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Cryptococcal Immune Reconstitution Inflammatory Syndrome in HIV-1–infected individuals: Literature Review and Proposed Clinical Case Definitions

Lewis J Haddow, MBChB PhD[1,2], **Robert Colebunders, MD PhD**[3,4], **Graeme Meintjes, MBChB**[5], **Stephen D Lawn, MBChB MD**[6,7], **Julian H Elliott, MBBS PhD**[8,9], **Yukari C Manabe, MD**[10,11], **Paul R Bohjanen, MD PhD**[12,13], **Somnuek Sungkanuparph, MD**[14], **Philippa J Easterbrook, MBBChir MPH**[1,2], **Martyn A French, MBChB MD**[15,16], and **David R Boulware, MD MPH**[12,13] **on behalf of the International Network for the Study of HIV-associated IRIS (INSHI)**

[1]Division of Immunology, Infection and Inflammatory Disease, King's College London, UK [2]Department of Infectious Diseases, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa [3]Institute of Tropical Medicine, Antwerp, Belgium [4]University of Antwerp, Antwerp, Belgium [5]Infectious Diseases Unit, GF Jooste Hospital; Department of Medicine, University of Cape Town, South Africa [6]Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK [7]The Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa [8]Infectious Diseases Unit, Alfred Hospital, Melbourne, Australia [9]Macfarlane Burnet Institute for Medical Research and Public Health, Melbourne, Australia [10]Infectious Diseases Institute, Makerere University School of Medicine, Kampala Uganda [11]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA [12]Center for Infectious Diseases & Microbiology Translational Research, Department of Medicine, University of Minnesota, Minneapolis, MN, USA [13]Division of Infectious Disease & International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA [14]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand [15]School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Australia [16]Department of Clinical Immunology, Royal Perth Hospital and PathWest Laboratory Medicine, Perth, Australia

Abstract

Cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) may present as a clinical deterioration or new presentation of cryptococcal disease following initiation of antiretroviral therapy (ART) and is believed to be caused by recovery of cryptococcus-specific immune responses. We have reviewed the existing literature on C-IRIS to inform the development of a consensus case definition specific for *paradoxical cryptococcal IRIS* in patients with known cryptococcal disease prior to ART, and a second definition for incident cases of cryptococcosis

[1]**Contact details**, Dr David Boulware, Division of Infectious Diseases, McGuire Translational Research Facility, University of Minnesota, 2001 6th Street SE, Minneapolis, , MN 55455, United States, boulw001@umn.edu, Tel 612-624-9996.

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developing during ART (here termed *ART-associated cryptococcosis*), a proportion of which are likely to be "unmasking" C-IRIS. These structured case definitions are intended for use in future clinical, epidemiologic and immunopathologic studies of C-IRIS, harmonizing diagnostic criteria, and facilitating comparisons between studies. As with tuberculosis-associated IRIS, these proposed definitions should be regarded as preliminary until further insights into the immunopathology of IRIS permit their refinement.

Keywords

HIV; cryptococcosis; diagnosis; immune reconstitution inflammatory syndrome; HAART

INTRODUCTION

Cryptococcal disease remains a major cause of morbidity and mortality in persons with advanced HIV/AIDS, particularly in Africa and South-East Asia (1–4). Cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) presents as a clinical deterioration of cryptococcal disease following rapid reversal of immune deficiency (5). This is thought to be mediated by recovery of Cryptococcus-specific immune responses, resulting in exaggerated inflammatory host responses. In HIV, this reversal is driven by antiretroviral therapy (ART), but C-IRIS can also occur after solid organ transplantation, with an estimated incidence of 4.8%, or in pregnancy (6,7).

The International Network for the Study of HIV-associated IRIS (INSHI) was established in 2006 to promote research collaboration and harmonization among IRIS researchers worldwide. Generic IRIS definitions are limited in their application because of the highly heterogeneous spectrum of underlying disease and clinical features of IRIS. We have undertaken a review of existing literature on the clinical and diagnostic features of C-IRIS, and used this to develop a consensus case definition for C-IRIS that can be used in both resource-limited and well-resourced settings.

Classification and terminology

Similar to the case definition of tuberculosis (TB)-associated IRIS (8), two distinct modes of presentation of C-IRIS are recognized. First, in up to one third of patients with cryptococcosis diagnosed pre-ART, "paradoxical" C-IRIS occurs following ART initiation. This presents as worsening or recurrence of treated cryptococcal disease in the same or new anatomical sites despite microbiologic treatment success (9–12). Second, new onset of cryptococcosis occurs in up to 1% of patients initiating ART in whom cryptococcosis was not recognized prior to ART (13–17).

