Improving Diagnosis of Central Nervous System Infections in High HIV-Prevalence Africa Settings

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James Milburn[1,2], Taddy Mwarumba[3], Rachita Suresh[1], Kebatshabile Ngoni[1], George Manenji[4], Ronan Doyle[2], Kathy Boyd[2], Lenon Gwaunza[3], Tiny Mazhani[5], Katharina Kranzer[1,6], Madisa Mine[7], Margaret Mokomane[5], Gift Ngwende[3], Chiratidzo Ndhlovu[3] and Joseph Jarvis[1,2]

[1]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana [2]London School of Hygiene and Tropical Medicine, London, UK [3]University of Zimbabwe, Harare, Zimbabwe [4]Parirenyatwa Hospital, Harare, Zimbabwe [5]University of Botswana, Gaborone, Botswana [6]Biomedical Research and Training Institute, Harare, Zimbabwe [7]National Health Laboratory, Gaborone, Botswana

BACKGROUND

- Central nervous system infections (CNSI) account for approximately 30% of early mortality in ART programmes.
- The epidemiology of CNSI in high-HIV prevalence African settings is poorly understood making presumptive diagnosis and empiric treatment challenging.
- Patients with CNSI who do not receive a diagnosis have mortality rates of up to 40% at 10 weeks indicating the presence of serious underlying pathology that needs appropriate diagnosis to guide effective treatment[1].

METHODS

- Enhanced diagnostic packages were introduced into routine CSF analysis at Princess Marina Hospital, Gaborone, Botswana in June 2021 and Parirenyatwa Hospital, Harare, Zimbabwe in October 2022.
- BioFIRE FilmArray-Meningitis/Encephalitis (FilmArray-ME) & Xpert MTB/RIF Ultra were performed on all samples with sufficient CSF volume and results returned to clinicians in real-time.
- Retrospective analysis was performed on stored samples sufficient CSF with *Toxoplasma gondii* PCR, rapid plasma reagin, *Treponema pallidum* particle agglutination assay and metagenomic sequencing.

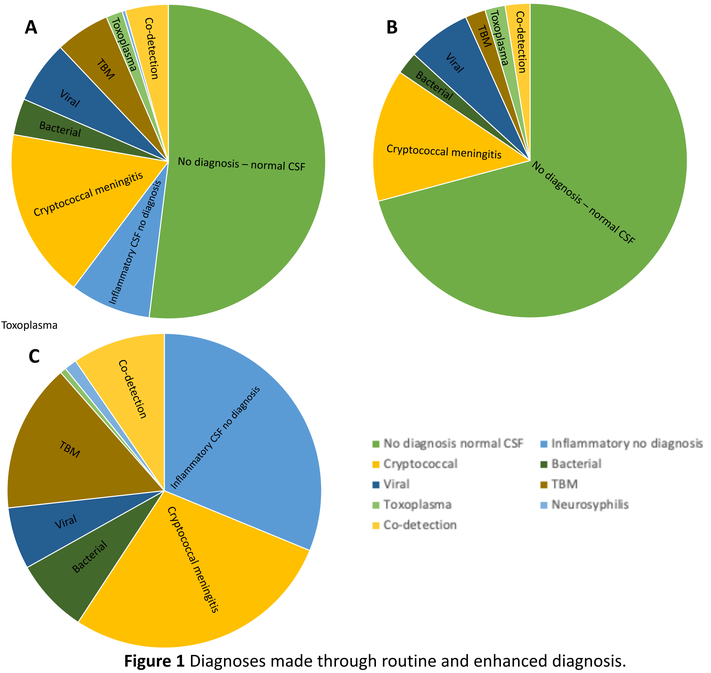


Figure 1 Diagnoses made through routine and enhanced diagnosis.
(A) All adults (B) Uninflammatory CSF and (C) Inflammatory CSF. Inflammatory CSF defined as CSF WCC >5 or CSF protein >1mg/mL and CSF glucose<2.2mmol/mL

The introduction of enhanced diagnostics packages in Botswana and Zimbabwe increased the diagnostic yield from 21.5% (126/586) to 39.4% (231/586)

Cryptococcal meningitis remains the most commonly diagnosed CNSI 51.1% (118/231) of all diagnoses

Relative increase in diagnostic yield with addition of enhanced diagnostics varied by patient group; 45.4% increase overall and 566.7% in CrAg negative CSF samples

Enhanced diagnostics decreased the proportion of patients with inflammatory and no diagnosis from 62.2% to 31.4%

