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Assessing the contribution of the immune reconstitution inflammatory syndrome to mortality in developing country antiretroviral therapy programs

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Coverage of antiretroviral therapy (ART) in low- and middle-income countries remains limited, reaching approximately 30% of those needing it by the end of 2007.[1] There has, however, been rapid progress in increasing access in developing countries with nearly 3 million people on treatment by the end of 2007, representing a 7.5 fold increase since 2003.[1] However, early mortality rates among adults in ART programmes in resource limited settings are high, and considerably exceed those in high-income settings, even after adjustment for immunodeficiency.[2,3] While knowledge of common causes of death is crucial to understanding this higher mortality, such data to date is limited with no systematic postmortem studies having been reported.[2]

A review of 5 observational cohort studies that reported on mortality in developing country ART cohorts suggested that tuberculosis (TB), cryptococcal meningitis and Kaposi's sarcoma are 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 few months, and sometimes 1–2 years, on ART even if virologically suppressed. Opportunistic infections occurring during early ART largely reflect persistent immunodeficiency, but in a subset the 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 counts and after having been diagnosed with opportunistic infections.[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]

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The study by Castelnuevo *et al* provides important data regarding the causes of death on ART in the context of a busy ART clinic from a developing country.[8] Mortality in the first 36 months on ART is indeed high (17%) and similar to that of other resource-limited settings with the leading causes concurring with those 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 with only 4 of 54 HIV-related deaths occurring in the first 3 months on ART (7%) attributed to IRIS. No cases of death were attributed to paradoxical TB-IRIS, confirming other reports that this is a condition that infrequently results in death.[5,9]

These findings need to be interpreted with two important caveats. Firstly, our understanding of IRIS, and particularly unmasking IRIS, is currently incomplete, and secondly, the retrospective design of this study may have resulted in the contribution of IRIS being underestimated. Furthermore, as the authors indicate, not all the findings may be generalisable to other low-income settings.

Current understanding of IRIS

A very wide range of clinical manifestations of IRIS are described.[7,10] Castelnuevo *et al* used case definitions 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, improvement on treatment for that opportunistic infection prior to ART, then clinical deterioration during early effective ART with recurrence of symptoms of the opportunistic infection and/or the finding of inflammatory manifestations involving one or more 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 are newly diagnosed with 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 an opportunistic infection that is diagnosed during early ART that has a normal presentation from a presentation that 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 diagnosed with new opportunistic infections 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 hypercytokinaemia[12] and this is likely 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 get a diagnosis, especially in resource poor settings? Almost a quarter of the deaths in 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, that biopsy or postmortem specimens may demonstrate, compared to what 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, that of bronchiolitis obliterans organizing pneumonia, that 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 on ART. While some patients will clearly fit the clinical case definitions of unmasking IRIS and others will clearly not have IRIS (for example, patients with an

opportunistic infection but no viral load or CD4 response to ART), there is a proportion 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 which prospectively assess for IRIS, and also study immunological changes and disease site pathology (tissue biopsy and post mortem specimens) in patients diagnosed with an opportunistic infection on ART may find that the role of unmasking IRIS in such cases (and particularly those patients who have a fatal outcome) is greater than studies using existing case definitions suggest.

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's sarcoma IRIS (KS-IRIS). A study from London which involved case ascertainment from clinical records found the incidence of KS-IRIS in patients who had a KS diagnosis at ART commencement was 7%.[14] A more recent prospective study conducted in Uganda where patients with KS were carefully assessed prospectively at regular intervals for predefined features of inflammatory exacerbations of KS lesions after starting ART found the incidence of KS-IRIS to be 50–75%.[15] While these differences may partly be due 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* state that nearly a quarter of deaths were due to undiagnosed infections demonstrating the difficulties with ascertainment of causes of mortality in this context without access to postmortem examinations.[8] In addition, limited access to facilities for mycobacterial culture and bacteriological blood culture may have reduced capacity for definitive diagnosis.

Generalisability

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 prior to 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 antigenaemia prior to ART and commencing fluconazole in many of those found to be positive could have reduced the risk of unmasking cryptococcal IRIS and its associated mortality, compared to settings where this is not routine practice. Irrespective of the contribution of IRIS, the finding that 8 of 11 patients who died of cryptococcal meningitis had asymptomatic cryptococcal antigenaemia at baseline underpins the importance of screening for and pre-emptively treating cryptococcal antigenaemia, especially in those with CD4 counts < 100 cells/ μ L.[17]

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