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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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was a key factor in the overall mortality
and may have been related to the
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is now regarded as standard of care [5].
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 ad-
junctive therapy in HIV-uninfected pa-
tients 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 pa-
tients with HIV-associated TB menin-
gitis 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; inter-
quartile 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 pre-
dictive 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 cerebro-
spinal 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 re-
result from reductions in the risk of new
opportunistic infections, rather than
from enhanced clearance of mycobacte-
rial 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 toxo-
plasmosis) might have been prevented
by earlier initiation of trimethoprim-
sulphamethoxazole prophylaxis.
A key concern with rapid ART initi-
ation 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 neurologi-
cal 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 com-
prised young, male intravenous drug
users, which is a population that is typ-
ically associated with considerable co-
morbidity. 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 im-
portant 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 im-
munodeficiency, late presentation, ad-
vanced CNS disease, and high rates of
comorbidity all conspire towards a dis-
mal 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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