

Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence

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Objectives: To measure the burden of disease and describe the epidemiology of cryptococcosis in Gauteng Province, South Africa.

Design and methods: The study was an active, prospective, laboratory-based, population-based surveillance. An incident case of cryptococcosis was defined as the first isolation by culture of any *Cryptococcus* species from any clinical specimen, a positive India ink cryptococcal latex agglutination test or a positive histopathology specimen from a Gauteng resident. Cases were identified prospectively at all laboratories in Gauteng. Case report forms were completed using medical record review and patient interview where possible.

Results: Between 1 March 2002 and 29 February 2004, 2753 incident cases were identified. The overall incidence rate was 15.6/100 000. Among HIV-infected persons, the rate was 95/100 000, and among persons living with AIDS 14/1000. Males and children under 15 years accounted for 49 and 0.9% of cases, respectively. The median age was 34 years (range, 1 month–74 years). Almost all cases (97%) presented with meningitis. Antifungal therapy was given to 2460 (89%) cases of which 72% received fluconazole only. In-hospital mortality was 27% (749 cases). Recurrences occurred in 263 (9.5%) incident cases. Factors associated with death included altered mental status, coma or wasting; factors associated with survival included employment in the mining industry, visual changes or headache on presentation.

Conclusions: This study demonstrates the high disease burden due to cryptococcosis in an antiretroviral-naive South African population and emphasizes the need to improve early recognition, diagnosis and treatment of the condition.

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Introduction

Sub-Saharan Africa carries the greatest burden of the world's AIDS epidemic, with more than 60% of the world's HIV-infected population (approximately 25 million individuals) residing there [1]. South Africa has the largest number of individuals living with HIV in a single country [1]: national sentinel surveillance surveys of ante-natal clinic attendees indicated that HIV seroprevalence increased from less than 1% in 1990 [2] to a median of 28% in 2002 [3]. In addition, HIV/AIDS accounted for 30% of all deaths and 38% of life years lost for the year 2000 [4,5]. Government provision of antiretroviral therapy was initiated in March 2004 as the 'Comprehensive HIV and AIDS Care, Management and Treatment Plan for South Africa' [6]; by September 2004, about 12 000 individuals were receiving highly active antiretroviral therapy (HAART) [7].

In the context of this rampant, largely untreated epidemic, opportunistic infections, including cryptococcal meningitis, are a major cause of morbidity, and a burden to the health care sector [4,8]. Although cryptococcosis is perceived to be common, accurate information on the disease burden in the general population and among HIV-infected persons in resource-poor settings is not available. In Thailand, the national surveillance for AIDS-defining illnesses found cryptococcosis to be the fourth most common opportunistic infection, accounting for 18.5% of all opportunistic infections reported [9]. A hospital-based study from Uganda reported 40.4 cases of cryptococcosis per 1000 person-years of observation [10]. Cryptococcal meningitis caused 37% of all deaths among a cohort of South African miners in 1998 [11]. Cryptococcal meningitis was the leading cause of meningitis in Rwanda in 1992 [12], and Zimbabwe in 1995 [13]. In South Africa, in Durban and Soweto, in-hospital mortality among HIV-positive cryptococcal meningitis patients was 64% [14] and 43% [15], respectively.

To quantify the burden of this disease in Gauteng and describe its epidemiology, we conducted population-based surveillance for cryptococcosis. Accurate estimates of the burden of AIDS-related opportunistic infections in South Africa where resources are limited are important to guide prevention and management strategies. Furthermore, as antiretroviral drugs become more widely available in South Africa, reliable opportunistic infection surveillance data will be useful to assess the impact of antiretroviral therapy.

Methods

Background

A population-based surveillance for cryptococcosis was conducted in Gauteng province, South Africa for 2 years, from 1 March 2002 until 29 February 2004. The participating institutions included all health-care facilities

in Gauteng; seven academic and 18 regional state hospitals, one military hospital, three mines-funded hospitals and numerous private clinics. The state hospitals use National Health Laboratory Services (NHLS) laboratories for diagnostic tests whereas non-state hospitals use non-NHLS laboratories.

In October 2001, the population of Gauteng was 8.8 million people [16]; 17% of the population of South Africa. The province includes the cities of Johannesburg, Tshwane (formerly Pretoria) and Soweto. In Gauteng in 2002 an estimated 1 449 899 people, 96.8% of whom were adults aged 18–64 years, were living with HIV/AIDS [17].

