Universal Prophylaxis, Targeted Prophylaxis, and/or Preemptive Therapy for Opportunistic Infections at the Time of Initiation of Combination Antiretroviral Therapy for Patients with Advanced HIV Infection

To the Editor—Despite expanded recommendations for the screening of human immunodeficiency virus (HIV) infection, many HIV-infected patients are still not diagnosed until their CD4 cell counts are critically low [1–3]. This unfortunate scenario occurs even more commonly in developing regions of the world than in industrialized countries [4]. Patients with advanced HIV infection often harbor opportunistic pathogens, although these infections may be subclinical or latent at presentation. After the initiation of highly active antiretroviral therapy (HAART), such patients are paradoxically at substantial risk of immune reconstitution inflammatory syndrome (IRIS), which exposes smoldering infections with sometimes serious (even life-threatening) consequences [5–15]. Similar concerns apply to treated or noncompliant patients experiencing viral rebound and immunologic failure when an effective regimen is reestablished [16].

Should comprehensive prophylaxis for opportunistic infections appropriate to the patient’s CD4 cell count be initiated routinely and concurrently along with HAART? Published guidelines provide little formulaic instruction about which strategies to use [17–19]. A blanket one-size-fits-all approach would require that patients with a CD4 cell count of <50 cells/μL start an onerous number of medications nearly simultaneously, which might lead to drug interactions, toxicities, and inconvenience. The steep price to be paid may be suboptimal adherence to the antiretroviral regimen. Alternatively, is there a role for targeted prophylaxis or preemptive therapy based on risk stratification derived from the clinical history, physical examination, and selective use of laboratory testing?

IRIS is predominantly a delayed reaction to endogenous pathogens acquired sometime in the past, and only complicates new infections encountered by serendipity during the short-lived window of vulnerability once efficacious antiretroviral therapy has been initiated. The burden, distribution, and replicative state of an organism during the early period of HAART define a continuum of risk for IRIS. In this light, the semantic distinction between prophylaxis and therapy may often be more apparent than real in practice. Treatment for latent tuberculosis is now accepted as preferable terminology to chemoprophylaxis. Despite common usage, secondary prophylaxis for herpes simplex virus or Pneumocystis infection largely represents suppressive therapy. Especially with mycobacterial infections, the pathogen load also contributes to the probability of developing resistance when prophylactic doses of a single agent, rather than full therapeutic regimens, are administered.

IRIS theoretically could be circumvented or diminished by the judicious use of antimicrobial and immunomodulatory drugs, and occasionally even by cancer chemotherapy or by the use of anticoagulant medication. For example, aggressive management of opportunistic infections for which effective specific therapies do not exist potentially involves starting corticosteroids coincident with HAART, as might be contemplated for a treatment-naive patient with few remaining CD4 cells and nonenhancing multifocal periventricular white matter lesions (or demonstrable JC virus in the cerebrospinal fluid) to prevent the unmasking of progressive multifocal leukoencephalopathy [13]. Unfortunately, even short courses of pharmacological doses of steroids can reactivate latent tuberculosis or endemic fungal infections or disturb the delicate host-parasite symbiosis in asymptomatic strongyloidiosis. Rapid tapering or full withdrawal of steroid therapy may ignite exacerbations of viral hepatitis, Pneumocystis pneumonia, central nervous system mass lesions, and a variety of diverse autoimmune phenomena.

Several articles in the 1 April 2009 issue of the journal help to frame and inform these concerns [20–23]. Jarvis et al [20] argue convincingly that screening treatment-naive patients with advanced HIV infection for cryptococcal antigenemia prior to starting HAART can reduce attributable mortality, at least in South Africa [24]. Aichelburg et al [21] advance the possibility that periodic testing with an interferon-γ release assay (QuantiFERON-TB Gold In-Tube assay; Cellestis) can identify patients at high risk of developing active tuberculosis in the short term. Different interferon-γ release assays may be more or less sensitive to the degree of lymphopenia at the time of testing [25, 26]. A multivariate model to predict impending AIDS-defining illness or death among patients starting HAART has recently been derived from an observational database of Asian patients by the TREAT Asia (Therapeutics Research, Education, and AIDS Training in Asia) investigators [22]. The accompanying editorial by Mocroft and Lundgren [23] speaks to the caveats and qualifications pertinent to prognostic models in both resource-constrained and more affluent healthcare delivery settings [27–31]. A unifying corollary implicit in all these reports is that risk stratification can direct targeted prophylaxis and/or preemptive therapy for HIV-infected patients with low CD4 cell counts who are about to initiate, resume, or change.
HAART; the objective of such interventions would be to diminish inflammatory flares precipitated by robust immune restoration that could disrupt otherwise efficacious and well-tolerated antiretroviral therapy.

