HIV-associated cryptococcal meningitis in Botswana: National incidence and temporal trends following antiretroviral therapy rollout

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Background

HIV-associated cryptococcal meningitis (CM) causes hundreds of thousands of deaths annually in sub-Saharan Africa (SSA)[1]
- Up to 20% of deaths in HIV-infected populations [2]

Most disease occurs in individuals with advanced disease, particularly those with CD4 T-cell count <100 cells/µL
- Recent cohort studies in SSA suggest antiretroviral therapy (ART) initiation continues to be delayed, leaving patients at high risk for CM and other opportunistic infections [3,4]

Botswana developed the first national ART in Africa and treatment is widely available
- Median CD4 count at ART initiation was 191 cells/µL in 2010 (IQR 115-239 cells/µL) [5]
- 2012 guidelines recommended started ART when CD4 count <350 cells/µL
- In 2013, median baseline CD4 count at ART initiation of 258 cells/µL (IQR 147-337 cells/µL) [6]

<u>Study aim</u>: To characterize the 2014 incidence of Cryptococcal meningitis in Botswana and evaluate temporal trends following rollout of ART
- Accurate characterization can guide disease prevention through cryptococcal antigen (CrAg) screening and targeted interventions to address gaps in the HIV care cascade

Methods

Identified all laboratories in Botswana that process cerebrospinal fluid (CSF) for evaluation of suspected meningitis from 2000 to 2014
- 2 referral hospital laboratories, 6 district hospital laboratories, 25 primary/private/mine/military laboratories
- Visited facilities to obtain full paper-based CSF records
- Obtained available electronic records from a national electronic medical record, Integrated Patient Management System (IPMS)
- Eliminated duplicate records
- Records stored in secure RedCaps online database

Methods

Determined number of cases and national incidence of cryptococcal meningitis using comprehensive CSF laboratory data from 2014
- "Case" defined as positive India ink stain, culture, and/or CrAg from CSF
- If a single patient had multiple CSF analyses within 3-week period, counted as single case
- UNAIDS Spectrum estimates utilized for population denominator estimates
- Incidence rate determined for total national population and HIV/AIDS-infected population stratified by age category

At largest national referral hospital (Princess Marina Hospital, Gaborone), evaluated temporal trends (2000-2014) in CSF studies over time
- Percentage of CSF samples positive for *Cryptococcus neoformans* by India ink, culture, and/or CrAg
- Evaluated bacterial, fungal, and AFB culture results to determine cryptococcal meningitis as cause of suspected meningitis relative to other pathogens

Results

Table 1. Nationwide incidence of cryptococcal meningitis in Botswana, 2014.

Variable	Value
Cryptococcal meningitis, # cases	320
Age, years, median (interquartile range)	37 (32-45)
Female gender, n (%)	125 (39)
Overall incidence, n/100,000 (95% CI)	15 (13-16)
Incidence in adult HIV-infected population, n/100,000 (95% CI)	78 (70-87)
Incidence in adult AIDS population, n/100,000 (95% CI)	250 (223-279)
Incidence by age group in HIV-infected population, n/100,000 (95% CI)	
15-19 years	93 (45-171)
20-24 years	45 (22-81)
25-29 years	55 (36-81)
30-34 years	97 (75-124)
35-39 years	90 (70-115)
40-44 years	88 (66-116)
45-49 years	86 (60-118)
50-54 years	77 (48-116)
55-59 years	50 (24-92)
60-64 years	58 (23-120)
65-69 years	51 (10-150)

Results

Figure 1. a) Percentage of CSF samples in adults positive for cryptoccoccal meningitis, Princess Marina Hospital 2000-2014; b) Number of CSF samples in adults positive for cryptococcal meningitis.

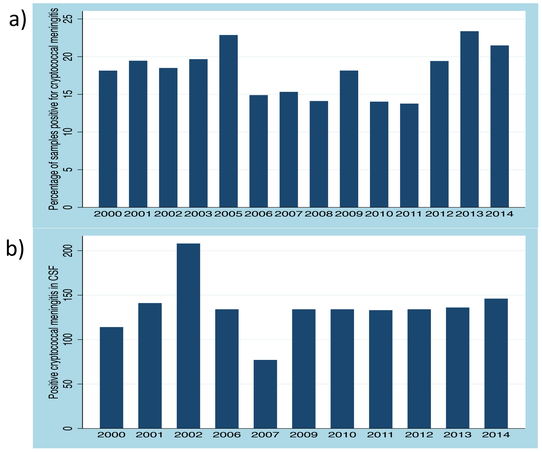

Table 2. Culture-confirmed pathogens of bacterial meningitis Princess Marina Hospital, 2000-2014.

Pathogen	n	Percent
All cerebrospinal fluid samples	10,557	100%
Culture negative	8706	82%
WBC 0-5 cells/µL	5349/7891	68%
WBC >5 cells/µL	2542/7891	32%
Lymph>50%	1158/1525	76%
PMN>50%	358/1525	23%
Cryptococcal meningitis	1625	15%
Streptococcus pneumoniae	147	1.4%
(Mycobacterium tuberculosis *	26	N/A)
Haemophilus influenzae	24	0.2%
Escherichia coli	11	0.1%
Other Streptococcus spp.	8	<0.1%
Klebsiella pneumoniae	7	<0.1%
Salmonella spp.	5	<0.1%
Coagulase-negative Staphylococcus	4	<0.1%
Neisseria meningitidis	3	<0.1%
Acinetobacter spp.	3	<0.1%
Pseudomonas aeruginosa	3	<0.1%
Staphylococcus aureus	2	<0.1%
Enterobacter spp.	1	<0.1%
Other	11	0.1%

*** Mycobacterial culture data only available 2010-2014**

Results

320 cases cryptococcal meningitis nationally in 2014 –incidence of 78/100,000 (95% CI: 70-87/100,000) in HIV-infected population
- Males (61%) > females (39%)
- High incidence in 4th decade of life, followed by declining incidence

At referral hospital, steady number of cases CM (largely unchanged 2009-2014)
- 15% CSF samples positive for Cryptococcal meningitis
- Most common laboratory-confirmed cause of meningitis

From national death registry audit of patients treated referral hospital 2012-2014, high case-fatality rate
- 47% (112/236) all-cause 10-week mortality (unpublished data)
- Standard 14-day induction therapy amphotericin B 1 mg/kg IV daily and fluconazole 800 mg PO daily

Limitations

Did not evaluate important clinical correlates in this retrospective laboratory records review
- E.g. previous HIV diagnosis in patients with incident CM, time from diagnosis, treatment default

Longitudinal data was from a single urban referral center that may not be representative of full country-level trends (e.g. rural areas)

Conclusions and Implications

In the first national meningitis audit in an African country, we observed a high ongoing burden of cryptococcal meningitis despite increasing availability of antiretroviral therapy
- Cryptococcal meningitis the most common laboratory-confirmed cause of meningitis

There is a need to improve understanding of factors influencing high incidence of disease in certain populations, e.g. men and young adults

Along with an increasing focus on HIV prevention and early ART initiation, continued need to address opportunistic infections in patients with HIV
- Role of screening for asymptomatic cryptococcosis as well as for potent, cost-effective treatment strategies

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