Published in final edited form as:

Lancet Infect Dis. 2010 December ; 10(12): 833–834. doi:10.1016/S1473-3099(10)70280-2.

The immune reconstitution inflammatory syndrome: a systematic review

Stephen D. Lawn^{a,b} and Robin Wood^a

^aThe Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.

^bClinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK.

Keywords

HIV; antiretroviral; immune reconstitution; IRIS; cryptococcal; tuberculosis

Dear Editor,

We read with interest the systematic review and meta-analysis of the immune reconstitution inflammatory syndrome (IRIS) by Muller and colleagues published in the April 2010 issue of *TLID*.¹ IRIS associated with antiretroviral therapy (ART) is a highly heterogeneous complication arising within the initial months of treatment. The authors are to be congratulated on providing an important summary of the frequency of IRIS associated with a range of HIV-associated diseases.

On reviewing the systematic review data-set, it is striking that some studies appear to be extreme outliers with unusually low frequencies of IRIS. For example, the study by Park *et al.* from South Korea is reported as showing a rate of TB IRIS of just 2%.² Similarly, our own study from Cape Town, South Africa, is reported as showing a rate of cryptococcal IRIS of just 2%.³ These results both lie well below the lower 95% credibility intervals of the meta-analysis summary estimates. We are concerned that data from both studies have been misinterpreted and that no regard has been given to the existence of two broad categories of IRIS which should be considered as separate entities within such an analysis.

‘Paradoxical’ IRIS is the term used to describe IRIS that occurs among patients already receiving treatment for an opportunistic disease and in whom immune recovery following subsequent initiation of ART triggers the clinical deterioration of that disease during the initial months of treatment. In contrast, ‘unmasking’ IRIS is the term used to denote the clinical phenomenon in which opportunistic disease that was not apparent at the time of ART initiation becomes clinically manifest as a result of ART-induced immune recovery. While risk of the former is strongly related to the timing of ART during the treatment of the opportunistic disease,⁴ the frequency of unmasking IRIS will vary according to the prevalence of the opportunistic disease in any given setting and the efficiency of pre-ART screening.^{5,6}

Correspondence: Stephen D. Lawn, Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925, Cape Town, South Africa. Tel +27 21 650 6970 Fax +27 21 650 6963 stevelawn@yahoo.co.uk.

Conflicts of interest

The authors have no conflicts of interest to declare

Tuberculosis (TB) and cryptococcal disease can each be associated with either form of IRIS. Since the denominators used to calculate the frequencies of these two forms of IRIS are mutually exclusive, the calculation of pooled summary estimates from data-sets reporting on both forms of IRIS makes little sense. We suspect this explains why the results from the study by Park *et al.*² and our own study⁴ appear to be outliers in the analysis of Muller and colleagues and we are concerned that this may in particular have undermined the meta-analysis summary estimate for the frequency of cryptococcal IRIS.

In their meta-analysis of cryptococcal IRIS, Muller and colleagues draw upon data from 6 studies, five of which relate exclusively to the risk of paradoxical IRIS in patients with known cryptococcal disease prior to starting ART. In these five studies, 67 cases of IRIS were reported among 245 patients with a crude frequency of approximately one quarter. However, data were also included from our cohort in Cape Town, South Africa.³ In this study, we described 6 cases of paradoxical cryptococcal IRS occurring among 18 patients with a pre-existing diagnosis of cryptococcal meningitis, giving a frequency of 33% (95%CI, 16–56%). This proportion is entirely consistent with the other 5 studies and it would have been entirely appropriate to include these cases in this form in the meta-analysis.

However, we also reported 3 cases of unmasking cryptococcal IRIS among the remaining cohort of 416 patients who did not have pre-existing cryptococcal disease. Muller and colleagues have unfortunately not distinguished between paradoxical and unmasking forms of disease and simply reported an overall rate of cryptococcal IRIS of 2% in the total cohort of 434 patients. As a result, the study appears as an extreme outlier within the meta-analysis data-set. Both the numerator and denominator used from our study to calculate the event frequency are entirely different to those obtained from the remaining 5 studies and so the meta-analysis summary estimate from the total of 6 studies is therefore unfortunately flawed. The impact of this will have been to underestimate the true frequency of paradoxical cryptococcal IRIS.

A further consequence of the failure to make the distinction between paradoxical and unmasking forms of IRIS is that no consideration has been given to the timing of ART in those with TB or cryptococcal meningitis. This is a critical determinant of the risk of paradoxical IRIS⁴ and may in part explain the considerable heterogeneity in rates between studies. This key variable is one which clinicians can control and thus is the subject of a number of ongoing randomised controlled trials. Notwithstanding these limitations, our own experience in the field is consistent with the important finding of Muller and colleagues that cryptococcal IRIS is the form of IRIS most strongly associated with mortality.^{7,8}

Acknowledgments

SDL is funded by the Wellcome Trust, London, UK. RW is funded in part by the National Institutes of Health (NIH) through a CIPRA grant 1U19AI53217-01 and RO1 grant (A1058736-01A1).

References

1. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis.* 2010; 10:251–261. [PubMed: 20334848]
2. Park WB, Choe PG, Jo JH, et al. Tuberculosis manifested by immune reconstitution inflammatory syndrome during HAART. *AIDS.* 2007; 21:875–877. [PubMed: 17415046]
3. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. *AIDS.* 2005; 19:2050–2052. [PubMed: 16260920]

4. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007; 21:335–341. [PubMed: 17255740]
5. Lawn SD, Kranzer K, Edwards DJ, McNally M, Bekker LG, Wood R. Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pre-treatment screening strategy. *AIDS*. 2010 in press.
6. Jarvis JN, Lawn SD, Vogt M, Bangani N, Wood R, Harrison TS. Screening for cryptococcal antigenemia in patients accessing an antiretroviral treatment program in South Africa. *Clin Infect Dis*. 2009; 48:856–862. [PubMed: 19222372]
7. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS*. 2005; 19:2141–2148. [PubMed: 16284464]
8. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS*. 2008; 22:1897–1908. [PubMed: 18784453]