Incident cryptococcosis during ART may result from the emergence of previously sub-clinical disease during immune reconstitution ("unmasking C-IRIS"), or simply be associated with persistent immunodeficiency. These two entities may be indistinguishable at present, therefore we favor the term "ART-associated cryptococcosis" for both unmasking C-IRIS and immunodeficiency-related cryptococcosis occurring on ART.

LITERATURE REVIEW

Literature search

We conducted a Medline search during the period up to June 2010 to identify published cohort studies, case-control studies, case series, and case reports in English describing or enumerating C-IRIS cases. We searched bibliographies of articles focusing on IRIS for other relevant reports. Studies and reports were categorized by whether they used a case definition

for IRIS (Table 1) or simply reported clinical and laboratory features (Table 2). Unpublished data and conference abstracts were not included. Where possible, the original source data was obtained from authors of cohorts.

There were 11 published cohort studies focusing on C-IRIS, comprising 142 cases from Brazil, France, Italy, South Africa, Thailand, Uganda, and the United States (U.S.) (9–12,14,18–24). A further 5 cohort or case-control studies that also reported other IRIS-associated conditions described an additional 23 cases of C-IRIS or ART-associated cryptococcosis (15,16,25–27), and case reports and series reported 48 cases (28–54). Overall, 183 of the 213 reported cases (85.9%) were paradoxical C-IRIS, while the remainder were either ART-associated cryptococcosis (n=25) or in individuals where the pre-ART history was unknown (n=3).

Almost all structured case definitions used to diagnose C-IRIS (9–12,15,21,26,52) focused on paradoxical presentations, and share three common criteria: (1) new or worsening clinical disease after ART initiation, (2) evidence of ART effectiveness, and (3) exclusion of alternative etiologies. The clinical and laboratory case definition criteria for C-IRIS were inconsistent between studies and were frequently subjective or imprecise (e.g. “evidence of immunological and/or virological response”) (12,21). Six of thirteen studies that used an IRIS definition required fungal cultures to be negative in paradoxical C-IRIS (9–12,18,19).

Paradoxical cryptococcal IRIS in HIV-infected patients receiving ART

In seven studies including a total of 598 patients with known cryptococcal disease initiating ART, the reported incidence of C-IRIS was 8–49% (9–12,14,19–21,23,24,27). Of 171 cases in which both the site and mode of presentation were published, 126 (73.7%) involved mainly meningeal disease (Table 1 and 2). Other common presentations were complications of central nervous system (CNS) disease (19 cases; 11%), lymphadenopathy (19 cases; 11%), pneumonitis (9 cases; 4.5%), multifocal disease (7 cases; 4.1%) and soft tissue disease (2 cases; 1.8%). Specific CNS features included intracranial cryptococcoma or abscess (20,22,35,41), spinal cord abscess (38), recalcitrant raised intracranial pressure (22,34,43), optic disk swelling (50), cranial nerve lesions (21,45), dysarthria (26), hemiparesis (21) and paraparesis (14,53). Non-CNS manifestations of paradoxical C-IRIS include fever (28,31,48), eye disease (9), suppurating soft tissue lesions (28,33,36), hypercalcemia (36) and pulmonary disease, including cavitating or nodular lesions (9,11,22,26,36,52).

The time of onset of paradoxical C-IRIS after ART varies widely, from 4 days up (31) to around 3 years (12,38), with a median time ranging from 1 to 10 months (9–12,14,18–21) in cohort studies. Reported CD4 counts prior to ART were typically below 50 cells/mm^3 (summarized in Table 1) but pre-ART viral loads (VL), virologic outcomes and follow-up CD4 counts were inconsistently reported. In case reports, individual data were usually reported, giving a median baseline CD4 count of 28 cells/mm^3 and VL of 5.6 $\log_{10}$ copies/mL, and CD4 count at event of 162 cells/mm^3 and VL of 2.4 $\log_{10}$ copies/mL.

One study reported comparable data for controls (21), although follow-up data were recorded at 6 months and not at the time of symptoms. In this South African study of 11 cases and 54 controls, the median baseline CD4 count in 6 cases was 28 cells/mm^3, rising to 162 cells/mm^3 after 6 months of ART, compared to 41 cells/mm^3 at baseline in controls, rising to 187 cells/mm^3 after 6 months (21). Baseline VL in cases was median 110,000 copies/mL, with a minimum fall of 1.6 $\log_{10}$ at the time of event, and all cases had VL <1000 copies/mL at 6 months. In controls, baseline VL was 150,000 copies/mL and at least 75% achieved VL <50 copies/mL at 6 months.

Mortality from paradoxical C-IRIS and ART-associated cryptococcosis ranges from 27–83% in Africa (9,14,15,21,22) and 0–20% in North America, Europe and South-East Asia (10,12,19,20,23). In sub-Saharan Africa, paradoxical C-IRIS is considered to be an important contributor to early mortality following ART (9,14,18,22).

