



High Prevalence of CNS Dissemination With Asymptomatic Cryptococcal Antigenemia

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Background

- Screening for serum cryptococcal antigenemia (sCrAg) among individuals with advanced HIV may reduce associated morbidity and mortality
- In 2011, WHO issued a conditional recommendation for sCrAg screening among ART-naïve adults with CD4<100 cells/ μ l and pre-emptive treatment with high dose fluconazole
- There is limited evidence to guide management of asymptomatic sCrAg+ and the impact of screening programs on morbidity and mortality is not well understood

Methods

We conducted an implementation science study at 20 outpatient HIV clinics in Harare, Zimbabwe. We enrolled HIV-infected participants who were >18 years of age with CD4 \leq 100 from April 2015—June 2016.

- Participants were excluded for signs/symptoms of meningitis or a recent diagnosis of CM and those enrolled were screened for sCrAg using a lateral flow assay (LFA)
- Those sCrAg negative were immediately initiated on ART or switched from a failing regimen
- Those sCrAg+ were offered a lumbar puncture (LP) and those with CNS disease received Amphotericin B with high dose fluconazole
- sCrAg+ participants who declined LP and those who were CSF CrAg negative received high dose fluconazole per WHO recommendation and initiated ART 4 weeks later
- All participants were screened for TB with symptom screen and referred for work-up if indicated
- Participant follow-up to 1 year is underway to determine all-cause mortality

Results

- Of 1598 screened, we enrolled 1336 asymptomatic participants with CD4 \leq 100 (Figure 1.)
- The seroprevalence of sCrAg was 9.9% and the median sCrAg titer was 1:20 (IQR 1:5; 1:160)
- There was no significant difference in baseline characteristics between sCrAg+ and sCrAg- participants
- Among those sCrAg+, 50.6% agreed to LP, and among these 19.4% were CSF CrAg+
- All-cause mortality to date is 8.9% (Figure 2) and death occurred in the health care facility in 73.1% of participant deaths
- Mortality among the sCrAg+ and sCrAg- groups was 17.4% and 8.0%, respectively (p=0.0003)
- A positive sCrAg was associated with a two-fold increased risk of death (OR 2.52 (95%CI 1.5-4.1), p<0.0001).

Figure 1. Prevalence of sCrAg among HIV-infected patients with CD4 \leq 100 and prevalence of CSF CrAg among those who accepted LP

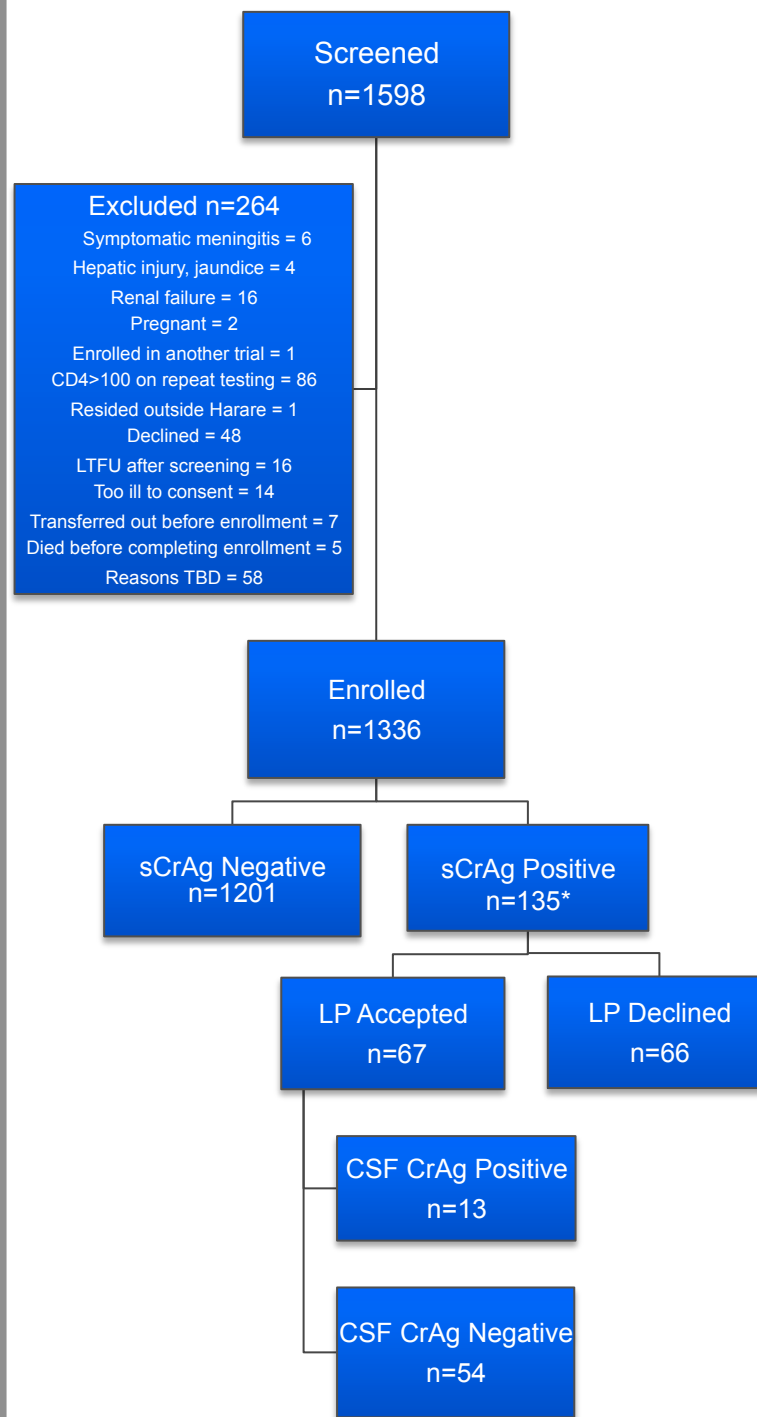
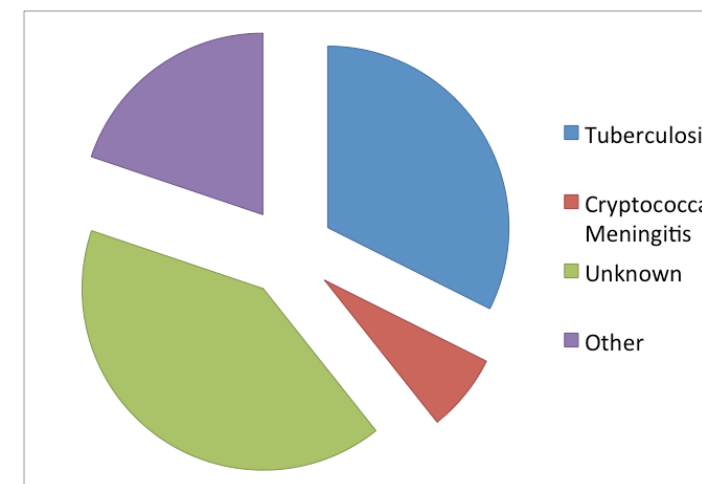


