EDITORIAL COMMENTARY

# Poor Prognosis of HIV-Associated Tuberculous Meningitis Regardless of the Timing of Antiretroviral Therapy

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**(See the article by Török et al, on pages 1374–1383.)**

Human immunodeficiency virus (HIV)–associated tuberculosis (TB) carries a high mortality risk and accounts for approximately 25% of global HIV/AIDS deaths each year [1]. Case management requires a combination of appropriate antituberculosis treatment, antiretroviral therapy (ART), and trimethoprim-sulphamethoxazole prophylaxis against other opportunistic infections [2]. ART reduces mortality by 64%–95% in patients with drug-susceptible TB [3], and trimethoprim-sulphamethoxazole prophylaxis halves mortality risk [4]. For patients with HIV-associated TB involving the central nervous system (CNS) or pericardium, adjunctive treatment with corticosteroids is also recommended [5].

Despite the clear benefits of ART, the optimal time to initiate ART during TB treatment has remained unclear, since this is associated with a complex series of competing risks that may vary between different settings and patient populations [6, 7]. However, the cumulative findings from observational studies and more recent randomized controlled trials indicate that delays in ART initiation are associated with increased mortality among patients with TB across a wide spectrum of baseline CD4+ cell counts [6, 8–11]. With this growing evidence base, the World Health Organization (WHO) has revised the ART guidelines for resource-limited settings on several occasions between 2002 and 2010, recommending progressively earlier initiation of ART during TB treatment [12]. The most recent revision of these guidelines, published in 2010, recommended that ART be given to all patients with TB regardless of CD4+ cell count, should be started as soon as possible after TB treatment is tolerated, and should not be initiated later than after 8 weeks of TB treatment [12]. However, these guidelines may be further refined as data emerge from additional trials being conducted in different settings and patient groups [6].

In this issue of *Clinical Infectious Diseases*, Török et al [13] present important findings from a well-conducted randomized controlled trial in Vietnam in which they investigated the optimum timing of ART among patients with TB meningitis. They studied a cohort of 253 patients who received local standard of care and compared the outcomes of patients randomized to start ART either during the first week of TB treatment or after 2 months of TB treatment. The primary end-point was mortality during a 9-month follow-up period. The double-blind placebo-controlled design was robust and adequately powered, and randomization was good. Case definitions were appropriate, and with careful microbiological investigation, a majority of cases were confirmed by culture. However, the overall finding was that there was no statistically significant difference in survival between the 2 study arms. Moreover, this negative finding was observed in patients across all TB meningitis severity grades.

So why was mortality not influenced by the timing of ART? Even taking into account the advanced immunodeficiency of these patients (median CD4+ cell count, 41 cells/μL), it was nevertheless striking that 58% (146 of 253) of the patients died during follow-up. It is well recognized that patients in resource-limited settings with WHO stage 4 disease (AIDS) and/or CD4+ cell counts <50 cells/μL have very high mortality risk both before ART [14] and during early ART [15], but mortality risk rapidly decreases in direct

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relationship with CD4+ cell count recovery [16]. However, in this study, overall mortality risk (and risk stratified by TB meningitis grade) was similar to that reported in studies of HIV-associated TB meningitis conducted in the same setting prior to the availability of ART [17, 18]. This questions the extent to which this patient group derived benefit from ART and, in fact, whether they benefitted at all.

Although causes of death were not defined, the overriding risk factor for death was the TB meningitis severity grade, which suggests that deaths may well have been largely attributable to TB meningitis rather than to other HIV-associated co-pathologies. It was also notable that 85 (58.2%) of the 146 deaths occurred within the first month of observation, which further suggests that many of the patients had such advanced disease at study entry that they simply could not be salvaged. Use of dexamethasone is an important adjunctive therapy in HIV-uninfected patients with TB meningitis in this setting and has been shown, in a randomized controlled trial, to improve survival by ~30% [18]. However, no conclusive benefit was demonstrated among patients with HIV-associated TB meningitis in the same study, which was conducted in the pre-ART era [18]. No trials involving corticosteroids have been performed among patients receiving ART, because the use of corticosteroids is now regarded as standard of care [5].

The high proportion of patients with advanced TB meningitis severity grades was a key factor in the overall mortality and may have been related to the prolonged symptom duration (median duration of symptoms, 21 days; interquartile range, 10–30 days) prior to study entry. Because the Hospital for Tropical Diseases in Ho Chi Minh City is a tertiary referral hospital that serves a population of 38 million people in southern Vietnam [17], referral delays from peripheral hospitals may be prolonged, and delays may be further compounded by the difficulties inherent in the diagnosis of TB meningitis. The prolonged interval between symptom onset and initiation of TB treatment is likely to have contributed to poor outcomes and must be reduced.

Four patients had multidrug-resistant TB meningitis, which is strongly predictive of death [19]; no second-line therapy was available for these patients. Drug resistance profiles of other isolates of *Mycobacterium tuberculosis* were not reported, but >40% of isolates from similar patients previously treated in this setting had isoniazid mono-resistance [17]. Although a previous study in this setting found that isoniazid mono-resistance was associated with slower mycobacterial clearance from cerebrospinal fluid (CSF) during treatment, this was not associated with adverse clinical outcomes [19]. However, in a study from the United States of a cohort of 1614 patients with positive CSF culture results, initial isoniazid resistance was associated with an adjusted odds of death of 2.1 (95% confidence interval, 1.30–3.29) [20]. This strongly suggests that the issue of isoniazid mono-resistance and outcomes of treatment for TB meningitis warrants further study.

