
# USE OF FLUCONAZOLE IN MANAGING CRYPTOCOCCAL MENINGITIS IN THE PEOPLE LIVING WITH HIV: COULD AFRICA'S MAIN ANTIFUNGAL BE LOSING ITS EFFICACY?

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## BACKGROUND

Cryptococcal Meningitis (CM) is a common manifestation of cryptococcosis caused by *Cryptococcus. spp.* CM is among the most common perilous opportunistic infections among people living with HIV. Cryptococcosis accounts for 15% of all HIV-related deaths worldwide with the highest prevalence in sub-Saharan Africa. The most common features of CM include elevated intracranial pressure, which may cause seizures, the onset of headache, confusion, altered consciousness, lethargy and sometimes fever as common symptoms in HIV-infected patients *(Guery et al., 2019).*

A stiff neck, the classical feature of meningitis, has only been reported in 20% of patients (*Mwaba et al., 2001).* The introduction of highly active antiretroviral therapy (HAART), especially when initiated early following HIV infection, has reduced AIDS-related deaths by more than 51% *(Lundgren et al., 2018; UNAIDS, 2015).* However, deaths from HIV-related Cryptococcal Meningitis (CM) remain high in excess of 50% *(Shroufi et al., 2021).*

The recommended induction treatment for CM involves a combination of amphotericin B and flucytosine for 1 week, followed by fluconazole for consolidation and maintenance treatment *(Perfect et al., 2010).* However, in resource-limited settings, such as Africa, fluconazole induction monotherapy is widely used. Fluconazole remains the mainstay therapy worldwide among HIV patients before and during antiretroviral treatment due to its safety and oral bioavailability *(Hope et al., 2019).*

## STUDY OBJECTIVE

The main objective of this study was to identify single nucleotide sequence polymorphisms in the coding region of the clinical isolates of *C. neoformans* SPP. *ERG11* gene and relate these to the fluconazole susceptibility patterns of these isolates taken from HIV infected patients in Uganda.

## METHOD

310 *C. neoformans* clinical Isolates obtained from celebral spinal fluid of HIV positive patients with CM Makerere University

Samples stored at -80°c in 20% glycerol Dept of Medical Microbiology, Makerere University

5 Fluconazole half-maximal inhibitory concentrations measured (IC50 range 0.25-32 µg/mL)
University of Minnesota

40 Clinical isolates of *C. neoformans* cultured for DNA extraction and amplification and sequencing of coding 600bp *ERG11* gene
University of Minnesota

Atim Priscilla as a laboratory investigator of the study

## FINDINGS

This paper describes important datasets that show the reducing efficacy of fluconazole, based on laboratory experiments that exposed different doses of the drug to 310 clinical isolates recovered from cerebrospinal fluid of patients infected with HIV and cryptococal meningitis in Uganda. Fluconazole IC50 is the half-maximal inhibitory concentration of the antifungal that is needed to inhibit isolate growth by half; a measure of the drug's efficacy in pharmacological research.

### Reduced efficacy of Flucanozole observed in vitro

From laboratory analyses of 310 clinical samples, recovered in patients with HIV and CM, exposed to different doses of fluconazole

