



Southern African HIV Clinicians Society
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Statement from the SA HIV Clinicians' Society

Thursday, 15 March 2018

Five points on 5-FC (flucytosine) for cryptococcal meningitis

Cryptococcal meningitis (CM) accounts for 15%-20% of all AIDS-related deaths resulting in over 100,000 deaths per year in sub-Saharan Africa. Mortality at 3 months among persons living with HIV (PLHIV) is estimated to be 70%. Although there has been a decline in the incidence of CM in South Africa (SA), almost half of PLHIV with CM are now antiretroviral treatment (ART)-experienced and an unchanged proportion of patients (approximately one third) die in hospital (<http://www.croiconference.org/sessions/declining-incidence-hiv-associated-cryptococcosis-south-africa-2005-2015>). Access to 5FC is key to tackling the significant mortality of HIV-associated CM in SA.

- 1) Adding 5-FC to an amphotericin B-containing treatment regimen reduces mortality associated with CM
 - The Advancing Cryptococcal Treatment for Africa (ACTA) trial was the largest clinical trial ever of treatment for CM. The ground-breaking results of this trial are published in the New England Journal of Medicine today (www.nejm.org)
 - The ACTA trial demonstrated that 5-FC was unequivocally superior to fluconazole (FLUC) as the companion drug with amphotericin B (AmB) in the induction phase, resulting in improved survival of patients
 - The combination of 1 week AmB + 5-FC was superior to all other treatments tested (including 2 weeks of AmB + 5-FC) in terms of survival at 10 weeks on treatment
 - New WHO guidelines for CM now recommend 1 week AmB + 5-FC as the preferred induction-treatment regimen (<http://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/>)
- 2) Adding 5-FC to amphotericin B shortens the induction-treatment regimen to 1 week
 - SA guidelines currently recommend that PLHIV with CM be given 2 weeks of AmB and FLUC as the induction-treatment regimen
 - Having 5FC available would not only improve patient outcomes, but allow for the average hospital admission duration for CM to be shortened from 2 weeks to 1 week with advantages to the health system
 - In the absence of 5-FC, clinicians should not reduce the duration of induction-phase AmB and FLUC from 2 weeks to 1 week
- 3) 5-FC is not registered in SA and is therefore not listed as an essential medicine at hospital-level or included in SA guidelines for CM

- SA clinicians can currently obtain 5-FC through a Section 21 application (<http://www.mccza.com/Publications/Index/8>)
- 4) 5-FC can be safely administered by the oral or nasogastric route without therapeutic drug monitoring among PLHIV with CM
 - There were concerns about the safety of 5FC but these relate to historical data where the 5-FC dose was higher and 5-FC was given for >2 weeks or in other patient groups (such as premature infants or critically-ill patients in renal failure).
- 5) We urgently need 5-FC given that over 6000 cases of CM are diagnosed in SA each year (www.nicd.ac.za)
 - 5-FC is an old, off-patent medicine but only 3 manufacturers are currently approved by stringent regulatory authorities worldwide

We call on generic manufacturers to urgently explore ways to make 5-FC available in SA for treatment of PLHIV with CM; importantly 5-FC is a relatively simple molecule to manufacture.



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Reference: Kaminski's Digital Image Library (<http://www.mycology.adelaide.edu.au>)