Except for those with multidrug-resistant TB, the mortality benefits of ART derived by patients with HIV-associated TB are likely to primarily result from reductions in the risk of new opportunistic infections, rather than from enhanced clearance of mycobacterial disease. However, the incidence of new AIDS-defining infections was nevertheless very high, affecting 25% of all patients in this study. The use of high-dose adjunctive dexamethasone may have contributed to this risk. It was also notable that prophylaxis with trimethoprim-sulphamethoxazole was only started after 4 weeks from the date of study inclusion, which was the period with the highest mortality risk. Some of the new AIDS-defining events (44 diagnoses of *Pneumocystis jirovecii* pneumonia and 3 diagnoses of toxoplasmosis) might have been prevented by earlier initiation of trimethoprim-sulphamethoxazole prophylaxis.

A key concern with rapid ART initiation is the higher risk of TB-associated immune reconstitution disease (IRD) [21], which is particularly severe when associated with opportunistic infections of the CNS [22]. Although IRD events involving the CNS were not specifically reported, all neurological events were carefully documented and occurred with similar frequency (in 40% of patients) in each arm of the study. Furthermore, the time to development of a neurological event or death did not differ between the arms. Thus, there was no evidence that early ART initiation was associated a higher frequency of CNS IRD events. Use of high-dose dexamethasone is likely to have ameliorated the frequency and severity of this complication.

The study population largely comprised young, male intravenous drug users, which is a population that is typically associated with considerable comorbidity. This may limit the extent to which the findings of this study can be generalized to other clinical populations. Hepatitis C infection and hepatitis B infection were detected among 51% and 14% of those patients who were tested, respectively. These coinfections may have contributed to the high frequency of grade 3 and grade 4 hepatitis observed in over one-fifth of patients during follow-up.

The main conclusion that this important study seems to suggest is that HIV-associated TB meningitis in this patient population has such a poor prognosis that the timing of ART makes no appreciable difference with regard to survival probability. Profound immunodeficiency, late presentation, advanced CNS disease, and high rates of comorbidity all conspire towards a dismal prognosis. Prognosis in this setting might be improved by earlier

presentation to the health services, minimization of referral delays, and accelerating diagnosis by using novel rapid molecular assays, for example [23]. Careful screening and prophylaxis for coinfections [24] is also important because multiple pathology appears to be the rule rather than the exception in these patients. More fundamentally, however, these data highlight the need for effective prevention of TB by using isoniazid preventive therapy and ART as complementary strategies [25]. In addition, the need for new effective drug treatments for TB meningitis is abundantly clear.

The fact that the findings of Torok et al [13] differ from those of other strategy trials investigating the optimum timing of ART during opportunistic infections should come as no surprise. Two other studies conducted in the United States [26] and Zimbabwe [27], for example, enrolled patients with acute non-TB opportunistic infections and cryptococcal meningitis, respectively, and overall mortality risks differed greatly (8.5% vs 64.8%). These cohorts also had different rates of comorbidity and standards of clinical care, and the competing risks favoring either early or deferred ART are likely to have differed substantially between cohorts. In patients with cryptococcal meningitis treated with oral fluconazole therapy (a fungistatic drug) in Zimbabwe, immediate initiation of ART, compared with initiation after 10 weeks, was associated with a much higher mortality risk (88% vs 54%) [27]. This suggests that, in the absence of adequate fungicidal therapy, early ART is harmful in this patient group. In contrast, in North American patients with non-TB acute opportunistic infections, including patients with cryptococcal meningitis who receive amphotericin, early ART was associated with a halving of the risk of progression to AIDS and death [26].

Careful comparison of differences in the outcomes of ART strategy trials involving patients with TB may yield further important insights. The Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) trial studied a cohort of patients with very advanced immunodeficiency (median CD4+ cell count, 25 cells/μL) and pulmonary and/or extrapulmonary TB but involved only 1 patient with a diagnosis of TB meningitis [10]. This compared a similar ART initiation strategy (ART within 2 weeks of treatment vs ART within 2 months) to that used by Torok et al [13]. Overall mortality in the CAMELIA study was much lower than that observed by Torok et al [13] (22.5% vs 57.7%), and mortality was 34% lower in the early ART initiation arm than it was in the deferred arm. What was intriguing was that this important mortality benefit accrued with increasing duration of follow-up, being most marked during the second year after randomization [10]. The mechanism underlying this delayed survival benefit is not clear and was not related to differences in immunological or virological response to ART. However, any potential long-term accrual of survival benefit would be unlikely to be seen in the cohort studied by Torok et al [13], because the high early mortality occurred very early during follow-up.

In summary, although several strategy trials examining the optimum timing of ART during opportunistic infections have found that early ART is beneficial [10, 11, 26], the exceptions are those studies involving patients with severe CNS infections in resource-limited settings [13, 27]. Thus, the question of the optimum timing clearly has more than one right answer [7]. The timing of ART is just one component of a complex package of care that must include optimum treatment for the opportunistic infection in question, optimum treatment of other comorbidities, and optimized prevention of new opportunistic infections. In the case of TB meningitis in Vietnam, the stark reality may be that the prognosis of the patients is so poor that adjustments in the timing of ART are largely futile. Thus, although efforts must be made towards earlier diagnosis and optimized delivery of the current standard of care, new solutions are desperately needed.

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