Reducing Mortality Associated with Opportunistic Infections among Patients with Advanced HIV Infection in Sub-Saharan Africa: Reply to DiNubile

To the Editor—We thank Dr. DiNubile for his letter in this issue of the journal [1]. We strongly agree that there is a great need for further development of strategies to reduce the major morbidity and mortality associated with opportunistic infections among patients enrolling in antiretroviral treatment (ART) programs, especially in resource-limited settings.

In sub-Saharan Africa, the large majority of patients continue to present to ART programs with advanced immunosuppression. Associated early mortality is high, with 8%–26% of patients dying during the first year of ART [2]. Despite major efforts to expand access to ART during recent years [3], the median CD4 cell count among patients initiating ART remains low [2]. Access to ART has been scaled up very rapidly in the Western Cape Province of South Africa, and yet the absolute number of patients with World Health Organization (WHO) stage 4 disease is actually increasing as maturation of the epidemic outstrips the capacity of health services to start treatment [4].

For ART programs in Africa, effective interventions to prevent this early mortality associated with opportunistic infections need to be targeted at the major causes of this mortality. Among the most important causes are tuberculosis, cryptococcal meningitis, and acute sepsis [2]. WHO guidelines recommend several interventions, including isoniazid preventative therapy against tuberculosis and cotrimoxazole prophylaxis against bacterial sepsis and Pneumocystis pneumonia [5]. Despite robust evidence for their efficacy, uptake of these interventions in many settings remains poor. Countries that have been slow to incorporate cotrimoxazole prophylaxis into clinical practice often cite ill-founded concerns about drug resistance [6, 7]. Although recommendations are for all patients with human immunodeficiency virus (HIV) infection to receive isoniazid preventative therapy once active tuberculosis has been excluded, <0.1% of these patients received this intervention in 2007 [8].

For ART programs in Africa, we have identified cryptococcal meningitis as a further key cause of death [2, 9]. However, public health policy recommendations regarding the use of fluconazole for prevention of cryptococcal meningitis are not clear. WHO guidelines suggest that the use of prophylactic fluconazole may be considered for patients with a CD4 cell count of ≤100 cells/μL in areas where cryptococcal meningitis is common [5]. However, in light of limited evidence of any survival benefit either before or during ART, of potential drug toxicities, of pharmacokinetic drug interactions, or of potential development of drug resistance, fluconazole is rarely used. Although universal primary fluconazole prophylaxis is effective at reducing the number of cases of cryptococcal meningitis [10], it involves treating large numbers of patients, with an estimated 10,000 doses of fluconazole required for each case prevented in a single study [11, 12].

As DiNubile [1] points out, however, prevention strategies can be broadly divided into “blanket one-size-fits-all” approaches and targeted interventions aimed at those most at risk. With regard to cryptococcal meningitis, we suggest that there is a strong case for screening for cryptococcal antigen (CrAg) and targeted preemptive therapy for those testing positive [13]. In our study, a negative plasma CrAg test result 2 weeks before the start of ART was associated with a 100% negative predictive value for the development of cryptococcal meningitis in the first year of ART [13]. In contrast, those testing positive had a substantial risk of cryptococcal disease and associated mortality. The vast majority (∼90%) of patients who are screened for CrAg do not have it and therefore have no need for prophylactic or preemptive therapy. Using antigen screening in this way permits identification of a limited number of patients at risk who can then receive more intensive treatment, while avoiding widespread and unnecessary drug exposure and the associated risk of development of drug resistance [14].

This view is supported by findings from a recent randomized placebo-controlled trial of primary fluconazole prophylaxis in Uganda [15]. As in previous studies, routine prophylaxis for HIV-infected patients reduced the risk of cryptococcal menin-

References
3. The Antiretroviral Therapy Cohort Collaboration (ART-CC). Variable impact on mortality of the epidemic outstrips the capacity of health services to start treatment [4].
ginitis. However, the overall number of cases of cryptococcal meningitis was low, probably because patients with a serum sample positive for CrAg at baseline were excluded, and therefore no mortality difference was observed between the intervention and placebo arms. In contrast to our study, the development of cryptococcal meningitis among a small proportion of patients who tested negative for CrAg may have been related to the fact that, during the first part of the study, ART was not available, and among those who started ART later, there was a median delay from screening to start of ART of 11 weeks.

Although antigen screening before the start of ART appears to be very useful for identifying those at risk of cryptococcal meningitis, the optimal management of patients with asymptomatic antigenemia remains unclear. We are currently embarking on studies that will address this key question and that will help inform policy recommendations. Further collaborative work will aim to develop a urinary antigen test, raising the possibility of a simple urine dipstick test, which would greatly simplify the screening procedure.

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