Risk factors for paradoxical C-IRIS have been reported in six studies (10–12,23,55), and retrospective cohorts indicate these may include higher HIV-1 viral load prior to ART (in a study including both ART-experienced and naïve patients) (10), earlier initiation of ART (10,12) and greater CD4 count increase in the first 6 months of ART (21). However, in three prospective cohorts, HIV-1 viral load, time to start ART, and baseline CD4 were not risk factors for C-IRIS (21–23). Markers of fungal burden may also be risk factors, i.e.; the presence of fungemia; and higher serum cryptococcal antigen (CrAg) titer at pre-ART diagnosis (23). However, two studies examining markers of fungal burden did not find an association between number of colony-forming units in the CSF and IRIS (21,22). In another prospective cohort, lack of initial CSF inflammation (CSF protein <50 mg/dL and WBC <25 cells/μL) prior to ART was associated with a seven-fold increase in IRIS risk (22).

ART-associated cryptococcosis

Infection with *Cryptococcus neoformans* can remain latent for years after initial exposure (56), and active disease may remain subclinical for some time in patients with advanced immunodeficiency, so it is not surprising that clinical cryptococcosis may emerge for the first time after ART initiation. The incidence of ART-associated cryptococcosis ranged from 0.2% to 1.6% in 6 studies including a total of over 2000 patients without evidence of cryptococcosis before initiating ART (13–17,27). However, the incidence may be as high as 33% in individuals with subclinical cryptococcal antigenemia without fluconazole preemptive therapy (57,58). Subclinical antigenemia is therefore the overwhelming risk factor for ART-associated cryptococcosis (17,57).

Of 25 cases of ART-associated cryptococcosis in which clinical features were described, the clinical spectrum and relative frequency of different manifestations were similar to that reported in paradoxical C-IRIS. Meningitis and/or CNS complications occurred in 17 cases (68.0%), skin or soft tissue lesions in 3 cases (12.0%), lymphadenopathy in 2 (8.0%), lung disease in 2 (8.0%), and disseminated disease in 1 (4.0%). In 13 cases where individual values were reported, the baseline median CD4 count was 19 cells/mm^3 and VL was 5.5 log_{10} copies/mL, and follow-up median CD4 count was 65 cells/mm^3 and VL was 2.6 log_{10} copies/mL.

One feature of ART-associated cryptococcal meningitis is the accelerated onset of severe illness over a few days (14,17,31,53) from the onset of symptoms, compared with the 1 to 2 week subacute course typically seen with cryptococcal meningitis (CM) in patients not receiving ART (9,59). We compiled all individually reported times of symptom onset: the median time on ART was 9 weeks (n=54, inter-quartile range (IQR) 2–26 weeks) in paradoxical C-IRIS cases and 4 weeks (n=19, IQR 2–10 weeks) in ART-associated cryptococcosis cases, although this was not statistically different (*P*=0.12, Wilcoxon rank-sum test).

In patients who develop new clinical cryptococcosis during ART, it may be very difficult to differentiate between IRIS-associated disease (caused by restoration of specific immune responses) and progression of untreated, occult cryptococcosis in the context of persisting immunodeficiency (60). The analogous situation in ART-associated tuberculosis has led to the use of the term “unmasking TB-IRIS” being reserved for a subset of cases with “heightened intensity of clinical manifestations” or “rapid, destructive necrotic

inflammation" (8,61–65). It may be that unusual ART-associated cryptococcosis cases with florid inflammatory features are more likely to occur with unmasking IRIS.

However, the clinical spectrum of ART-associated cryptococcosis does not appear to differ significantly from that seen in the pre-ART era, when 75–90% of cryptococcosis presented as meningitis and/or encephalitis, and the remainder were mainly pneumonitis, lymphadenopathy, or cutaneous lesions (66). Therefore, while we acknowledge that most post-ART cases of cryptococcosis may be *suspected* unmasking C-IRIS, we propose that such cases should be reported as ART-associated cryptococcosis until further evidence becomes available to support meaningful clinical discrimination between C-IRIS and immunodeficiency disease.

PROPOSED CASE DEFINITIONS FOR CRYPTOCOCCAL IRIS

We have developed case definitions for paradoxical C-IRIS and ART-associated cryptococcosis based on published data on the clinical and diagnostic features. The case definition for paradoxical C-IRIS (Table 3) applies to patients with recognized pre-ART cryptococcal disease who subsequently deteriorate while on ART. The definition of ART-associated cryptococcosis (Table 4) applies to those without recognized cryptococcosis at the time of initiating ART, who develop cryptococcosis on ART. While these definitions are focused on HIV-related IRIS, we anticipate their modification for use in other, non-HIV situations where there is reversal of immunosuppression (5–7).