Obviously, many practical questions remain unanswered, and the devil likely resides in the details. For example, *Pneumocystis jiroveci* prophylaxis might be universally prescribed for patients with a CD4 cell count of <200 cells/μL, whereas in the absence of an exposure history, only patients with a positive tuberculin skin test result or a positive interferon-γ release assay result would receive antituberculous treatment, regardless of CD4 cell count [32]. What tests should be performed and for which populations of patients? Also, what should be the CD4 cell count threshold for testing and the initiation of therapy? When should full-treatment regimens be administered instead of prophylactic doses? What circumstances might tip the risk-benefit ratio in favor of delaying HAART for a brief period to allow pathogen-specific therapy [15, 19, 33–36]? How long must therapy be continued for exclusively opportunistic infections once immune competence is presumably restored? Given the global economic climate, would another programmatic extension for HIV-infected patients with subthreshold CD4 cell counts who are about to begin HAART be feasible and affordable without sacrificing more solid, evidence-based interventions?

After excluding clinically overt disease at baseline, caregivers need to address the possibility of occult, latent, or misdiagnosed low-grade infections and malignancies. HIV infection itself may be wrongly presumed to be the sole cause of nondescript symptoms and signs. In this context, to supplement the history and examination of a patient, the following procedures and tests merit consideration before the initiation of HAART for patients with very low CD4 cell counts: a chest radiograph; a purified protein derivative skin test and/or an interferon-γ release assay; a rapid plasma reagin titer and/or a microhemagglutination assay; a determination of serum creatinine and alanine aminotransferase levels; hepatitis B and C serologies with reflexive quantification by nucleic acid amplification tests [37–39]; serum (or urine) cryptococcal (or histoplasmal) antigen assays; a qualitative or quantitative polymerase chain reaction assay for cytomegalovirus DNA or pp65 antigen testing (in addition to a dilated fundoscopic examination [34]); mycobacterial blood (and possibly stool) culture; fecal examination to detect *Strongyloides* larvae; stool culture to detect *Salmonella* species; human papillomavirus DNA or cytologic screening tests for cervical and other anogenital cancers to accompany pelvic and rectal examinations with or without anoscopy [40–45]; magnetic resonance imaging of the brain to detect latent central nervous system disease (such as incipient progressive multifocal leuкоencephalopathy); cosyntropin stimulation testing; and assessment of fasting glucose and lipid profiles. Some, all, or none of these procedures or tests may be appropriate for use in up-front investigations of certain patient populations and situations. However, for directing further diagnostic and therapeutic interventions, indiscriminate testing cannot substitute for the knowledge gleaned from a patient’s medical history, epidemiologic circumstances, and physical findings.

Inflammatory exacerbations of mild, subclinical, or latent infections may be precipitated by the initiation of otherwise successful HAART as an overzealous and dysregulated immune system is restored. IRIS can be responsible for substantial morbidity and mortality, particularly among HIV-infected patients immuno-compromised by extremely low CD4 cell counts. Preemptive therapy to reduce the pathogen load could theoretically lessen the intensity of the inflammatory reaction. Despite the paucity of persuasive supporting data, the clinical circumstances are frequent enough and the associated threat of serious IRIS real enough to warrant more explicit advice about how to prevent this potentially devastating complication when the next generation of antiretroviral treatment guidelines are debated [46, 47]. Of course, if we are successful in identifying and treating HIV-seropositive persons earlier in the course of their infection than has been the reality to date, many of the steps proposed above would become increasingly irrelevant [2, 4, 31, 48–53].

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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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