Assessing the Contribution of the Immune Reconstitution Inflammatory Syndrome to Mortality in Developing Country Antiretroviral Therapy Programs

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(See the article by Castelnuovo et al, on pages 965–72.)

Coverage of antiretroviral therapy (ART) in low- and middle-income countries remains limited and, by the end of 2007, reached only ~30% of those individuals who needed it [1]. However, there has been rapid progress in increasing access to ART in developing countries; nearly 3 million people were receiving treatment by the end of 2007, which represented a 7.5-fold increase since 2003 [1]. Nonetheless, early mortality rates among adults enrolled in ART programs in resource-limited settings are high and considerably exceed those in high-income settings, even after adjustment for immunodeficiency [2, 3]. Although knowledge of common causes of death is crucial to understanding this higher mortality, to date, such data have been limited, and no systematic post-mortem studies have been reported [2].

A review of 5 observational cohort studies from developing countries that reported on mortality among ART cohorts has suggested that tuberculosis (TB), cryptococcal meningitis, and Kaposi sarcoma are the leading causes of death in these settings [2]. Given that immune restoration is a time-dependant process, patients who initiate ART when profoundly immunosuppressed remain at risk for opportunistic infections for the first several months—and sometimes for the first several years—of ART, even if they have experienced virological suppression. Opportunistic infections that occur during the early period of ART largely reflect persistent immunodeficiency, but in a subset of patients, immune reconstitution inflammatory syndrome (IRIS), which results from dysregulated and excessive inflammatory responses directed at the antigens of opportunistic infections, influences the clinical presentation and course [4]. More-advanced immunodeficiency at ART initiation has been identified as a risk factor for IRIS. IRIS is thus a frequent early complication of ART in resource-limited settings, where patients often initiate ART late with low CD4 cell counts and after having received a diagnosis of opportunistic infection [4–6]. It has been suggested that IRIS may be an important contributor to the higher mortality rates reported from cohorts in these settings [7].

The study by Castelnuovo et al [8] provides important data regarding the causes of death among patients who are receiving ART in the context of a busy ART clinic from a developing country. Mortality within the first 36 months of ART is indeed high (17%) and is similar to that in other resource-limited settings, with the leading causes of death concurring with the findings of previous studies [2, 8]. Almost 60% of these deaths occurred within the first 3 months of ART. The contribution of IRIS to this mortality was relatively small; only 4 (7%) of the 54 HIV-related deaths that occurred within the first 3 months of ART were attributed to IRIS. No cases of death were attributed to paradoxical TB-IRIS, which confirmed other reports that this is a condition that infrequently results in death [5, 9].

These findings need to be interpreted with 2 important caveats. First, our understanding of IRIS, and particularly of unmasking IRIS, is currently incomplete. Second, the retrospective design of this study may have resulted in an underestimation of the contribution of IRIS. Furthermore, as the authors indicate, not all of the findings may be generalizable to other low-income settings.
Current understanding of IRIS. A very wide range of clinical manifestations of IRIS have been described [7, 10]. Castelnuovo et al [8] used case definitions that were similar to published definitions to ascertain cases [6, 7, 11]. Current case definitions of IRIS are reliant on a characteristic course of clinical events and the development of clinically apparent inflammatory manifestations. For paradoxical forms of IRIS, the characteristic course of events involves diagnosis of an opportunistic infection before ART initiation, improvement during treatment for that opportunistic infection before ART initiation, and clinical deterioration during early effective ART, with recurrence of symptoms of the opportunistic infection and/or the finding of inflammatory manifestations involving ≥1 organ system. Alternative causes for deterioration need to be excluded. Unmasking IRIS is not as clearly defined, and the consensus case definition for unmasking TB-IRIS that has been proposed is provisional [6]. Unmasking IRIS describes patients who have received a new diagnosis of an opportunistic infection during early ART, the presentation or course of which is associated with features of an excessive inflammatory response. The central difficulty is differentiating between an opportunistic infection that is diagnosed during early ART that has a normal presentation and an infection in which the presentation is the result of unmasking IRIS.