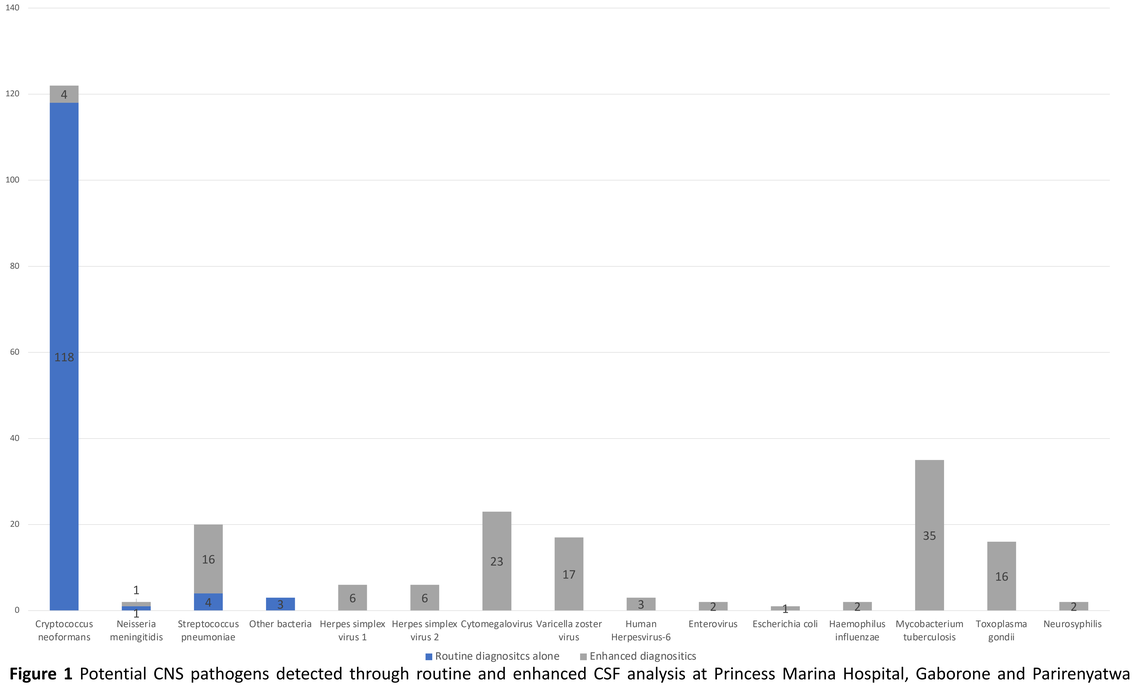


Figure 1 Potential CNS pathogens detected through routine and enhanced CSF analysis at Princess Marina Hospital, Gaborone and Parirenyatwa Hospital, Harare.

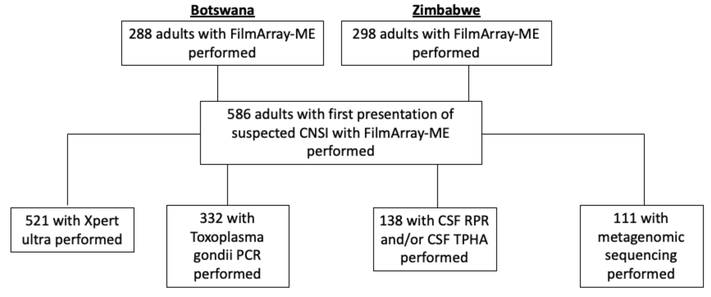


Figure 3 Inclusion and analysis populations

RESULTS

- The median age of study participants was 41 (IQR 35-48), 53.3% were male, and the median CD4 count was 107 cells/µL (IQR 40-262)
- 45.9% (269/586) were established on ART the remainder were either ART naïve or had cycled out of treatment services
- Through routine CSF analysis alone there were 126 microbiologically confirmed CNSIs, 93.7% (118/126) were cryptococcal meningitis and 90.6% (107/118) of cryptococcal meningitis cases were diagnosed using cryptococcal antigen (CrAg) testing
- The addition of enhanced diagnostics increased the total number of diagnoses to 231, a relative increase of 45.4%.
- Restricting analysis to CrAg negative patients, 18 CNSI diagnoses were made through routine analysis compared to 120 diagnoses made with the addition of enhanced diagnostics, a relative increase of 566.7%.
- After conventional analysis 62.2% (97/156) of patients with inflammatory CSF did not have a diagnosis with the addition of enhanced diagnostics 31.4% (49/156) of patients with inflammatory CSF did not have a diagnosis
- Metagenomic sequencing was performed on 111 CSF samples, sequencing detected an additional 54 organisms in 42/111 patients, however the clinical relevance of some organisms are uncertain.

CONCLUSIONS

- Enhanced diagnostic platforms substantially increased diagnostic yield in patients with suspected CNSI in Botswana and Zimbabwe.
- There was significant variation between population groups suggesting targeted use may be possible. The most clinically and cost-effective diagnostic algorithms need to be defined.

REFERENCES

1. Tenforde, M. W. *et al.* Mortality in adult patients with culture-positive and culture-negative meningitis in the Botswana national meningitis survey: a prevalent cohort study. *Lancet Infect Dis* **19**, 740–749 (2019).