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Outcomes of cryptococcal meningitis in antiretroviral naïve and experienced patients in South Africa

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Cryptococcal meningitis (CM) is a major cause of mortality in HIV-infected patients in much of the world, causing an estimated 504,000 deaths annually in sub-Saharan Africa alone (1). Despite rapid scale-up of antiretroviral therapy (ART) coverage in South Africa, the burden of CM is still high, because ART coverage is barely keeping pace with the number of new HIV-infected patients developing stage IV disease (2). As access to ART expands, increasing numbers of patients are presenting with CM after initiating ART, and CM has emerged as a major cause of morbidity and mortality in African ART programmes (3). Little data is available regarding the presentation and clinical features of CM in patients on ART, and evidence is conflicting on whether short-term outcomes are better in those already on ART at presentation when compared to ART-naïve patients (4-6). We therefore examined these issues in a cohort of patients presenting with CM in Cape Town.

The study was performed at GF Jooste Hospital, a public-sector adult referral hospital serving a population of 1.3 million. *Cryptococcus* is the commonest cause of meningitis at the hospital, accounting for 63% of microbiologically confirmed cases (7). All patients presenting with laboratory confirmed CM between 1st January 2007 and 31st December 2008 were prospectively identified, and clinical and laboratory data were collected with approval from the Research Ethics Committee of the University of Cape Town. Patients were classified according to whether they were taking ART at initial presentation, and the primary end-point of in-hospital mortality was recorded for all patients.

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Author's contributions

JNJ conceptualized and designed the study, collected and analyzed the data and drafted the manuscript. GM and TSH provided critical input and helped redraft the manuscript into its final form.

During the study period the initial treatment of CM consisted of two weeks of induction therapy with amphotericin B (1mg/kg), followed by fluconazole 400mg daily for 8 weeks. As part of ongoing clinical studies 71 patients received additional induction treatment, all of whom were ART naïve (61 received flucytosine, 39 received IFN γ , and 8 received fluconazole, all with amphotericin B). Statistical comparisons were made using the Kruskal-Wallis, χ^2 or Fisher's exact tests. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression modeling adjusting for potential confounders (variables were included in the logistic regression model if they were significantly associated with the primary outcome in bivariate analysis ($p < 0.05$) or if they were deemed clinically relevant based on previous reports).

During the 2-year period there were 301 episodes of CM, of which 69 were relapses (described in detail elsewhere (8)), and 2 were in HIV-negative patients, leaving 230 HIV-positive patients admitted with a first episode of CM. ART status was unknown in 2 patients, who were excluded from the analysis. Of the remainder, 80% (183) were ART-naïve and 20% (45) were on ART at presentation. Median time from ART initiation to presentation with CM was 41 days (IQR 18-87). Demographic and clinical features were similar in ART-naïve and experienced patients, as were CSF cell counts and biochemistry (table 1). ART-experienced patients had lower fungal burdens, as evidenced by the lower proportion of India-ink positivity (56% vs 72%, $p = 0.03$), and fewer had abnormal mental status (31% vs 47%, $p = 0.05$). Median duration of hospitalization was 15 days (IQR 13-20 days). In-hospital mortality was 29% in ART-experienced patients, versus 31% in ART-naïve patients ($p = 0.77$), with a median time to death of 10 and 13 days respectively. In a multivariate model including the previously identified potential confounders (6) of sex and concurrent TB treatment, along with adjustment for factors significantly associated with the primary outcome in bivariate analysis (administration of a second agent during induction therapy, OR 0.49, 95%CI 0.3-0.9, $p = 0.03$) the relationship between ART status and in-hospital mortality remained non-significant (OR 0.69, 95%CI 0.3-1.5, $p = 0.3$).

