


Reducing the Burden of Tuberculosis Presenting during the Initial Months of Antiretroviral Therapy in Resource-Limited Settings

To the Editor—The high burden of tuberculosis within antiretroviral therapy (ART) programs in resource-limited settings is challenging [1, 2]. We read with interest the article by Koenig et al [3] from Haiti in which they reported a very high mortality rate (27% at 1 year) among patients with tuberculosis diagnosed during the first 3 months of ART. This observation is important and is entirely consistent with other data from sub-Saharan Africa [1, 2]. However, it was also reported that, in both adjusted and unadjusted analyses, mortality in this patient group was substantially greater than that among patients with either prevalent tuberculosis diagnosed before the initiation of ART or incident tuberculosis diagnosed at some time beyond 3 months of ART [3]. Data from the latter 2 groups were pooled to form a combined comparator group with a low overall tuberculosis risk.

The much higher mortality risk among patients with tuberculosis presenting during early ART compared with that among patients with tuberculosis at baseline differs from the findings of previous studies [1, 2], and we are concerned that this observation could be misinterpreted as showing that ART has a deleterious impact on survival. We wonder whether this may be the result of patient selection. The mortality rate among patients with advanced immunodeficiency just before starting ART in resource-limited settings is extremely high, and tuberculosis during this period is difficult and time-consuming to diagnose [4–7]. Thus, during this period many deaths occur among patients with tuberculosis (whether or not it has been diagnosed). Only selected patients in whom tuberculosis diagnosis was possible and who survived long enough to start ART could form the pre-ART group. Such patient selection may have substantially diminished the observed mortality risk in the pre-ART group. This would be consistent with the Kaplan-Meier plot, which shows an unusually low frequency of death during the first 6 weeks of tuberculosis treatment in the comparator arm containing this patient group.

Notwithstanding this potential limitation, we agree that tuberculosis is very likely to be an important contributor to early mortality during ART [4]. The key question is how to tackle this problem. Koenig and colleagues suggested that many patients with incident tuberculosis during early ART are likely to have active tuberculosis that was present at baseline but remained undiagnosed. In agreement with this suggestion, we recently estimated that, in our South African ART cohort, ~40% of the tuberculosis cases presenting during this period were due to the “unmasking” of asymptomatic or minimally symptomatic disease that was present at baseline [8].

In a more recent study, moreover, all patients entering our program without a preexisting tuberculosis diagnosis were (regardless of symptoms) systematically screened by culturing induced sputum samples. The yield of culture-confirmed tuberculosis diagnoses among these patients at baseline was extremely high (25%) [9] and was ≈2-fold higher than what had been diagnosed during routine program screening in preceding years [1]. Of note, during follow-up the proportion of patients who presented with tuberculosis during the first 3 months of ART was, correspondingly, ≈2-fold lower than that previously observed.

Thus, following the observation by Koenig and colleagues of a very high mortality rate among patients presenting with tuberculosis during the first 3 months of ART, we have found that effective baseline screening substantially reduces incident tuberculosis during this period. This suggests a need for routine pre-ART tuberculosis screening with high-sensitivity tests (such as automated liquid culture of sputum) and highlights an urgent need for much more rapid and sensitive diagnostics for use in this clinical setting. It remains to be demonstrated, however, whether this strategy would also reduce mortality risk.

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Reply to Lawn et al

To the Editor—We thank Lawn et al [1] for their interest in our study [2]. We agree that tuberculosis is likely a major cause of mortality among patients with advanced AIDS and that early initiation of antiretroviral therapy (ART) is critical. Our finding of a high mortality rate among patients with tuberculosis diagnosed during the early ART period—likely due to active disease that was present at baseline but that remained undetected—suggests that routine pre-ART screening for tuberculosis would be beneficial. We agree that this should not delay the initiation of ART for patients with advanced AIDS.

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Presence of High-Titer Neutralizing Antibodies against Enterovirus 71 in Intravenous Immunoglobulin Manufactured from Chinese Donors

To the Editor—Enterovirus 71 (EV71) has been widely recognized as the major pathogen that causes hand, foot, and mouth disease (HFMD). In recent years, severe forms of HFMD—including fatal encephalitis, aseptic meningitis, and poliomyelitis-like paralysis—have been associated with EV71 infections [1]. Especially in China, EV71 outbreaks have raised public and media concerns in light of the millions of infections that have occurred, which have caused hundreds of deaths in young children [2]. No vaccine or antiviral drugs are currently available; several candidates are in development.

There is an extensive body of literature supporting the value of intravenous immunoglobulin for viral infections. One report has shown that intravenous immunoglobulin at a neutralization titer of 1:32 should decrease the severity of enterovirus infection [3]. The potential of intravenous immunoglobulin therapy for severe EV71 infections is not well understood. Thus, we sought to determine the level of EV71 neutralizing antibody in commercial intravenous immunoglobulin manufactured from Chinese plasma donors. Nine liquid intravenous immunoglobulin preparations from the 7 major Chinese manufacturers were 2-fold serially diluted for microneutralization tests. EV71 antibody titers were measured by standard protocols on human rhadomyosarcoma cells, using 3 Chinese isolates and the prototype BrCr strain. The results showed that high-titer EV71 neutralizing antibodies (>1:128) were present in all 9 Chinese intravenous immunoglobulin preparations. In contrast, undetectable levels (<1:8) of EV71 antibodies were present in an intravenous immunoglobulin preparation of Canadian origin (Privigen; CSL Behring Canada).

Although EV71 infections in adults rarely result in clinical symptoms, the infection rate among adults might be high. A recent report demonstrated that ~75% of German adults have EV71 antibodies [4]; thus, we further determined the seroprevalence of EV71 antibodies in Chinese plasma donors. A total of 1012 samples from Chinese donors were collected, and microneutralization tests were performed as described above. The results showed that 89 of the samples (8.8%) contained high-titer EV71 neutralizing anti-