Diagnostic criteria for paradoxical C-IRIS (Table 3)

Clinical features—From our literature review, we identified five main clinical syndromes in paradoxical C-IRIS and ART-associated cryptococcosis: (1) meningitis, accounting for around 70% of cases; (2) space-occupying CNS lesions; (3) lymphadenopathy, typically necrotic; (4) pneumonitis; (5) soft tissue or subcutaneous mass lesions, typically suppurative. Other localized sites such as bone, prostate and peritoneum have been described in non-HIV-infected individuals and may be possible sites of C-IRIS disease, but have not been reported in ART-treated individuals.

There may be vigorous inflammatory signs with granulomatous lesions and/or evidence of necrosis, with or without organisms on fungal staining and culture (28,32,33,38,39,42,46). Unpublished data suggest that elevated C-reactive protein (CRP) and IL-6 concentrations precede the development of C-IRIS, compared with ART-treated individuals with cryptococcosis who do not experience IRIS (67). At time of C-IRIS, a marked type-1 CD4 T-helper (Th1) response is present in serum and CSF (22,55). Prior to ART, persons with increased Th2 responses (e.g. IL-4) may be at increased risk of subsequent C-IRIS (unpublished data). The emerging paradigm of IRIS pathogenesis suggests that persons at risk for C-IRIS have a paucity of inflammation and ineffective antigen clearance prior to ART (22), followed by antigen presentation on ART and a robust and probably dysregulated antigen-specific and generalized pro-inflammatory response (55,60,68–71). A central pathogenic role for an alteration in Th1/Th2 balance has also been proposed (72,73).

The CSF profiles in paradoxical C-IRIS cases frequently show an increased CSF white blood cell count (WBC) and opening pressure (OP) ≥25 cm of CSF, but the range of values overlaps considerably with those observed in patients with CM prior to ART or non-IRIS relapses of CM due to therapeutic failure (21,22). In one series of 14 paradoxical C-IRIS cases and 45 controls with non-IRIS CM, higher CSF opening pressures (OP) (median 45 vs. 31 cm CSF) and CSF WBC (56 vs. 12 cells/μL) were reported in IRIS than in non-IRIS cryptococcal meningitis (10). However, the interpretation of these findings is limited because the control group for comparing WBC counts included pre-ART as well as post-

ART cases of cryptococcal meningitis, and high CSF OP and WBC formed part of the diagnostic criteria for IRIS. In addition, these findings were not confirmed by three other studies of similar or larger size (18,21,22). Therefore, at present it is not possible to recommend a pre-defined threshold in CSF OP or WBC to reliably distinguish IRIS from non-IRIS CM, and further studies are needed in this area. Cytokine profiles at time of clinical deterioration may distinguish C-IRIS from CM-relapse with increased pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-12, IL-17) present in the CSF of C-IRIS (22).

Timing of onset of symptoms—We propose an upper time limit of 12 months after ART initiation is based on the reported time of onset in published studies. It appears that C-IRIS has a relatively delayed onset compared to other diseases such as TB, where the median onset of paradoxical TB-IRIS is as early as 2–4 weeks of ART (74,75). Rare, late presentations of cryptococcal disease can occur (12,19,38,42,45), in which cases it becomes essential to exclude ART failure and relapse with fluconazole-resistant organisms.

Confirmation of a therapeutic response to ART—Confirmation of a virologic response to ART is recommended, but not essential, for the diagnosis of C-IRIS. A specific VL threshold (reduction in VL of <1 $\log_{10}$ (15,25,52,62) at the time of clinical event) has been suggested in the literature as an exclusion criterion for IRIS. However, there has never been any experimental validation of the best time to perform VL assays, or the best threshold value. In contrast, studies designed to validate the INSHI TB-IRIS clinical case definition (8) have shown that the absence of CD4 and VL criteria does not significantly impact on the case definition's performance (76,77). Several other major studies examining the epidemiology of IRIS have also omitted CD4 or VL criteria in their case definition (15,25,26,78–81).

While the lack of a virologic response to ART may support an alternate diagnosis of treatment failure, suboptimal responses to combination ART may still be consistent with IRIS (the syndrome was originally described during zidovudine monotherapy (82)). ART-naïve patients with good adherence typically have excellent virologic responses to ART in the first 6 months of therapy (83). In the largest prospective cohort to date, only 5 out of 144 (3.5%) probable IRIS events had virologic failure (27). Therefore one may reasonably assume that ART-naive individuals who are reasonably adherent will have had an early virologic response and partial immune reconstitution within days or weeks of initiating ART, in the absence of another reason, and the lack of available virologic data does not exclude IRIS. In settings where viral load is readily available, a threshold of 1 $\log_{10}$ reduction in VL at the time of clinical deterioration may be employed. In all settings, an assessment of adherence to ART is essential in patients presenting with suspected C-IRIS.