All eligible laboratories and public hospitals were visited prior to commencement of surveillance by the Gauteng Cryptococcal Surveillance Initiative Core Committee (K.M., H.C.B., S.G., B.R.M., N.M., P.M. and H.J.K.) to encourage participation in the study. Two workshops were conducted for laboratory staff at which the public health benefit of this surveillance was explained, and training in the laboratory diagnosis of cryptococcosis was provided. From 2002 on, the Diflucan Partnership Program, sponsored by Pfizer, made fluconazole available free of charge to public hospitals for treatment and secondary prophylaxis of cryptococcal meningitis and oropharyngeal candidiasis [18].

Case definitions

An incident case of cryptococcosis was defined as the first isolation by culture of any *Cryptococcus* species from any clinical specimen, or a positive India ink or cryptococcal latex agglutination test on cerebro-spinal fluid (CSF) or other body fluid, or a positive histopathology specimen for cryptococcosis, from a Gauteng resident. Cases that met this definition but had a previous admission for cryptococcosis were defined as 'recurrent cases'. HIV infection was defined as evidence in the medical records, or history on interview, of a reactive HIV enzyme immunoassay. AIDS was defined as a CD4 cell count ≤ 200 cells/ μ l, or evidence in the medical record or history of an AIDS-defining illness according to US Centers for Disease Control and Prevention (CDC) definitions [19] in a patient with documented HIV infection.

Case identification and ascertainment

Cases were identified prospectively by surveillance officers who visited all laboratories weekly to review records. Monthly electronic audits of the NHLS laboratory information system were conducted to capture cases missed by surveillance officers. Three surveillance officers completed case report forms using medical record reviews or patient interviews. Only basic demographic and laboratory data from privately insured and military patients were obtained. The Gauteng Cryptococcal

Surveillance Initiative Core Committee managed all aspects of the surveillance.

Ethical issues

Ethics clearance and permission to perform record reviews and patient interviews, after informed consent was obtained, was given by institutional review boards of the Gauteng Department of Health, the University of the Witwatersrand, the University of Pretoria, Aurum Health of the Anglo American Corporation and Goldfields mining house.

Laboratory methods

The diagnostic tests for cryptococcosis used at all laboratories included culture and India ink; the cryptococcal latex agglutination test was available at some academic and mining hospitals and all non-NHLS laboratories. All laboratories submitted all isolates of *Cryptococcus* species to the Mycology Reference Unit (MRU) of the National Institute for Communicable Diseases (NICD) of the NHLS. Isolates were submitted on Sabouraud's dextrose agar slants in screw-top glass vials. In the MRU, the isolates were plated onto Sabouraud's dextrose agar to confirm purity. Genus identification was confirmed by growth at 37°C, brown discoloration on Niger seed agar, and urease hydrolysis. Isolates with indeterminate reactions were subjected to API20C Aux (BioMerieux Durham, North Carolina, USA) testing. All isolates of *Cryptococcus* underwent speciation using canavanine–glycine–bromothymol blue (CGB) agar. A proportion of isolates were submitted to the Mycotic Diseases Branch Fungus Reference Unit at the US Centers for Disease Control and Prevention (Atlanta, Georgia, USA) for serotyping using Cryptocheck (Iatron, Tokyo, Japan).

Statistical analysis

Census data for Gauteng were obtained from the 2001 census [16]. Estimates of the prevalence of HIV infection in the Gauteng population were obtained from the Medical Research Council and Actuarial Society of Southern Africa's report on the HIV/AIDS profile of the provinces of South Africa [17].

Statistical analysis of data was performed in SAS for Windows, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). A multinomial logit model was fitted to the three-level outcome of hospital death within 2 days of hospital admission, hospital death more than 2 days after admission, and survival until discharge or transfer. Odds ratios reported are defined as: odds of dying in the first 2 days (or after 2 days) after admission compared to surviving until discharge/transfer for those having a particular characteristic. The following variables were considered for inclusion into the multivariable model (regardless of the significance on the univariate analysis): coma, convulsions, altered mental status, blurred/poor vision, sixth cranial nerve palsy, headache, neck

stiffness, nausea, CD4 cell count < 200 cells/ μ l, wasting, extra pulmonary tuberculosis, pulmonary tuberculosis, previous diagnosis of *Pneumocystis jiroveci* pneumonia, any previously documented AIDS-defining illness, being employed in the mining industry, gender, receiving tuberculosis medications, isolate identified as *Cryptococcus neoformans* (as opposed to *Cryptococcus gattii*), and whether the patient received any amphotericin B, fluconazole only, or no treatment. The initial model was selected using the forward selection procedure in SAS, and using a significance level of < 0.05. Assessment of possible confounding by variables not found to be statistically significant from the forward selection method was done by entering each variable into the multivariable model and assessing the impact on the parameter estimates.

