ART Initiation within the First 2 Weeks of Cryptococcal Meningitis Is Associated with Higher Mortality: A Multisite Randomized Trial

David Boulware*[1], D Meya[2,3], C Muzoora[4], M Rolfes[1], K Huppler Hullsiek[1], A Musubire[2,3], K Taseera[4], H Nabeta[2,3], C Schutz[5], G Meintjes[5], and Cryptococcal Optimal ART Timing Trial
[1]Univ of Minnesota, Minneapolis, US; [2]Infectious Disease Inst, Kampala, Uganda; [3]Makerere Univ, Kampala, Uganda; [4]Mbarara Univ, Uganda; and [5]Univ of Cape Town, South Africa

Background: Cryptococcal meningitis (CM) accounts for 25% of AIDS-related mortality in Africa. Optimal timing of ART initiation after CM is unknown. We hypothesized early ART initiation during hospitalization could lead to more rapid immune reconstitution and improved survival.

Methods: The Cryptococcal Optimal ART Timing (COAT) Trial was a randomized strategy trial for HIV^+, ART-naïve persons with a first episode of CM assessing if early ART initiation (1-2 weeks after CM diagnosis; prior to hospital discharge) results in superior 26-week survival compared to deferred ART initiation (5 weeks after CM diagnosis; as an outpatient). Induction antifungal therapy was amphotericin B and fluconazole 800 mg/day for 14 days followed by oral fluconazole. Lumbar punctures controlled intracranial pressure (median = 3). Hazard ratios (HR) compare early ART to deferred ART.

Results: 177 persons (of 500 planned) were randomized (115 in Kampala and 35 in Mbarara, Uganda; 27 in Cape Town, South Africa) before the trial was halted early by the Data and Safety Monitoring Board (DSMB) for substantial excess 6-month mortality with early ART (40/88) compared to deferred ART (27/89) (hazard ratio [HR] = 1.7, 95% confidence interval [CI]1.1-2.8; $p = 0.03$). In the early and deferred ART groups, median (IQR) $CD4^+$ counts were 19 (9-69) and 28 (11-76) cells/μL; days from CM diagnosis to ART initiation were 8 (7-8) and 36 (34-38). Most mortality occurred 2-5 weeks after CM diagnosis: 21/75 early ART vs 8/80 deferred ART (HR = 3.1, $p = 0.007$). Increased overall mortality occurred with early ART especially among those with altered mental status (Glasgow Coma Scale <15) before randomization (HR = 3.0, 95%CI 1.0-8.8, $p = 0.05$) and those with cerebrospinal fluid (CSF) white blood cells (WBC) <5 cells/μL at randomization (HR = 5.1, 95%CI 1.7-15.4, $p = 0.004$). Through 26 weeks, CD4 recovery, HIV viral suppression, adverse events (Grade 3-5), ART-tolerability, immune reconstitution inflammatory syndrome (IRIS), CM-relapse, microbiologic clearance, and Karnofsky score did not differ between arms. Causes of death for early vs deferred ART, respectively, included: cryptococcosis (21 vs 10), septicemia (8 vs 5), TB (2 vs 2), and IRIS-related (1 vs 2). CM IRIS incidence was 13% (11/86) with receipt of early ART vs 10% (7/68) with deferred ART.

Conclusions: Deferred ART initiation 5 weeks after cryptococcosis had improved 26-week survival compared to inpatient initiation of ART 1 week after CM diagnosis, especially in those with altered mental status or a paucity of CSF inflammation.