

Understanding Causal Pathways in Cryptococcal Meningitis Immune Reconstitution Inflammatory Syndrome

Authors: Joseph N. Jarvis^{1,2,3,4*}, Thomas S. Harrison⁵

Affiliations:

1. Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK
2. Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana
3. Botswana University of Pennsylvania Partnership, Gaborone, Botswana
4. Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA, USA
5. Centre for Global Health, Institute for Infection and Immunity, St. George's University of London, UK

* Corresponding author: Botswana Harvard AIDS Institute Partnership, Private Bag BO320, Gaborone, BOTSWANA. Email: joseph.jarvis@lshtm.ac.uk

HIV-associated cryptococcal meningitis continues to pose a major clinical challenge. Mortality rates of 20-40% have been reported in recent clinical trials using currently recommended amphotericin-based treatments[1, 2], and the clinical course of illness in those who do survive is frequently complicated by prolonged or recurrent disease[3, 4]. Immune reconstitution inflammatory syndrome (IRIS) occurs in 15-20% of individuals who survive their initial illness and initiate antiretroviral therapy (ART), causing a further substantial burden of morbidity and mortality[3-6]. Determining the underlying immune pathology of IRIS, with a view to developing effective prevention or treatment and enabling safe and rapid initiation of ART is, therefore, of considerable importance, and a core component of improving patient outcomes from this severe opportunistic infection.

The development of cryptococcal IRIS (C-IRIS) is strongly associated with a poor baseline inflammatory response, an accompanying high organism or antigen load, and rapid immune reconstitution from a low baseline CD4⁺ cell count on ART[3, 7-9]. Although the specific host and pathogen attributes leading to the paucity of effective immune responses and defective antigen clearance during the initial cryptococcal meningitis episode are unknown, human studies suggest that persistently elevated cryptococcal antigen levels despite antifungal therapy leads to increased pro-inflammatory signalling from antigen-presenting cells, with a lack of effective antigen clearance due to the absence of adequate T-cell help[10-14]. Development of cryptococcal IRIS has been strongly associated with high CNS expression of the chemokines MCP-1(CCL2) and MIP-1 α (CCL3) at initial CM presentation and at ART initiation[12, 13] which, following immune restoration with ART, is hypothesized to result in an influx of inflammatory cells into the CNS, excessive dysregulated local inflammation, and IRIS[11-13, 15, 16].

In this issue of *the Journal of Infectious Diseases*, Yoon *et al.* report a novel association between plasma antibody responses at the time of ART initiation and the development of C-IRIS in a well characterised patient cohort from South Africa[17]. Lower levels of plasma IgM antibodies to the

cryptococcal polysaccharide antigen glucuronoxylomannan (GXM), laminarin (Lam) – a β -(1.3)-glucan containing polysaccharide, and pustulan – a β -(1.6)-glucan, and total plasma IgM, were associated with higher risk C-IRIS. Given our lack of detailed understanding of C-IRIS immunopathology, and the focus of most C-IRIS research to date on macrophage / monocyte[8, 16, 18, 19] and T-cell mediated immunity[5, 12, 13, 20], these findings offer potentially important new insights into the mechanisms of disease and offer interesting avenues for future research. The role of antibody-mediated protection in HIV-related cryptococcal infection remains uncertain[21, 22] and, as Yoon and colleagues discuss in their article, although animal model and in vitro studies[23-27], along with some human data[28-30], support a role for natural antibody immunity in the host defense against cryptococcal infection, the mechanisms involved remain unclear.

The observation that less robust IgM antibody responses to fungal antigens at the time of ART initiation were associated with higher likelihood of subsequent C-IRIS may indicate an important role for antibody-mediated protection during cryptococcal meningitis, and fit with the overarching hypothesis that a poor initial immune response and subsequent failure of effective immune clearance of cryptococcal antigens are key predisposing factors for IRIS. Such attributions of causality must be made with caution, however. The South African patient cohort from which the samples were derived is one of the largest and best characterized to date[3], but remains a relatively small sample. Few data were available regarding baseline characteristics of patients prior to antifungal therapy. And adjustments, which are difficult for multiple factors in a small study, were not made for some of the known predictors of C-IRIS, including CSF cytokine and chemokine levels. Prior studies performing detailed immune-phenotyping in HIV-associated cryptococcal meningitis have demonstrated the complex interplay between innate and adaptive immune response and the close correlation of many of the soluble and cellular immune markers measured[13, 18-20], making interpretation of potential mechanisms of protection problematic. The correlation seen in the current study between IgM levels and CD4⁺ cell counts, known to play a critical role in C-IRIS pathogenesis[15], highlights the

difficulty of untangling the relative contributions of interconnected elements of the effective host immune response, even given the adjustment made for CD4 cell counts in the study.

The findings of Yoon and colleagues provide further impetus for larger prospective studies to better determine the role of the host immune response in HIV-related cryptococcal infection, both to understand causal pathways to C-IRIS and, also, the immune correlates of outcome more generally. These studies should include detailed clinical and microbiological characterization of cases with longitudinal follow-up, sample collection for immune phenotyping, including antibody responses and, ideally, genotyping, with the ultimate aim of identifying pathways amenable to intervention to reduce the high rates of morbidity and mortality due to cryptococcal meningitis worldwide[31]. Pending these studies, efforts should be focused on reducing the incidence of C-IRIS through the use of rapidly fungicidal antifungal drug combinations[1, 2] and appropriately timed ART initiation[32, 33] based on evidence from randomized controlled trials, and ensuring clinicians recognize C-IRIS early and manage cases appropriately. Data from our recent trials suggest that with these steps in place the morbidity related to C-IRIS can be reduced substantially in patients initiating ART following cryptococcal meningitis[1, 4, 34], and C-IRIS should no longer carry the devastating prognosis that has historically been associated with the condition.

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