Results

Incidence

Between 1 March 2002 and 29 February 2004, 3004 case report forms were recorded. After exclusion of 179 non-Gauteng residents, 58 cases that were non-incident on entry into the study and 14 non-cryptococcal cases, 2753 incident cases were identified. Population denominators were as follows: overall population, 8 837 178; persons living with HIV, 1 449 899; children under 14 years with HIV, 31 488. The overall incidence rate was 15.6/100 000 (men = 15.2/100 000; women = 15.8/100 000). Rates by racial group were: black = 20.7/100 000, mixed race = 2.7/100 000, Indian/Asian = 0.7/100 000, white race = 0.4/100 000. Age-adjusted rates are shown in Fig. 1. Among HIV-infected persons, the rate was 95 per 100 000, and among persons living with AIDS 14 per 1000. In HIV-infected children under 14 years of age, the incidence was 38/100 000. No seasonality in isolation rate was observed.

Demographic characteristics

Males accounted for 49% of cases. The median age was 34 years (range, 1 month–74 years). Children under 15 years of age accounted for 24 (0.9%) cases. The majority of patients (98%) were black. Most cases were identified at

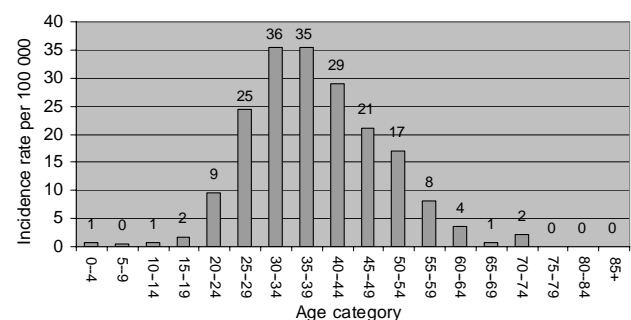


Fig. 1. Age adjusted rates of cryptococcosis observed during population-based surveillance in Gauteng, 2002–2004.

the seven academic hospitals (46%) and the regional hospitals (43%), with a smaller proportion coming from non-public centers (11%). Unemployed individuals accounted for 57% of all cases and miners for 9% of cases.

Laboratory diagnostic tests for clinical episodes of cryptococcosis

Lumbar punctures were performed on 97% of cases: 97% of the CSF specimens from these case-patients had India ink performed, 96% had CSF sent for culture, and 55% had CSF tested for cryptococcal antigen. Of the 2467 specimens tested by both culture and India ink, 2434 (99%) were culture positive, 2390 (98%) of which were also India ink positive. Of the 1377 specimens tested by both culture and cryptococcal antigen, 1349 (98%) were culture positive, 1343 (98%) of which were also cryptococcal antigen positive. Blood cultures were performed on 473 (17%) of all cases; 344 (73%) were positive. In 3% of cases, blood culture was the only culture performed and it yielded growth of cryptococci. Seven incident cases had a simultaneous finding of a negative lumbar puncture for cryptococcosis and a positive blood culture. Histological stains indicated the presence of *Cryptococcus* in eight cases; (liver and lymph node). Nine cultures other than CSF or blood yielded growth of *C. neoformans* (ascitic fluid, bone marrow, fine needle aspirate of unspecified site, synovial fluid, pericardial fluid, pleural fluid, pus, skin and sputum).

The MRU received 2570 isolates from the participating laboratories of which 1912 were viable. Fourteen non-cryptococcal cases were identified, and excluded from the database. Three *Cryptococcus albidus* and one *Cryptococcus laurentii* were identified. The CGB agar testing indicated that 46 were *C. gattii*. The Mycotic Diseases Branch of the CDC received 219 isolates from 186 cases for serotyping. Laboratory results are tabulated in Table 1.

Clinical characteristics

Almost all cases (97%) presented with signs and symptoms that warranted a diagnostic lumbar puncture, indicating the presence of meningitis. Clinical manifestations and

Table 1. Serotype distribution of 1912 cryptococci isolated during population-based surveillance in Gauteng from 2002–2004.

Designation	Number of strains
<i>Cryptococcus neoformans</i>	1862
Serotype A (<i>C. neoformans</i> var <i>grubii</i>)	143
Serotype D (<i>C. neoformans</i> var <i>neoformans</i>)	0
Serotype AD	0
Serotype not determined	1719
<i>Cryptococcus gattii</i>	46
Serotype B	19
Serotype C	22
Serotype not determined	5
Other <i>Cryptococcus</i> species	4
<i>Cryptococcus albidus</i>	3
<i>Cryptococcus laurentii</i>	1
Total number of viable isolates received	1912

Table 2. Symptoms, signs and concurrent illnesses present on admission in cases of cryptococcosis observed during population-based surveillance in Gauteng, 2002–2004.

