
Reply to DiNubile

To the Editor—DiNubile [1] gives a thoughtful review of some of the issues surrounding the timing and use of prophylaxis for opportunistic infections at the time of initiation of combination antiretroviral therapy (ART) in patients with advanced human immunodeficiency virus (HIV) infection. We would add a couple of further observations regarding these issues in developing countries. First, in developing countries, the availability of even fairly routine laboratory and diagnostic tests is often very limited, so extensive screening tests are not feasible in resource-limited situations. Indeed, one of the goals of our study [2] was to develop a model to predict the risk of AIDS or death among HIV-infected patients receiving combination ART in Asia in situations in which very limited tests are available, with a view to allowing some further interventions that might improve survival rates. Second, after initiation of combination ART among patients with advanced immunodeficiency, the mortality rate in developing countries is often very high, of the order of 20% in 1 year [2, 3]. Third, background rates of some opportunistic infections (eg, tuberculosis [4]) are generally much higher in developing countries in Asia and Africa, compared with developed countries, making these issues of timing and use of prophylaxis even more important.

How can the poor outcomes of HIV-infected patients starting combination ART in developing countries be improved? First, it would be much better to have HIV-infected people diagnosed, and treated earlier, at higher CD4 cell counts, prior to developing opportunistic infections. Lack of access to confidential HIV testing results and the stigma associated with HIV infection remain barriers in developing countries [5]. An earlier diagnosis of HIV infection, before a patient becomes seriously ill with an opportunistic infection, might improve the outcome. Second, as DiNubile [1] discusses, there is currently great uncertainty surrounding a number of strategic issues concerning the timing of opportunistic infection prophylaxis when initiating combination ART. These uncertainties are probably greatest in developing countries, and methods to identify patients with hidden opportunistic infections based on simple laboratory or clinical tests, perhaps targeted to opportunistic infections that carry a particularly poor prognosis [6], may improve clinical outcomes. Because of the large numbers of patients with advanced immunodeficiency who are starting combination ART and the high mortality rates (ie, 20% of patients die within 1 year), some simple, strategic randomized studies with overall mortality as the endpoint might provide some important answers relatively quickly.

Increased HIV testing and the proper timing and use of opportunistic infection prophylaxis are 2 areas that could benefit enormously from more research in developing countries, and there are a number of initiatives to support such research. However, we would also echo the sentiments of the Sydney declaration [7]—that a portion of the funding being made available to provide HIV treatment in developing countries should be used to fund research that could help us learn how best to use these treatments in developing countries.

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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% to 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-