Our C-IRIS case definitions do not include any criteria based on the patient's CD4 count. As with VL changes, some authors have incorporated a rise in CD4 count as a diagnostic criterion for IRIS (15,52,62), but several major studies have omitted this measure (15,25,26,78–81). The main arguments for this omission have been presented above as well as in a published review (8). The number of $CD4^+$ T cells measured in peripheral blood does not necessarily reflect function nor how many CD4 cells are actually present at the site of an opportunistic infection. In addition, there may be functional immunological improvements even in the absence of a CD4 count rise. In one prospective C-IRIS cohort study, 30% (11 of 36) persons with C-IRIS and with sterile CSF cultures and virologic responses had <25 cell/μL CD4 increase from their pre-ART baseline (22). Furthermore, data from cohort studies on IRIS associated with non-tuberculous mycobacterial infection suggest that restoration of a pathogen-specific cellular immune response may occur without an increase in the circulating $CD4^+$ T-cell count (84).

Exclusion of other causes—With regard to exclusion of other causes of disease, we have emphasized the importance of adherence to ART and antifungal therapy, successful response to ART, and exclusion of co-morbidity such as other common pathogens or malignancy. However, in some settings this may be problematic because of limited diagnostic capabilities. As a minimum requirement, TB (using staining for acid fast bacilli) and bacterial disease should be excluded. Indeed IRIS associated with dual co-infection is possible, and ART-associated pulmonary TB has been reported in patients with pre-ART CM (9).

Discriminating C-IRIS from drug toxicity is not usually problematic as there are few drug effects likely to mimic the syndrome. Two rare but plausible considerations are hepatic cryptococcal lesions mimicking drug-related hepatotoxicity (85), and aseptic meningitis induced by trimethoprim/sulfamethoxazole (86).

Pre-ART history—Paradoxical C-IRIS can occur after initiation ART in treatment-naïve individuals, re-initiation of ART, or switching regimen after virologic failure. To meet the antecedent criteria of paradoxical C-IRIS, the pre-ART diagnosis of cryptococcosis may be defined by locally-available diagnostic facilities, e.g. India ink stain, fungal culture, and CSF or serum cryptococcal antigen detection. Two scenarios may fall outside the definition of paradoxical C-IRIS: patients with known cryptococcosis who have discontinued antifungal therapy prior to initiating ART, and cases where a provisional pre-ART diagnosis of cryptococcosis is confirmed after ART initiation.

Role of fungal culture and antigen detection in diagnosing paradoxical C-IRIS —In an ideal setting, quantitative CSF culture should be used to assist the diagnosis of C-IRIS presenting with meningitis. Yet, in contrast with several published definitions (9–12,18,19), our view is that a negative cryptococcal culture is not an absolute requirement for a diagnosis of paradoxical C-IRIS. Our reasoning is that the timing of CSF culture sterility is variable, with approximately 50% of patients becoming culture negative within 2 weeks, 66% by 4 weeks, and 80% by 6 weeks of amphotericin-based therapy (9,87–91). The reality in sub-Saharan Africa is that many cryptococcus-infected patients only receive oral fluconazole (18,92–95) therapy, and CSF sterilization is delayed compared with amphotericin B (89). Even in patients receiving high-dose fluconazole therapy (800–1200mg daily), up to 20% may have persistent positive CSF cultures after 12 weeks (96,97). Thus if patients commence ART shortly after antifungal therapy, they may still be CSF culture positive when they present with paradoxical IRIS. In the largest prospective cohort to date, 32 of 33 subjects with meningitis C-IRIS had negative CSF cultures (22). The single person with culture-positive C-IRIS had a quantitative CSF culture with a very low 70 colony forming units(CFU)/ mL (22).

While accepting the difficulties in diagnosing C-IRIS when cultures remain positive, we favor an approach informed by the expected range of therapeutic responses to antifungal therapy. The management implications of this are discussed below. Although the likelihood of a positive fungal culture and the risk of C-IRIS both decrease over time, we believe a positive fungal culture after 3 months of antifungal therapy is likely to indicate failure of antifungal therapy and therefore propose excluding such events from the paradoxical C-IRIS definition.

Serum and CSF CrAg titers are unhelpful in the diagnosis of C-IRIS. In the above prospective Ugandan cohort (n=101), 25% of patients had <4-fold decrease in CSF CrAg titer at time of their C-IRIS event (22).

