Randomised controlled trial

Delaying initiation of ART for 5 weeks improves survival in patients with HIV infection with cyrptococcal meningitis

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Commentary on: Boulware DR, Meya DB, Muzoora C, *et al*. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med* 2014;370:2487–98.

Context

Cryptococcal meningitis (CM) is a major cause of mortality for individuals with HIV infection in Africa. Early initiation of antiretroviral therapy (ART) has been shown to decrease mortality in a number of opportunistic infections such as tuberculosis (TB) and *Pneumocystis jirovicii* pneumonia, but may increase mortality in central nervous system-related opportunistic infections such as TB meningitis.[1] The timing of ART however remains controversial for CM.[2 3]

Methods

The study by Bouleware and colleagues is a randomised trial that assigned 177 HIV-infected ART-naïve patients from Uganda and South Africa who were recently diagnosed with CM (median of 7–8 days) to either receive ART within 48 h of randomisation (early ART) or 4 weeks after randomisation (delayed ART). The selection and randomisation processes were well outlined and baseline characteristics of the patients were similar in the two treatment groups. Patients completed standard cryptococcal induction therapy with 2 weeks of amphotericin B (0.7–1 mg/kg/day) in combination with high-dose fluconazole (800 mg daily). This was followed by modified consolidation therapy with high dose fluconazole (800 mg daily) for at least 3 weeks, then fluconazole 400 mg daily for a total consolidation phase of 12 weeks. The primary end point was survival at 26 weeks. Secondary outcomes were survival at 46 weeks, cryptococcal immune reconstitution inflammatory syndrome (IRIS), relapse of CM, fungal clearance, virological suppression (HIV RNA level <400 copies/mL) at 26 weeks, significant adverse events and ART discontinuation for more than 3 days. Methods of defining these secondary outcomes were clearly stated.

Findings

At 26 weeks, 45% of participants who had received ART within 2 weeks of diagnosis of CM had died compared with 30% of those whose ART was delayed for 5 weeks (HR 1.73; 95% CI 1.06 to 2.82, p<0.05). Most deaths occurred in the first 2–5 weeks after diagnosis. During this time, 28% died in the early ART group compared with 10% in the delayed ART group (HR=3.10; 95% CI 1.37 to 7.00, p<0.01). Subgroup analysis of participants with a cerebrospinal fluid (CSF) white cell count <5 cells/mm^3 at randomisation showed that mortality was higher in the early ART group (HR 3.87; 95% CI 1.41 to 10.58, p<0.01). The authors identified no other baseline characteristics that were associated with higher mortality.

There was no difference in the frequency of cryptococcal IRIS, relapse of CM, fungal clearance, virological suppression at 26 weeks, significant adverse events and ART discontinuation for more than 3 days between the two groups.

There was no benefit for early ART in those participants with a high mortality risk, including those with CD4 cell counts less than 50 cells/mm^3 (HR 1.74; 95% CI 0.93 to 3.24) and those with altered mental status (HR 2.96; 95% CI 1.00 to 8.80). Early ART was also not favourable for those with a lower mortality risk, such as those with a lower CSF cryptococcal antigen titre after 7 days of antifungal therapy.

Commentary

This trial provides evidence to support deferring the initiation of ART in patients with CM to at least 5 weeks after diagnosis and effective antifungal therapy; delaying ART led to a significant reduction in mortality. The main factor associated with high risk of death was the absence of CSF pleocytosis at the time of randomisation. In other studies the lack of CSF pleocytosis has been linked to an increased risk of developing IRIS, and although IRIS was not identified as the primary cause of mortality, the authors acknowledge that it could have had a role as early IRIS events may have been difficult to distinguish clinically from progression of cryptococcosis.

Early study termination with recruitment of less than half of the proposed cohort may have overestimated the size of the effect of early ART on mortality, and also affected the subgroup analyses. The authors acknowledge this limitation and indicate the timing of ART in subgroup populations such as those with CSF pleocytosis cannot be ascertained from this study.

Patients in this study received antifungal therapy in line with international guidelines, whereas in resource-limited settings, therapy may be suboptimal, with many people receiving fluconazole monotherapy. The finding that the mortality difference is apparent even with optimal treatment of cryptococcal disease makes these results likely applicable to resource-limited and resource-rich settings.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

References

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