosed HIV[3]
- UK: 5% CrAg positivity, 88% in patients of African origin[4]

[1]Meya DB, et al. CID. 2010;51(4):448–455
[2]Chen S, et al. CID. 2000;31(2):499-508.
[3]Kirby Institute. UNSW Sydney; 2017.
[4]Patel S, etal. Journal of Infection. 2013 Jan 31;66(1):75-9.

What do the guidelines say?

Guideline	Comment	Recommendation
WHO[1]	Pre-emptive screening and treatment of all patients with CD4 count < 100/uL, particularly in areas with >3% prevalence is desirable if feasible	Consider asymptomatic screening if prevalence >3%
US DHHS/IDSA[2]	"Routine testing for cryptococcal infection by determination of serum cryptococcal antigen levels ...is not recommended"	Symptomatic screen
BHIVA[3]	"We recommend tests for …Cryptococcus …disease are not performed routinely but if the patient has relevant symptoms"	Symptomatic screen
ASMH[4]	Per US guideline	Per US guideline

[1]World Health Organization. (2016)
[2]USDHHS/IDSA (2013)
[3]Angus B, et al. BHIVA guidelines (2016)
[4] http://arv.ashm.org.au/

Conclusions

- Late HIV diagnoses still occur in Australia
- Cryptococcal infection may present with a fulminant illness, albeit rarely, which may be hard to distinguish from bacterial infection
- Cryptococcal IRIS likely played a significant role in our patient's deterioration
- Although routine cryptococcal antigen screening is not recommended in most international guidelines, we suggest a role for targeted cryptococcal antigen screening in patients with low CD4 count from countries where HIV-associated cryptococcal disease is more common

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VIDS Victorian Infectious Diseases Service

References

Huson MA, Stolp SM, van der Poll T, Grobusch MP. Community-acquired bacterial bloodstream infections in HIV-infected patients: a systematic review. Clin Infect Dis. 2014;58:79–92

Huson MA, Grobusch MP, van der Poll T. The effect of HIV infection on the host response to bacterial sepsis. Lancet Infectious Diseases. 2015 Jan 31;15(1):95-108.

Barbier F, Roux A, Canet E, Martel-Samb P, Aegerter P, Wolff M, Guidet B, Azoulay É. Temporal trends in critical events complicating HIV infection: 1999–2010 multicentre cohort study in France. Intensive care medicine. 2014 Dec 1;40(12):1906-15

Janssen S, Schutz C, Ward A, Nemes E, Wilkinson KA, Scriven J, Huson MA, Aben N, Maartens G, Burton R, Wilkinson RJ. Mortality in Severe Human Immunodeficiency Virus-Tuberculosis Associates With Innate Immune Activation and Dysfunction of Monocytes. Clinical Infectious Diseases. 2017 Mar 24;65(1):73-82.

Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and preemptive treatment into routine HIV care. Journal of acquired immune deficiency syndromes (1999). 2012 Apr 15;59(5):85.

Meya DB, Manabe YC, Castelnuovo B, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010;51(4):448–455

Lozano F, Gomez-Mateos J, Irles JA, Meléndez B, Martin E. Fulminant septic shock in AIDS patients caused by disseminated cryptococcosis. European Journal of Clinical Microbiology & Infectious Diseases. 1999 Mar 25;18(2):151-2

Gariani K, Rougemont M, Renzi G, Hibbs J, Emonet S, Schrenzel J. Fulminant atypical Cryptococcus neoformans pneumonia confirmed by PLEX-ID. International Journal of Infectious Diseases. 2014 May 31;22:17-8.

Haddow L.J. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis. 2010;10(11):791–802

References

French MA, Lenzo N, John M, Mallal SA, McKinnon EJ, James IR, Price P, Flexman JP, Tay-Kearney ML. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV medicine. 2000 Apr 1;1(2):107-15.

Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1–infected cohort. Clinical Infectious Diseases. 2006 Feb 1;42(3):418-27.

Grant PM, Komarow L, Andersen J, Sereti I, Pahwa S, Lederman MM, Eron J, Sanne I, Powderly W, Hogg E, Suckow C. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. PloS one. 2010 Jul 1;5(7):e11416.

Manabe YC, Campbell JD, Sydnor E, Moore RD. Immune reconstitution inflammatory syndrome: risk factors and treatment implications. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2007 Dec 1;46(4):456-62.

Lortholary O, Fontanet A, Memain N, Martin A, Sitbon K, Dromer F. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS. 2005;19:1043–1049.

Chang CC, Dorasamy AA, Gosnell BI, Elliott JH, Spelman T, Omarjee S, Naranbhai V, Coovadia Y, Ndung'u T, Moosa MY, Lewin SR. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. AIDS. 2013 Aug 24;27(13):2089-99.

Morgenthaler NG, Kostrzewa M. Rapid identification of pathogens in positive blood culture of patients with sepsis: review and meta-analysis of the performance of the sepsityper kit. International journal of microbiology. 2015 Apr 27;2015.

Dutertre M, Cuzin L, Demonchy E, Puglièse P, Joly V, Valantin MA, Cotte L, Huleux T, Delobel P, Martin-Blondel G, Dat'AIDS Study Group. Initiation of Antiretroviral Therapy Containing Integrase Inhibitors Increases the Risk of IRIS Requiring Hospitalization. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2017 Sep 1;76(1):e23-6.

World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. World Health Organization; 2016.

References

Angus B, Brook G, Awosusi F, Barker G, Boffito M, Das S, Dorrell L, Dixon-Williams E. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals.

French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. Aids. 2004 Aug 20;18(12):1615-27.

Chen S, Sorrell T, Nimmo G, Speed B, Currie B, Ellis D, Marriott D, Pfeiffer T, Parr D, Byth K. Epidemiology and host-and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Clinical infectious diseases. 2000 Aug 1;31(2):499-508.

Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2017. Sydney: Kirby Institute, UNSW Sydney; 2017.

Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. Jun 26 2014;370(26):2487-2498. Available at http://www.ncbi.nlm.nih.gov/pubmed/24963568.