Symptom, sign or concurrent illness	Percentage of cases
Symptoms and signs	
Headache	2147 (78%)
Neck stiffness	1900 (69%)
Fever	1514 (55%)
Nausea and vomiting	1129 (41%)
Altered mental status	853 (31%)
Seizures	248 (9%)
Coma	83 (3%)
6 th cranial nerve palsy	28 (1%)
Concurrent opportunistic infections	
Oral thrush	853 (31%)
Pulmonary tuberculosis	660 (24%)
Wasting	308 (11%)
<i>Pneumocystis pneumonia</i> (PCP)	110 (4%)
Pneumonia other than PCP	83 (3%)
Chronic diarrhoea	83 (3%)
Extrapulmonary tuberculosis	55 (2%)
No concurrent illnesses	1152 (42%)

concurrent opportunistic infections present on admission are tabulated in Table 2. None of the following non-HIV-related risk factors for cryptococcal infection were identified: rheumatologic disease, organ transplant, Hodgkins' disease, leukaemia. Nine patients presented with chronic lung disease, one of whom was HIV negative. Concurrent cryptococcal skin lesions were identified in two cases.

HIV testing and characteristics of known HIV-infected persons

An HIV test was offered to 705 cases on incident admission (some of these patients gave a history of a positive test), of whom 634 were tested. Results were available for 611 of these tested cases, of which 11 (2%) were seronegative. On incident admission, 1375 (50%) of all cases gave a history of a previous positive test for HIV infection. Among all cases, 1761 (64%) either reported a previous HIV positive test or had a positive result from this admission. The rest were discharged or died not knowing their HIV infection status.

Among those who knew their HIV status (1375), 772 (53%) had AIDS prior to this incident admission. The median CD4 cell count in all patients (HIV seropositive or negative) for whom a test result was available (20% of the group) was 37 cells/ μ l (range, 0–955). Nineteen (1%) HIV-positive patients had a CD4 count above 200 cells/ μ l on incident admission (range, 204–574; median 250). Among the 918 patients who did not have their HIV serostatus ascertained, 85 had CD4 cell counts available. Of these, five (6%) were above 200 cells/ μ l.

Treatment and outcome

Of all cases, 2460 (89%) received antifungal therapy while admitted. No antifungal therapy was given to 162 cases, of whom 59 (36%) died within 2 days of admission, and

39 (24%) were identified by blood culture alone resulting in a delayed diagnosis of cryptococcosis. Of the treated cases, 454 (18%) received amphotericin B only, 1770 (72%) received fluconazole only, and 234 (9%) received fluconazole and amphotericin B. Two case-patients received amphotericin B and another non-fluconazole drug. A total of 749 (27%) cases died during the admission. Among discharged cases 587 (32%) were treated for *Mycobacterium tuberculosis*, and 868 (47%) were prescribed trimethoprim-sulphamethoxazole. Four cases were receiving highly active antiretroviral therapy (HAART); [zidovudine/lamivudine plus efavirenz (two cases) and zidovudine/lamivudine plus indinavir (two cases)]. Mean duration of hospitalization for those cases that survived was 10 days (range, 0–373 days), and for those cases that died was 5 days (range, 0–195 days). All case-patients admitted to public hospitals were eligible for fluconazole on discharge through the free fluconazole programme, although this may not have happened in practice.

Recurrent cryptococcosis

During the period of surveillance, 263 (9.5%) incident cases were hospitalized with recurrent cryptococcosis. The median time interval from discharge for incident disease to readmission was 59 days (range, 2–440). One hundred and ninety-eight (75%) cases were re-admitted to different hospitals. Mortality during hospitalization for any subsequent episode of cryptococcosis was 25%.

Predictors of incident mortality

The multivariable model included 2424 incident cases with complete information. Deaths within 2 days of

admission numbered 178, and 529 deaths occurred after day two of admission, while 1717 patients were discharged or transferred. Table 3 lists odds ratios and 95% confidence intervals for the final multivariable model. Patients presenting with altered mental status, coma or wasting were more likely to die, both within the group that died before two calendar days of admission and within the group that died more than two calendar days after admission. Patients who were employed in the mining industry or who presented with visual changes or headache were less likely to die, both within the group that died before two calendar days and within the group that died after more than two calendar days. No particular factor could be identified that was significantly associated with death or protective for death before 2 days that was not also significantly associated with death or protective for death after 2 days. Reassuringly, receipt of any antifungal therapy was protective for death although this association was not significant for the group that died after more than 2 days.