### Polymorphisms in the Fluconazole target gene exist

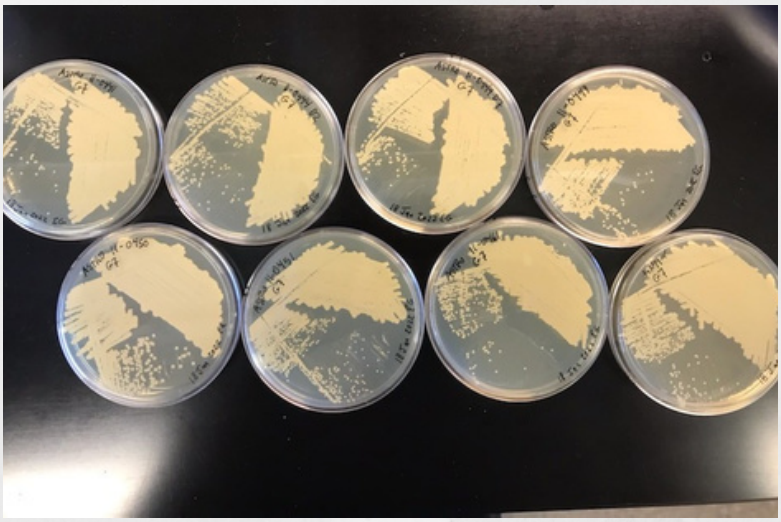
Single Nucleotide Polymorphisms (SNPs) in the *ERG11* gene observed. The gene encodes cytochrome P450 14α-demethylase, a fluconazole target.

### High frequency of CM clinical isolates with high Fluconazole IC50 (43.9%) observed

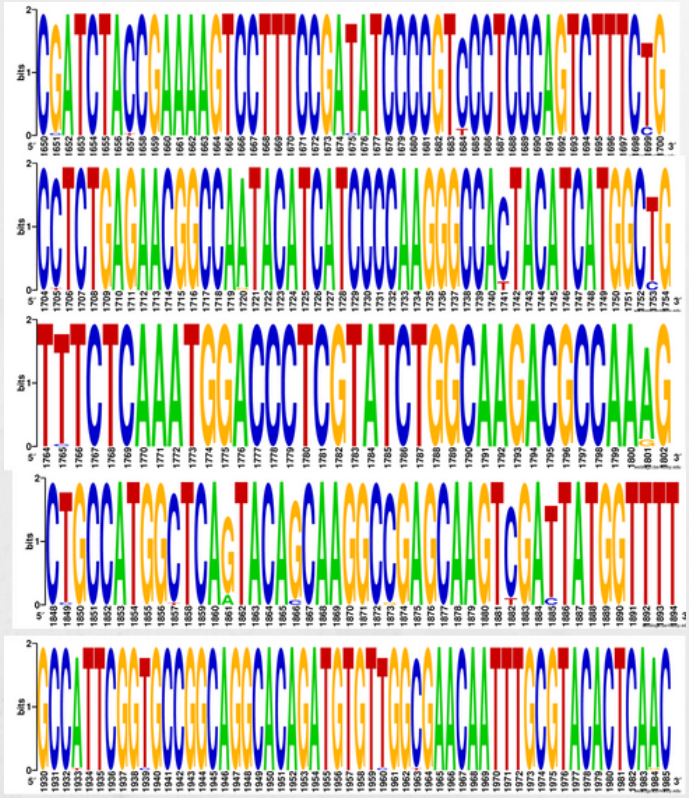
The study demonstrated high fluconazole $IC_{50}$ values that are associated with poor clinical outcomes

### Polymorphisms associated with efficacy of fluconazole.

The SNPs observed were not the main cause of the high fluconazole $IC_{50}$ observed in these isolates.



Cultures of *C.neoformans* clinical isolates.



Sequence logo showing SNPs within the *C.neorformans ERG11* gene

## RECOMMENDATIONS

Larger studies involving more clinical isolates and genome-wide association studies on these isolates is needed to investigate the genetic variations within the high and low fluconazole $IC_{50}$ isolates.

Development of new non-azole drugs as well as combination therapy approaches that utilize drugs with different modes of action in the management of CM should be considered.

There is urgent need for wider access to drugs like flucytosine and liposomal Amphotericin B in many African countries as the recommended regimens for induction therapy over fluconazole monotherapy.

Atim PB, Meya DB, Gerlach ES, Muhanguzi D, Male A, Kanamwanji B, Nielsen K. Lack of Association between Fluconazole Susceptibility and *ERG11* Nucleotide Polymorphisms in *Cryptococcus neoformans* Clinical Isolates from Uganda. *Journal of Fungi*. 2022; 8(5):508. https://doi.org/10.3390/jof8050508

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