It is possible that we do not yet understand the full spectrum of effects that unmasking IRIS may have in patients who have received a new diagnosis of opportunistic infection in the first months of ART. Could IRIS contribute to increased disease severity and poorer outcome through exacerbating systemic inflammatory responses, without evidence of focal inflammatory manifestations on clinical examination? Paradoxical TB-IRIS is accompanied by hypercytokinemia [12], and this is likely to be a feature of unmasking forms of IRIS that may drive such a systemic inflammatory response syndrome. Through similar mechanisms, could IRIS result in more rapid clinical deterioration, leading to patients dying before having the opportunity to access medical facilities and receive a diagnosis, especially in resource-poor settings? Almost one-quarter of the deaths during the first year of this study were due to undiagnosed infections. Might there be evidence of greater degrees of inflammation in tissues affected by these opportunistic infections, which biopsy or postmortem specimens might demonstrate, compared with that which is clinically apparent? In a recent case report of fatal unmasking TB-IRIS, severe inflammation in lung tissue was found at postmortem examination with unusual histologic features (bronchiolitis obliterans organizing pneumonia), which likely contributed to the fatal outcome [13].

The presentation of opportunistic infections in HIV-infected patients is, in any event, heterogeneous, as are the immunopathological mechanisms underlying opportunistic infection presentations among patients who are receiving ART. Although some patients will clearly fit the clinical case definitions of unmasking IRIS and others will clearly not have IRIS (eg, patients with an opportunistic infection but no viral load or CD4 cell response to ART), there is a proportion of patients in whom it may be impossible to clinically exclude the contribution of an excessive inflammatory component to the presentation and course of their illness [6]. Future studies that prospectively assess for IRIS and also study immunological changes and disease site pathology (tissue biopsy and postmortem specimens) in patients who have received a diagnosis of an opportunistic infection while receiving ART may find that the role of unmasking IRIS in such cases (particularly for those patients who have a fatal outcome) is greater than studies that use existing case definitions have suggested.

Study design. The ability to confidently exclude the contribution of IRIS to mortality may be impacted by applying case criteria retrospectively, particularly if there was no prospective ascertainment of IRIS cases. An example of the difference between retrospective and prospective ascertainment of IRIS cases has been seen with Kaposi sarcoma IRIS. A study from London, UK, that involved case ascertainment from clinical records found that the incidence of Kaposi sarcoma IRIS among patients who had a Kaposi sarcoma diagnosis at ART initiation was 7% [14]. A more recent prospective study conducted in Uganda, where patients with Kaposi sarcoma were carefully assessed prospectively at regular intervals for predefined features of inflammatory exacerbations of Kaposi sarcoma lesions after starting ART, found the incidence of Kaposi sarcoma IRIS to be 50%– 75% [15]. While these differences may partly be attributable to differences between the cohorts, it is almost certain that the difference in study design explains at least part of the difference in findings.

Castelnuovo et al [8] state that nearly one-quarter of deaths were due to undiagnosed infection, demonstrating the difficulties with ascertainment of causes of mortality in this context without access to postmortem examinations. In addition, limited access to facilities for mycobacterial culture and bacteriological blood culture may have reduced the capacity for definitive diagnosis.

Generalization of results. In any given clinical context, the relative prevalence of opportunistic infections, degree of access to facilities for their diagnosis, and the extent of opportunistic infection screening and treatment before ART initiation could all impact on the occurrence of IRIS and its contribution to mortality, as well as its definitive diagnosis. In other ART cohorts, cryptococcal IRIS has been associated with substantial mortality [16]. With this in mind, the practice in this cohort of screening patients regardless of symptoms for cryptococcal antigenemia prior to ART ini-
tiation and commencing fluconazole therapy in many of those who were found to have positive results could have reduced the risk of unmasking cryptococcal IRIS and its associated mortality, compared with settings in which this is not routine practice. Irrespective of the contribution of IRIS, the finding that 8 of 11 patients who died of cryptococcal antigenemia, especially for those individuals with CD4 cell counts <100 cells/µL [17].

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