Discussion

These results provide a comprehensive description of the epidemiology of cryptococcosis in Gauteng, and the opportunity to generate population-based data that are rarely available from African countries with high HIV prevalence. They also reveal the high mortality associated with this disease and highlight important aspects of the healthcare of HIV seropositive patients that can be improved.

Table 3. Multivariate analysis of factors associated with mortality among persons hospitalized with cryptococcosis during population-based surveillance for cryptococcosis, Gauteng province, South Africa, 2002–2004 (n = 2424).

Characteristic	Comparison: death within 2 days of admission with those who survived			Comparison: death after 2 days of admission with those who survived		
	No. died within 2 days of admission (%) n = 178	No. survived (%) n = 1717	OR ^a (95%CI) ^c	No. died beyond 2 days of admission (%) n = 529	No. survived (%) n = 1717	OR ^b (95%CI) ^c
Altered mental status at presentation	70 (39.3)	465 (27.1)	1.7 (1.2–2.4)	241 (45.6)	465 (27.1)	2.0 (1.6–2.4)
Coma at presentation	19 (10.7)	28 (1.6)	5.3 (2.7–10.5)	33 (6.2)	28 (1.6)	3.7 (2.1–6.3)
Wasting at presentation	4 (2.2)	4 (0.2)	11.8 (2.7–50.6)	6 (1.1)	4 (0.2)	4.4 (1.2–16.6)
No AFTx ^d vs. any AFTx during hospitalization	55 (30.9)	65 (3.8)	8.8 (5.7–13.5)	34 (6.4)	65 (3.8)	1.4 (0.9–2.2 ^e)
Visual changes at presentation	24 (13.5)	376 (21.9)	0.8 (0.5–1.2 ^e)	77 (14.6)	376 (21.9)	0.7 (0.5–0.9)
Headache at presentation	118 (66.3)	1483 (86.4)	0.6 (0.4–0.8)	391 (73.9)	1483 (86.4)	0.6 (0.5–0.8)
Employed in a mining job	6 (3.4)	225 (13.1)	0.4 (0.2–0.8)	20 (3.8)	225 (13.1)	0.3 (0.2–0.5)

^aOR – odds ratio, the odds of dying within 2 days of admission as compared to surviving, for those with the characteristic of interest versus those without the characteristic of interest.

^bOR – odds ratio, the odds of dying after 2 days of admission as compared to surviving, for those with the characteristic of interest versus those without the characteristic of interest.

^c95% CI, 95% confidence interval.

^dAFTx, antifungal treatment.

^eNot significant at 0.05.

The incidence of cryptococcosis in the general population of Gauteng, South Africa in this study (15/100 000 population) was greater than that reported from pre-HAART studies in countries from which population-based or national data have been published; namely the USA, (1.8–6.7/100 000 population [20,21] and France [22]. This high incidence reflects high HIV-seroprevalence in South Africa [17]. However, the incidence of cryptococcosis among Gauteng residents with AIDS (14/1000) was lower than that reported from pre-HAART USA (17–66/1000 [20]), and France (35/1000 [21]). Although we used an estimated denominator obtained from the mathematical model of the Actuarial Society of Southern Africa for the numbers of persons living with AIDS [17], we believe these rates underestimate the true incidence of cryptococcosis in Gauteng due to multiple factors: First, in the absence of an antiretroviral therapy, clinicians may not pursue a diagnosis aggressively in patients who present with 'end stage' AIDS, but choose to apply palliative or 'home-based' care [23]. Both doctors and patients may believe the prognosis of their advanced HIV condition to be very poor, and the latter may go to their traditional homes outside Gauteng where many die [23]. Second, since the overwhelming majority of patients in this study presented with meningitis, it is likely that non-meningeal presentations of cryptococcosis are missed. In the pre-HAART population-based series from the USA [20], France [21] and Northern Territory of Australia [24], larger proportions of patients with extra-meningeal presentations were described (only 60, 78 and 65% respectively presented with meningitis). Third, environmental exposure to pathogenic cryptococci in Gauteng is likely to be more frequent than in USA and France, as the rate of cryptococcosis amongst HIV-infected Gauteng children appears high, even though paediatric cryptococcosis is recognized to be uncommon [21,25,26].

Regarding laboratory diagnostics, the India ink test proved to have excellent sensitivity for cryptococcal meningitis, contrary to experience in the northern hemisphere where its sensitivity has ranged from 25–50% [27,28]. This may be a function of the late presentation of the patients, a higher central nervous system burden of organisms in a population of incident untreated cases, failure of laboratories to culture cryptococci when the India ink test is negative (the diagnosis is missed) or greater experience of laboratory technologists in this setting where cryptococcosis is relatively common.