A large proportion (20%) of adults with a first episode of HIV-associated CM in our setting are now presenting following ART initiation. Although these patients had favourable prognostic signs (9), with lower fungal burdens and less abnormal neurology, the outcomes were poor; no better than in ART-naïve patients in both direct and multivariate comparisons. These results differ from a smaller series of 92 patients from Botswana (6), where although there was no significant difference in acute mortality between ART-experienced ($n = 26$) and naïve patients with CM in a direct comparison (8% vs 21%, $p = 0.2$), adjusted multivariate analysis suggested improved in-hospital outcomes (6). In contrast, our results are in keeping with data reported in a previous small series from our hospital (5), which found no difference in acute (10 week) mortality in ART-experienced versus ART-naïve with CM (33% vs 38%, $p = 0.8$), or in rates of clearance of *Cryptococcus* from the CSF in the two groups. However, mortality at 1 year was significantly lower in the ART-experienced group (41% versus 76% $p = 0.03$), suggesting that while ART may not affect outcomes from CM in the acute setting, it leads to a substantial reduction in mortality by rapidly reducing susceptibility to other opportunistic infections (5). This is supported by data from a study comparing outcomes of CM in the pre- and post-ART eras in France (4). Although acute mortality remained unchanged following introduction of ART (18% vs 21%), long-term outcomes were markedly improved.

It has been suggested that patients developing CM shortly after ART initiation may develop a more inflammatory “unmasking” disease phenotype as cellular immune function is restored; a form of the immune reconstitution inflammatory syndrome (IRIS) (10). While there was evidence that the ART-experienced patients did have lower fungal burdens at presentation, and CM occurred shortly following ART initiation in most cases, few other

differences in either clinical or laboratory findings were noted to support this, and there was no evidence of increased CSF cellularity. Further immunological and pathological studies are needed to understand the causes of high mortality in this group, which is in contrast to patients who develop a relapse, or “paradoxical”, CM-IRIS, who tend to have higher CD4 cell counts, less severe disease, and a lower in-patient mortality of 13% (8).

The proportion of patients presenting with CM following ART initiation is likely to increase as the global ART roll-out continues. Our data shows that these patients present with severe disease, and have a high acute mortality. This highlights the importance of ongoing efforts to develop and implement preventative strategies. The majority of these cases present within the first few months following ART initiation, and could potentially be prevented through cryptococcal antigen screening at ART initiation with pre-emptive therapy for those testing antigen positive (11).

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Table 1

Demographic, clinical and laboratory features and outcomes of cryptococcal meningitis in 228 ART-naïve and –experienced patients with cryptococcal meningitis.

| | ART naïve (183) | On ART (45) | <i>p</i> -value |
|-------------------------------------|-----------------|---------------|-----------------|
| Sex (% (<i>n</i>) male) | 51% (94) | 42% (19) | 0.27 |
| Age (years) | 34 (29-41) | 33 (28-39) | 0.23 |
| History of TB | 73% (126) | 83% (34) | 0.18 |
| On TB treatment | 44% (78) | 61% (25) | 0.05 |
| Headache | 94% (171) | 98% (40) | 0.41 |
| Cough | 31% (48) | 24% (8) | 0.40 |
| Abnormal mental status | 47% (86) | 31% (14) | 0.05 |
| Symptom duration (days) | 7 (5-21) | 6 (4-14) | 0.04 |
| Time ART-CM (days) | ----- | 41 (18-87) | ----- |
| CD4 cell count* (cells/ μ L) | 36 (17-82) | 38 (18-78) | 0.87 |
| CSF lymphocytes ($\times 10^6$ /L) | 19 (2-102) | 23 (6-74) | 0.94 |
| CSF neutrophils ($\times 10^6$ /L) | 0 (0-4) | 0 (0-3) | 0.31 |
| CSF protein (g/dL) | 1.0 (0.6-1.9) | 1.0 (0.6-1.8) | 0.98 |
| CSF glucose (mmol/L) | 2.1 (1.3-2.7) | 1.6 (1.2-2.7) | 0.14 |
| India-Ink positive [†] | 72% (130) | 56% (25) | 0.03 |
| Culture positive | 88% (161) | 78% (35) | 0.08 |
| In hospital mortality | 31% (57) | 29% (13) | 0.77 |
| Time to death (days) | 13(3-40) | 10 (2-32) | 0.74 |

All figures are medians (IQRs) unless marked otherwise.

* CD4 cell counts at time of presentation with cryptococcal meningitis.

[†] note: cryptococcal antigen (CRAG) tests and titres were only performed in patients with a negative India-ink test, hence cannot be used to reflect fungal burdens in the cohort, and are therefore not presented.