Table 1. Characteristics of HIV-infected participants with CD4 \leq 100 enrolled at 20 HIV outpatient clinics Harare, Zimbabwe, April 2015-June 2016

| | Overall (n=1336) | sCrAg + (n=135) | sCrAg - (n=1201) | P value |
|------------------------------|-------------------|-------------------|-------------------|---------|
| Age, n (range) | 37 (31, 43) | 38 (33, 43) | 37 (31, 43) | |
| Male n (%) | 752 (56.6%) | 80 (60.6%) | 672 (56.2%) | 0.33 |
| CD4 count (median, IQR) | 32 (14, 56) | 28 (12, 48) | 32 (14, 57) | 0.10 |
| HIV VL (n=191) (log cp/ml) | 5.42 (5.1, 5.77) | 5.3 (5.0, 5.8) | 5.4 (5.1, 5.8) | 0.25 |
| On ART at enrollment n (%) | 138 (10.4%) | 14 (10.6%) | 124 (10.3%) | 0.94 |
| Months on ART (median (IQR)) | 47.7 (26.4, 63.2) | 47.7 (27.9, 63.5) | 48.1 (17.1, 56.5) | 0.75 |
| \geq 2 TB Symptoms* n (%) | 289 (21.9%) | 266 (22.3%) | 24 (18.1%) | 0.30 |

*TB symptoms – fever, cough, night sweats, weight loss, Data represents files with complete data at time of analysis, and do not represent the complete sample size

Figure 2. All-cause mortality to date



Results (Cont)

- LP was declined by 49.5% of sCrAg+ participants; the most common reason cited was concern for death
- Mortality was higher in the CSF CrAg+ compared with the CSF CrAg- (30.8% and 13% respectively, p=0.12).
- Mortality was similar in those who accepted and those who declined LP (16.4% vs 18.1%, p=0.79).
- Individuals who had 2 or more symptoms of TB at enrollment were at increased risk of death (OR 2.48 (95%CI 1.7-3.7), p<0.0001).
- Tuberculosis was the cause of death in 35.3%, cryptococcal disease 7.6%. Cause of death was unknown in 41%.

Conclusions

- The seroprevalence of sCrAg among asymptomatic PLHIV with advanced disease was high at 9.9%
- Cryptococcal antigenemia is associated with elevated risk of death
- Cryptococcal antigenemia and 2 or more symptoms concerning for TB were both associated with a two-fold increased risk of death among severely immunosuppressed PLHIV with CD<100
- The prevalence of CNS dissemination among asymptomatic sCrAg+ individuals is high.
- Lumbar puncture may be warranted to guide management however we did not observe a mortality benefit to lumbar puncture in asymptomatic individuals who are sCrAg+ in this cohort

Limitations

- Study is ongoing with ongoing data collection and patient follow-up
- Implementation Science research implemented within the context of routine clinical care.

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