During this surveillance, 2.6% of cases with an isolate available had infection with *C. gattii* (19/46 were serotype B, 22/46 were serotype C). This represents the largest case series of *C. gattii* infection from the African continent, and the largest case series of *C. gattii* cases in AIDS patients in the world [29–32]. These findings together with those of Litvintseva *et al.* [31] who found 24 serotype C *C. gattii* isolates amongst 176 (13.6%) clinical

strains collected in sub-Saharan Africa (Botswana and Malawi) suggest that serotype C has a wider distribution and a greater prevalence in AIDS patients than previously thought.

The high hospital mortality of cryptococcosis observed in this series (27%) may be related to the late presentation of patients for healthcare, possibly augmented by inadequate initial medical management of some cases. This is supported by our findings of high proportions of patients with coma (24%), advanced systemic illness manifested as wasting (29%), and patients who did not receive antifungal medication (36%) dying within the first 2 days of the hospital admission. Employment in the mining industry in Gauteng possibly allows for better access to medical care, leading to earlier diagnosis and better outcome of cryptococcal infection. Patients presenting with visual changes or headache were less likely to die in hospital; it is possible that these symptoms are present in early disease, facilitating early diagnosis and management. As our study was not designed to assess predictors of hospital mortality, we were unable to make valid comparisons of outcome between groups receiving amphotericin B or fluconazole. However within the first 2 days, provision of any antifungal treatment was protective against hospital death. This association was not significant for those that died in hospital after 2 days; in this antiretroviral-naïve population, a study looking at outcome after hospital discharge would be better placed to comment on efficacy of antifungal therapy.

Recently, patients with cryptococcosis who are subsequently treated with HAART were found to be at risk for immune reconstitution inflammatory syndrome (IRIS), caused by unmasking of latent cryptococcosis [33–35] or development of paradoxical reactions resembling exacerbations of the primary infection [36]. IRIS due to cryptococcosis is described as a major cause of early mortality in a South African antiretroviral programme [37] both as incident and recurrent disease in patients who commence antiretroviral therapy. Therefore, physicians treating patients with AIDS in South Africa may need to consider CSF analysis on patients with a history of cryptococcosis, or screening serum with cryptococcal antigen prior to initiation of HAART to identify patients at risk for IRIS.

Other findings from this study highlight gaps still present in the care of HIV-infected South African patients. The large proportion of patients for whom cryptococcosis was the HIV-presenting illness implies that voluntary counseling and testing programmes [6] did not reach sufficient individuals in Gauteng during the study period. Almost half of those cryptococcosis patients who knew themselves to be HIV seropositive on admission for incident cryptococcosis already had AIDS before their presentation: this group may have benefited from fluconazole primary prophylaxis, which is an evidence-based intervention [38]

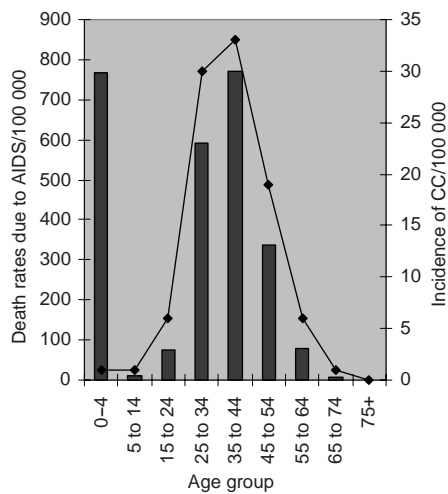


Fig. 2. Death rates attributable to HIV/AIDS in Gauteng, 2000 [4,5] and age-adjusted incidence of cryptococcosis (CC) in Gauteng, 2002–2004. Vertical bars, death rate due to AIDS; line graph, incidence of CC.

and a cost-effective approach that is used routinely in Thailand where fluconazole is available cheaply [39]. The large number of patients who died or were discharged not having been offered an HIV test or who were discharged without trimethoprim–sulphamethoxazole prophylaxis, suggests that the testing and care opportunity afforded by the admission for cryptococcosis were lost.

In South Africa neither AIDS nor HIV are notifiable conditions. Figure 2 illustrates the remarkable concordance in the adult population of the age-adjusted rates of cryptococcosis with estimated mortality due to AIDS during the same period. Cryptococcosis, as an opportunistic infection in HIV/AIDS, is preventable as witnessed by the enormous decline in rates amongst AIDS patients in the post-HAART era [40–42]. A decline in cryptococcosis rates in South Africa in years to come may imply a decreased mortality due to AIDS. National surveillance for cryptococcosis in South Africa was started in January 2005 by the Group for Enteric, Respiratory and Meningitis pathogens of South Africa (GERMS-SA) and will provide an objective assessment of the impact of antiretroviral therapy on AIDS in South Africa. The results of these and surveillance activities for other opportunistic infections may guide development of more adequate prevention strategies resulting in improved quality of life of HIV-infected persons.

