FORUM

Starting ART following cryptococcal meningitis: The optimal time has yet to be defined

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Ever since the public sector rollout of antiretroviral therapy (ART) in 2004, the question of the optimal time to start ART following diagnosis of an opportunistic infection has aroused controversy among South African HIV clinicians and researchers.

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Patients with cryptococcal meningitis (CM) in Southern Africa present with median CD4$^+$ counts <50 cells/μl,[1-4] with a high prevalence of co-morbidities such as tuberculosis (TB) and Kaposi's sarcoma. In this context, the challenge is to balance the competing risks of morbidity and mortality from each additional week of advanced immunosuppression – well demonstrated in South African (SA) HIV cohorts waiting to start antiretroviral therapy (ART)[5] – with those from immune reconstitution inflammatory syndrome (IRIS) occurring within the confined space of the central nervous system, when ART is commenced in the presence of a high fungal antigen load.[6,7]

The first Southern African CM guideline[8] published in 2008 recommended treatment with 1 mg/kg/day amphotericin B for 2 weeks – a regimen known to drive down the cryptococcal burden rapidly in cerebrospinal fluid (CSF), with many patients having sterile CSF by day 14.[1] At this time, given the lack of evidence regarding ART timing in CM, it was recommended to start ART 2 - 4 weeks after commencing amphotericin B.[8] This window pragmatically coincided with the timing of hospital discharge, and the switch from amphotericin induction therapy to consolidation with fluconazole, with the aim of having asymptomatic patients with sterile or almost-sterile CSF counselled and ready to start ART at outpatient follow-up 4 weeks into antifungal therapy.

Since 2007, two randomised controlled trials (RCTs) of ART timing following CM have been completed in Africa. In the first, conducted by Makadzange *et al.*[9] in Zimbabwe, patients receiving fluconazole monotherapy for CM were randomised to start ART at ≤72 h v. 10 weeks.[9] The study found excess mortality in the immediate ART arm, most probably due to IRIS, although this information was not collected systematically.[9] Notwithstanding this trial's small sample size and large early loss to follow-up,[10-12] it confirmed the clinical impression that starting ART extremely early was harmful, but it did not provide guidance on what to do in the context of amphotericin-based treatment, nor provide information on ART timing between 3 days and 10 weeks, which represent a far earlier and far later ART-initiation time-point, respectively, than most clinicians would consider in practice.

The Cryptococcal Optimal ART Timing (COAT) trial[13] conducted in Uganda and SA was designed to address these questions, randomising patients treated with amphotericin-based induction (1 mg/kg/day amphotericin B with 800 mg/day fluconazole) to early (1 - 2 weeks, median 8 days) v. deferred (4 - 6 weeks, median 36 days) ART. The trial was halted prematurely (N=177 patients randomised) due to excess mortality in the early ART arm, with the most pronounced difference in mortality occurring between days 8 and 30 after CM diagnosis: 21/75 (28%) early ART v. 8/80 (10%) deferred ART (hazard ratio 3.1; p<0.01). This difference occurred despite an apparently similar incidence of CM-IRIS in the two groups (13% v. 10%).[13]

Based on significant differences in mortality in an RCT conducted in an African context following amphotericin treatment, the 2013 Southern African HIV Clinicians Society guidelines committee felt compelled to move the recommended ART start window to 4 - 6 weeks, in line with the delayed ART group of the COAT trial. This generated some debate among panel members, with some favouring the 4-week time-point.

For all the clear advantages of RCT data, the two ART timing studies do not say anything about a preference between the better-performing study arm and intermediate time-points such as 2, 3 and 4 weeks – they only tell us that the worst-performing arms (i.e. during the first 2 weeks of induction therapy) do not represent the right time to start. Ten weeks

was not prioritised over 6 weeks in the Makadzange *et al*. study,[9] and 5 weeks was not prioritised over 3 or 4 weeks in the COAT trial.

We are unlikely to have any further ART timing RCTs for CM in the near future, given the large cohorts required to power an RCT of ART start at 2 v. 4 weeks post CM treatment. Thus, we may need to edge towards a preferred time based on observational clinical cohort data. In successive SA clinical trial cohorts between 2005 and 2010,[1-4] in which all patients received amphotericin-based induction treatment, with our SA partners we have gradually decreased the median time to ART start from CM diagnosis from 6 weeks[1] to just 23 days (in our latest trial).[4] Despite the concerns of confounding by historic trends in the severity of CM and HIV of patients at presentation, in all four studies[1-4] the median $CD4^+$ count was <50 cells/μl, the median baseline fungal burden was high (approximately 5 $\log_{10}$ CFU/ml in the CSF), and the percentage of altered mental status – the most significant indicator of poor prognosis in CM – ranged from 13% to 37%, with the latest trial[4] enrolling those with the highest rates.

One-year survival analysis of the combined cohort from the four trials (*N*=171 patients), who started ART at a median of 31 days (interquartile range 23 - 46) following a CM diagnosis, showed an earlier flattening of the survival curve in those who started ART within 1 month compared with those who started beyond 1 month.[7] Despite an association of day-14 fungal burden and subsequent CM-IRIS, there was no association of earlier ART initiation and IRIS, and patients who developed IRIS did not have a higher mortality. While CM was the presumed cause of 85% of the deaths in the first 2 weeks, the majority (67%) of deaths after 2 weeks were attributed to other illnesses related to advanced immunosuppression, which might have been prevented through earlier ART initiation.

The absence of RCT evidence favouring the 2 - 4-week time-points does not translate into evidence against these time-points. Our clinical cohort data and experience in managing HIV patients with CM in the SA setting makes us strong advocates of an ART start time of 4 weeks from CM diagnosis: a time-frame that is being applied in a recently commenced phase III randomised trial of CM treatment at four sites in Africa (ACTA trial, ISRCTN 45035509), and which we believe represents a pragmatic approach based on a synthesis of all available evidence.

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