Recurrence of cryptococcal symptoms may be caused by the host immune system (i.e. IRIS), ongoing immunosuppression, sequelae of existing disease, or failure of antifungal therapy. Conceptually it is easier to consider these mechanisms in distinction from one another, but more than one may exist concurrently. For example, suboptimal antifungal therapy or suboptimal adherence may attenuate the decline in pathogen burden prior to ART and provoke a more vigorous cryptococcus-specific immune response on ART than would have occurred with more effective antifungal treatment. The development of paradoxical TB-IRIS in cases of undiagnosed drug-resistant TB has recently been highlighted (98). Furthermore, whether the antigen is derived from live organisms, dead intact organism, or cellular debris, may not be critical in propagating an immune response leading to IRIS.

Definitions of ART-associated cryptococcosis and unmasking C-IRIS (Table 4)

As already discussed, there is inherent uncertainty in differentiating ART-associated cryptococcosis caused by restoration of a cryptococcus-specific immune response (i.e. unmasking C-IRIS) from cryptococcosis caused by persisting immunodeficiency on ART. Clinical management may be influenced by this distinction, and both causes are important in regions of high cryptococcal prevalence.

Given the relative lack of evidence, our criteria to distinguish between immune deficiency-related cryptococcosis and unmasking IRIS are provisional at this stage. While specific criteria or clinical cut-offs may improve the objectivity of our definition, they introduce unnecessary arbitrariness into the diagnostic process. As with tuberculosis (61) and other OIs (60), there may be a continuous spectrum between immunodeficiency-associated cryptococcosis and C-IRIS, rather than two distinct entities.

Pre-ART screening for cryptococcosis—Although clinically recognizable cryptococcosis should be absent at ART initiation, the presence of mild symptoms prior to ART should not preclude the diagnosis if appropriate screening for cryptococcal infection was initially negative. Occult cryptococcal antigenemia can occur in asymptomatic individuals prior to ART, particularly in resource-limited settings with high cryptococcal prevalence (57,99). Although patients with untreated antigenemia are more likely to develop clinical cryptococcosis (57,99–101), we have observed ART-associated cryptococcosis in persons who were serum CrAg-negative prior to ART in South Africa and Uganda, albeit rarely (unpublished data). Similarly, a placebo-controlled study of fluconazole primary prophylaxis in Uganda reported ART-associated cryptococcosis in 1.0% of individuals receiving placebo and ART, all of whom were serum CrAg-negative at a median of 11 weeks pre-ART (13). Therefore, neither a positive nor negative serum CrAg prior to the start of ART is an exclusion criterion for ART-associated cryptococcosis. However, pre-ART screening for cryptococcal antigenemia may be a useful strategy for identifying and treating subclinical infection and reducing the incidence of ART-associated cryptococcosis in high prevalence regions.

PREVENTION AND MANAGEMENT OF CRYPTOCOCCAL IRIS

Prevention of paradoxical C-IRIS has been a justification for delaying ART initiation, yet there is unclear evidence supporting such rationale. In two retrospective studies, earlier ART initiation (<4–8 weeks) was associated with increased risk of C-IRIS (10,12), but in two prospective observational cohorts, timing of ART initiation was not associated with C-IRIS (21,22). Two randomized controlled trials have been completed to address the question of when to start ART, using mortality as their primary outcome. In the ACTG a5164 trial, delaying ART to 6 weeks after starting OI therapy did not decrease the incidence of IRIS compared to starting ART within 2 weeks, but it did increase mortality (102). Only 35 (12%) subjects in the trial had cryptococcosis, compared to 63% with pneumocystis, and

only aggregated data were reported (102). In a second trial of 54 subjects from Zimbabwe, initiation of ART at a median of 24 hours after starting antifungal therapy was associated with increased mortality compared to a delay of 10 weeks (103). The causes of death were unclear and C-IRIS was not assessed (103). We do not support either approach to the timing of ART in this study as recommended clinical practice. A clinical trial is currently planned to definitively answer when to start ART after CM, and whether earlier ART is associated with excess C-IRIS risk (NCT01075152).

For treatment of cryptococcosis, published expert guidelines do not consider IRIS in detail (104,105). Intensification of antifungal therapy is indicated in all severe C-IRIS cases (e.g. intracranial space-occupying lesions or extracranial disease impinging on vital structures), any with positive culture, and patients suspected to have received a suboptimal antifungal regimen.

Case reports have noted beneficial responses of C-IRIS to immune modulating therapies, including corticosteroids (12,37,47,52), NSAIDs (33), and thalidomide (12) a randomized controlled trial of high-dose oral prednisone in mild to moderate TB-IRIS reported an overall reduction in inpatient days (106)and outpatient therapeutic procedures, but there is no evidence of therapeutic benefit of steroids in either C-IRIS or non-IRIS cryptococcal meningitis (107). Potential risks associated with corticosteroids in immunosuppressed patients include development of *Strongyloides* hyperinfection, worsening of Kaposi's sarcoma, or inappropriate administration during culture-positive cryptococcal relapse. Aggressive control of raised intracranial pressure by therapeutic lumbar punctures (59,105) and optimization of antifungal therapy should take priority, regardless of whether one is able to confirm or exclude the diagnosis of C-IRIS.