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References

- UNAIDS. Factsheet on Sub-Saharan Africa. www.unaids.org. Accessed October 2005.
- Department of Health. *Summary report: national HIV and syphilis antenatal seroprevalence survey in South Africa 1990*. Pretoria, South Africa: Directorate Health Systems Research, Research Co-ordination and Epidemiology, Department of Health 1991.
- Department of Health. *Summary report: national HIV and syphilis antenatal seroprevalence survey in South Africa 2002*. Pretoria, South Africa: Directorate Health Systems Research, Research Co-ordination and Epidemiology, Department of Health 2003.
- Bradshaw D, Nannan N, Laubscher R, Groenewald P, Joubert J, Nojiliana B, *et al.* *South African National Burden of Disease Study 2000; Estimates of provincial mortality*. Cape Town: Burden of Disease Research Unit, Medical Research Council and Actuarial Society of Southern Africa. 2005.
- Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojiliana B, Norman R, *et al.* **Initial burden of disease estimates for South Africa, 2000.** *S Afr Med J* 2003; **93**:682–688.
- Department of Health. *Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa*. Pretoria South Africa: Department of Health; November 2003.
- Department of Health. *Monitoring Review: Progress Report on the Implementation of the Comprehensive HIV and AIDS Care, Management and Treatment Programme*. September 2004. Health Information, Evaluation and Research Cluster, Department of Health 2004. www.doh.gov.za. Accessed on 07 September 2006.
- World Health Organization. *Global tuberculosis control: surveillance, planning, financing*. Geneva: World Health Organization; 2005, Report no. WHO/HTM/TB/2005.349.
- Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson K. **Clinical presentation and risk behaviours of patients with acquired immunodeficiency syndrome in Thailand, 1994–1998: Regional variation and temporal trends.** *Clin Infect Dis* 2001; **32**:955–962.
- French N, Gray K, Watera C, Nakiyingi J, Lugada E, Moore M, *et al.* **Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults.** *AIDS* 2002; **16**:1031–1038.
- Corbett EL, Churcyard GJ, Charalambos S, Samb B, Moloi V, Clayton TC, *et al.* **Morbidity and mortality in South African gold miners: impact of untreated disease due to human immunodeficiency virus.** *Clin Infect Dis* 2002; **34**: 1251–1258.
- Bogaerts J, Roubroy D, Taelman H, Kagame A, Aziz MA, Swinne D, *et al.* **AIDS-associated cryptococcal meningitis in Rwanda (1983–1992): epidemiologic and diagnostic features.** *J Infect* 1999; **39**:32–37.
- Heyderman RS, Gangaidzo IT, Hakim JG, Mielke J, Taziwa A, Musvaire P, *et al.* **Cryptococcal meningitis in human immunodeficiency virus-infected patients in Harare, Zimbabwe.** *Clin Infect Dis* 1998; **26**:284–249.
- Moosa MYS, Coovadia YM. **Cryptococcal meningitis in Durban, South Africa: a comparison of clinical features, laboratory findings and outcome for human immunodeficiency virus (HIV)-positive and HIV-negative patients.** *Clin Infect Dis* 1997; **24**:131–134.
- Bergemann A, Karstaedt AS. **The spectrum of meningitis in a population with high prevalence of HIV disease.** *QJ Med* 1996; **89**:499–504.
- Statistics South Africa. *Census in brief/Statistics South Africa*. Pretoria: Statistics South Africa; 2003. www.statssa.gov.za. Accessed on 07 September 2006.
- Dorrington R, Bradshaw D, Budlenders. *HIV/AIDS profile of the provinces of RSA – indicators for 2002*. Cape Town: Centre for Actuarial Research, Medical Research Council and Actuarial Society of Southern Africa; 2002.

