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Response to “HIV immune reconstitution syndrome in sub-Saharan Africa”

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To the Editor:

We wish to respond to editorial comment “HIV immune reconstitution syndrome in sub-Saharan Africa” by Dr. Easterbrook. While our prospective study [1] suggested that the immune reconstitution inflammatory syndrome (IRIS) may have less impact on antiretroviral treatment (ART) programmes in resource limited settings than previously suggested by retrospective studies, Dr Easterbrook questions whether our experience from Johannesburg is representative for sub-Saharan Africa and whether our study has underestimated the IRIS burden. In order to accurately draw conclusions from our study, we wish to clarify a few of our findings.

Dr. Easterbrook correctly states a number of factors may influence the incident estimate of a disease or outcome, and no single ART programme is representative of all patients across sub-Saharan Africa. We believe our estimate of IRIS is accurate for a number of reasons. First, outpatient clinics are the most representative setting for ART programmes. Few inpatients initiate ART because of eligibility screening, adherence counseling, and the urgent need for diagnosis and treatment for their inpatient condition. While such patients are theoretically at increased risk for IRIS, the overall number of such patients is few.

Second, while the patient population consisted of an urban cohort in a tertiary referral ART clinic, baseline data were comparable to other reported cohorts [2–4]. 63% had a history of one or more opportunistic infections (OI), and 92/423 (21.8%) had one or more OI within 30 days of ART initiation, most commonly tuberculosis, oral candidiasis, and pneumonia. Cotrimoxazole was prescribed in over 86% of patients. “Comorbid illnesses” referred to chronic, non-infectious conditions, such as hypertension and diabetes, and is reflective of the young and predominantly female characteristics of the cohort.

Third, while Dr Easterbrook questions the rigor of baseline screening, our data demonstrate baseline screening is relatively comprehensive. Symptom-based screening for TB at baseline included 179/423 (43%) of patients having ≥ 2 AFB smears and/or a BACTEC culture obtained prior to ART. Of the 16 “unmasking” TB-IRIS cases, 12 (75%) were screened with AFB sputa,

BACTEC cultures, and/or chest radiographs. Of the 4 unscreened patients, 3 were asymptomatic at baseline and demonstrated abdominal or lymphadenitis manifestations, likely indicating subclinical disseminated TB at ART initiation. The remaining patient completed TB therapy 18 months prior to ART and was asymptomatic at initiation. These patients manifested abrupt onset of symptoms 22–34 days after ART initiation, supporting the IRIS diagnosis. While the systematic screening of all patients initiating ART, independent of symptoms, using sputum and chest radiographs could influence the proportion of “unmasking” versus paradoxical IRIS, the reality of employing such a strategy in an endemic TB setting would be unsustainable in a resource-limited health care system.

Fourth, we employed an active case finder to identify patients with missed visits, and loss to follow-up (12.6%) was similar to other Southern African cohorts (0–15%) [5]. Even assuming IRIS was present in these patients and associated with a significant mortality, the effect of these patients on the overall incidence rate would be modest.

Lastly, case finding was active. In addition to scheduled clinic visits, patients were also evaluated at patient-initiated unscheduled visits, whether IRIS-related symptoms or not. According to South African guidelines, patients procured their ART medications monthly in the pharmacy clinic, affording additional opportunities to identify problems related to ART.

To date, no objective measure of immune reconstitution is readily available to the practicing clinician. A ≥ 1 log reduction in viral load was included in our IRIS case definition in order to provide as much *objective* immunological evidence as possible to exclude ART noncompliance and HIV viral resistance at the time of IRIS evaluation. Our study is the first to prospectively apply some, albeit imperfect, measure of immune reconstitution. We agree that it is not likely to be predictive of IRIS events, but included it in the analysis to address findings of previous studies [6]. What is sorely needed is a practical, objective measure of immune reconstitution to support IRIS case definitions. Until such a measurement is available, IRIS definitions which rely solely on clinical signs and symptoms in developed *or* resource-limited settings will be plagued by the lack of immunological validation and the subjectivity of their application across heterogeneous patient populations.

We hope these data provide insight into the clinical spectrum of this difficult complication of ART therapy and will aid clinicians involved in the treatment of HIV-infected patients in sub-Saharan Africa. Future prospective studies should focus on pathogen-specific IRIS in diverse populations to characterize and measure its clinical spectrum, elucidate the underlying immunopathology, and identify methods for its prevention.

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