AMBITION-cm : intermittent high dose AmBisome on a high dose fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa : study protocol for a randomized controlled trial

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Cryptococcal meningitis (CM) is a leading cause of mortality among HIV-infected individuals in Africa. Poor outcomes from conventional antifungal therapies, unavailability of flucytosine, and difficulties administering 14ădays of amphotericin B are key drivers of this mortality. Novel treatment regimes are needed. This study examines whether short-course high-dose liposomal amphotericin B (AmBisome), given with high dose fluconazole, is non-inferior (in terms of microbiological and clinical endpoints) to standard-dose 14-day courses of AmBisome plus high dose fluconazole for treatment of HIV-associated CM.; This is an adaptive open-label phase II/III randomised non-inferiority trial comparing alternative short course AmBisome regimens. Step 1 (phase II) will compare four treatment arms in 160 adult patients (≥18ăyears old) with a first episode of HIV-associated CM, using early fungicidal activity (EFA) as the primary outcome: 1) AmBisome 10ămg/kgăday one (single dose); 2) AmBisome 10ămg/kgăday one and AmBisome 5ămg/kgăday three (two doses); 3) AmBisome 10ămg/kgăday one, and AmBisome 5ămg/kgădays three and seven (three doses); and 4) AmBisome 3ămg/kg/d for 14ădays (control); all given with fluconazole 1200ămg daily for 14ădays. STEP 2 (phase III) will enrol 300 participants and compare two treatment arms using all-cause mortality within 70ădays as the primary outcome: 1) the shortest course AmBisome regimen found to be non-inferior in terms of EFA to the 14-day control arm in STEP 1, and 2) AmBisome 3ămg/kg/d for 14ădays (control), both given with fluconazole 1200ămg daily for 14ădays. STEP 2 analysis will include all patients from STEP 1 and STEP 2 taking the STEP 2 regimens. All patients will be followed for ten weeks, and mortality and safety data recorded. All patients will receive consolidation therapy with fluconazole 400-800ămg daily and ART in accordance with local guidelines. The primary analysis (for both STEP 1 and STEP 2) will be intention-to-treat.; ISRCTN10248064 . Date of Registration: 22 January 2014.

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