18. Wertheimer AI, Santella TM, Lauver HJ. **Successful public/private donation programmes: A review of the Diflucan Partnership Program in South Africa.** *J Int Assoc Physicians AIDS Care* 2004; **3**:74–79.
19. Centers for Disease Control and Prevention. **1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *MMWR (Morb Mortal Wkl Rep)* 1992; **41**(RR-17):1–19.
20. Hajjeh RA, Conn LA, Stephone DS, Baughman W, Hamill R, Graviss E, *et al.* **Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons.** *J Infect Dis* 1999; **179**:449–454.
21. Friedman GD, Jeffrey Fessel W, Udaltsova NV, Hurley LB. **Cryptococcosis: the 1981–2000 epidemic.** *Mycoses* 2005; **48**:122–125.
22. Dromer F, Mathoulin S, Dupont B, Laporte A. **Epidemiology of cryptococcosis in France: a 9-year survey (1985–1993) French Cryptococcosis Study Group.** *Clin Infect Dis* 1996; **23**:82–90.
23. Uys RL. **Aspects of the care of people with HIV/AIDS in South Africa.** *Public Health Nurs* 2003; **20**:271–280.
24. Fisher D, Lo D, Burrow J, Currie B. **Cryptococcus neoformans in tropical northern Australia; predominantly variant gattii with good outcomes.** *Aust NZ J Med* 1993; **23**:678–682.
25. Likasitwattanakul S, Poneprasert B, Sirisanthana V. **Cryptococcosis in HIV-infected children.** *Southeast Asian J Trop Med Public Health* 2004; **35**:935–939.
26. Gumbo T, Kadzirange G, Mielke J, Gangaidzo IT, Hakim JG. **Cryptococcus neoformans meningoencephalitis in African children with acquired immunodeficiency syndrome.** *Pediatr Infect Dis J* 2002; **21**:54–56.
27. Chuck S, Sande MA. **Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome.** *N Engl J Med* 1989; **321**:794–799.
28. Clark RA, Greer D, Atkinson W, Valanis GT, Hyslop N. **Spectrum of Cryptococcus neoformans infection in 68 patients infected with human immunodeficiency virus.** *Rev Infect Dis* 1990; **12**:768–777.
29. Bennett JE, Kwon-Chung KJ, Howard DH. **Epidemiologic differences among serotypes of Cryptococcus neoformans.** *Am J Epidemiol* 1997; **105**:582–586.
30. Sorrell TC. **Cryptococcus neoformans variety gattii.** *Med Mycol* 2001; **39**:155–168.
31. Litvintseva A, Thakur R, Reller B, Mitchell G. **Prevalence of clinical isolates of Cryptococcus gattii serotype C among patients with AIDS in Sub-Saharan Africa.** *J Infect Dis* 2005; **192**:888–892.
32. Karstaedt AS, Crewe-Brown HH, Dromer F. **Cryptococcal meningitis caused by Cryptococcus neoformans var gattii, serotype C, in AIDS patients in Soweto, South Africa.** *Med Mycol* 2002; **40**:7–11.
33. Shelburne SA III, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL. **Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy.** *Medicine* 2002; **81**:213–227.
34. Woods ML, MacGinley R, Eisen DP, Allworth AM. **HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection.** *AIDS* 1998; **12**:1491–1494.
35. King MD, Perlino CA, Cinnamon J, Jernigan JA. **Paradoxical recurrent meningitis following therapy of cryptococcal meningitis: an immune reconstitution syndrome after initiation of highly active antiretroviral therapy.** *Int J STD AIDS* 2002; **13**:724–726.
36. Lortholary O, Fontanet A, Memain N, Martin A, Sitbon K, Dromer F, French Cryptococcosis Study Group. **Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France.** *AIDS* 2005; **19**:1043–1049.
37. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. **Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme [Letter].** *AIDS* 2005; **19**:2050–2051.
38. Chang L, Phipps W, Kennedy G, Rutherford G. **Antifungal interventions for the primary prevention of cryptococcal disease in adults with HIV.** *Cochrane Database Syst Rev* 2005; **20**:CD004773.
39. Tuli K, Clark T, Ningsanond P, Morgan J, Laosiritawor Y, Kongsin S, *et al.* **Primary prophylaxis against systemic fungal infections among persons living with AIDS in Thailand: a cost-effectiveness analysis.** *Tenth Conference on Retrovirus and Opportunistic Infections*, Boston, February 2003 [abstract # 795].
40. Mirza SA, Phelan M, Rimland D, Graviss E, Hamill R, Brandt ME, *et al.* **The changing epidemiology of cryptococcosis: and update from population-based active surveillance in 2 large metropolitan areas.** *Clin Infect Dis* 2003; **36**:789–794.
41. Sacktor N, Lyles RH, Skolasky R, Kleeberger C, Selnes OA, Miller EN, *et al.*, Multicenter AIDS Cohort Study. **HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998.** *Neurology* 2001; **56**:257–260.
42. Dromer F, Matholin Pelissier, Fontanet A, Ronin O, Dupont B, Lortholary O; French Cryptococcosis Study Group. **Epidemiology of HIV-associated cryptococcosis in France (1985–2001): comparison of the pre- and post-HAART eras.** *AIDS* 2004; **18**:555–562.

Appendix

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