EVALUATION OF THE C-IRIS CASE DEFINITIONS

Our structured case definitions for C-IRIS and ART-associated cryptococcosis provide tools for future clinical, epidemiologic and immunopathologic studies of C-IRIS, allowing investigators to harmonize diagnostic criteria and facilitating comparison of studies, pooling of data and meta-analyses. Specifically, we recommend future reports avoid pooling paradoxical C-IRIS and ART-associated cryptococcosis cases together as one entity, but to report each separately.

Evaluation of these case definitions will require comparison with expert opinion, given current absence of an objective gold standard. The use of cut-offs in CSF parameters and inflammatory biomarkers in C-IRIS requires particular evaluation (108). Evidence for specific diagnostic cut-offs is conflicting and the entity of "unmasking IRIS" remains controversial, so future alterations to our case definitions are anticipated. In developing case definitions of rheumatologic and other complex syndromes, researchers evaluated the sensitivity and specificity of detailed candidate criteria, and used data-mining techniques to identify the best combination of criteria (109–111). As with TB-IRIS case definitions, these proposed C-IRIS definitions should also be regarded as preliminary until further insights into the immunopathology of IRIS and the development of diagnostic tools permit their refinement.

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References

1. WHO. Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector. Progress report. 2007 Apr [cited 3 Oct. 2008]. Available from: http://www.who.int/hiv/mediacentre/universal_access_progress_report_en.pdf
2. Holmes CB, Losina E, Walensky RP, Yazdanpanah Y, Freedberg KA. Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa. Clin Infect Dis 2003;36:652–662. [PubMed: 12594648]
3. Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson KE. Clinical presentation and risk behaviours of patients with acquired immunodeficiency syndrome in Thailand, 1994–1998: regional variation and temporal trends. Clin Infect Dis 2001;32:955–962. [PubMed: 11247718]
4. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 2009;23(4):525–530. [PubMed: 19182676]
5. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis 2007 Jun;7(6):395–401. [PubMed: 17521592]
6. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, et al. An immune reconstitution syndrome-like illness associated with Cryptococcus neoformans infection in organ transplant recipients. Clin Infect Dis 2005 Jun 15;40(12):1756–1761. [PubMed: 15909263]
7. Singh N, Perfect JR. Immune reconstitution syndrome and exacerbation of infections after pregnancy. Clin Infect Dis 2007 Nov 1;45(9):1192–1199. [PubMed: 17918082]
8. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8:516–523. [PubMed: 18652998]
9. Kambugu A, Meya DB, Rhein J, O'Brien M, Janoff EN, Ronald AR, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis 2008;46(10):1694–1701. [PubMed: 18433339]
10. Shelburne SA, Darcourt J, White WA, Greenberg SB, Hamill RJ, Atmar RL, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. Clin Infect Dis 2005;40(7):1049–1052. [PubMed: 15825000]
11. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White AC Jr, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005;19(4):399–406. [PubMed: 15750393]
12. Lortholary O, Fontanet A, Memain N, Martin A, Sitbon K, Dromer F. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS 2005;19(10):1043–1049. [PubMed: 15958835]
13. Parkes-Ratanshi, R.; Kamali, A.; Wakeham, K.; Levin, J.; Nabiryo Lwanga, C.; Kenya-Mugisha, N., et al. Successful primary prevention of cryptococcal disease using fluconazole prophylaxis in HIV-infected Ugandan adults. 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Canada. 2009.
14. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS 2005;19(17): 2050–2052. [PubMed: 16260920]
15. Murdoch DM, Venter WDF, Feldmann C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS 2008;22:601–610. [PubMed: 18317001]
16. Michelet C, Arvieux C, Francois C, Besnier JM, Rogez JP, Breux JP, et al. Opportunistic infections occurring during highly active antiretroviral treatment. AIDS 1998;12:1815–1822. [PubMed: 9792382]

17. Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, et al. Serum cryptococcal antigen (CRAG) screening is a cost-effective method to prevent death in HIV-infected persons with CD4 <100/mcL starting HIV therapy in resource-limited settings. Clin Infect Dis. 2010 *In Press*.
18. Bicanic T, Harrison T, Niepieklo A, Dyakopu N, Meintjes G. Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. Clin Infect Dis 2006;43(8):1069–1073. [PubMed: 16983622]
19. Sungkanuparph S, Jongwutiwes U, Kiertiburanakul S. Timing of cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in patients with AIDS and cryptococcal meningitis. J Acquir Immune Defic Syndr 2007;45(5):595–595. [PubMed: 17704683]
20. Antinori S, Ridolfo AL, Fasan M, Magni C, Galimberti L, Milazzo L, et al. AIDS-associated cryptococcosis: a comparison of epidemiology, clinical features and outcome in the pre- and post-HAART eras. Experience of a single centre in Italy. HIV Med 2008;10(1):6–11. [PubMed: 19125961]
21. Bicanic T, Meintjes G, Rebe K, Williams A, Loyse A, Wood R, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. Journal of Acquired Immune Deficiency Syndromes 2009;51(2):130–134. [PubMed: 19365271]
22. Boulware DR, Bonham SC, Meya DB, Wiesner DL, Park GS, Kambugu A, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. J Infect Dis. 2010 *In Press*.
23. Sungkanuparph S, Filler SG, Chetchotisakd P, Pappas PG, Nolen TL, Manosuthi W, et al. Cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in AIDS patients with cryptococcal meningitis: a prospective multicenter study. Clin Infect Dis 2009;49(6): 931–934. [PubMed: 19681708]
24. da Cunha Colombo ER, Mora DJ, Silva-Vergara ML. Immune reconstitution inflammatory syndrome (IRIS) associated with *Cryptococcus neoformans* infection in AIDS patients. Mycoses. 2010 in press.
25. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clin Infect Dis 2006;42(11):1639–1646. [PubMed: 16652323]
26. Manabe YC, Campbell JD, Sydnor E, Moore RD. Immune reconstitution inflammatory syndrome. Risk factors and treatment implications. J Acquir Immune Defic Syndr 2007;46:456–462. [PubMed: 18077835]
27. Haddow LJ, Easterbrook PJ, Mosam A, Khanyile NG, Parboosing R, Moodley P, et al. Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion versus 2 case definitions in a South African cohort. Clin Infect Dis 2009;49:1424–1432. [PubMed: 19788360]
28. Blanche P, Gombert B, Ginsburg C, Passeron A, Stubei I, Rigolet A. HIV combination therapy: immune restitution causing cryptococcal lymphadenitis dramatically improved by anti-inflammatory therapy. Scand J Infect Dis 1998;30:615–616. [PubMed: 10225395]
29. Legendre U, Battegay M, Nuttli I, Dalquen P, Nuesch R. Simultaneous occurrence of 2 HIV-related immune reconstitution diseases after initiation of highly active antiretroviral therapy. Scand J Infect Dis 2001;33:388–389. [PubMed: 11440230]
30. McCombe JA, Auer RN, Maingat FG, Houston S, Gill MJ, Power C. Neurologic immune reconstitution inflammatory syndrome in HIV/AIDS: outcome and epidemiology. Neurology 2009;72(9):835–841. [PubMed: 19255411]
31. Woods ML, MacGinley R, Eisen D, Allworth AM. HIV combination therapy: partial immune reconstitution unmasking latent cryptococcal infection. AIDS 1998;12:1491–1494. [PubMed: 9727570]
32. Lanzafame M, Trevenzoli M, Carretta G, Lazzarini L, Vento S, Concia E. Mediastinal lymphadenitis due to cryptococcal infection in HIV-positive patients on highly active antiretroviral therapy. Chest 1999;116:848–849. [PubMed: 10492309]

33. Manfredi R, Pieri SA, Stefano AP, Chiodo F. The changing face of AIDS-related opportunism: Cryptococcosis in the highly active antiretroviral therapy (HAART) era. Case reports and literature review. Mycopathologia 1999;148:73–78. [PubMed: 11189746]
34. Cinti SK, Armstrong WS, Kauffman CA. Case report. Recurrence of increased intracranial pressure with antiretroviral therapy in an AIDS patient with cryptococcal meningitis. Mycoses 2001;44:497–501. [PubMed: 11820264]
35. Breton G, Seilhean D, Cherin P, Herson S, Benveniste O. Paradoxical intracranial cryptococcoma in a human immunodeficiency virus-infected man being treated with combination antiretroviral therapy. Am J Med 2002;113:155–157. [PubMed: 12133755]
36. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clinical Infectious Diseases 2002;35(12):e128–e133. [PubMed: 12471589]
37. King MD, Perlino CA, Cinnamon J, Jernigan JA. Paradoxical recurrent meningitis following therapy of cryptococcal meningitis: an immune reconstitution syndrome after initiation of highly active antiretroviral therapy. Int J STD AIDS 2002;13(10):724–726. [PubMed: 12396546]
38. Rambeloarisoa J, Batisse D, Thiebaut JB, Mikol J, Mrejen S, Karmochkine M, et al. Intramedullary abscess resulting from disseminated cryptococcosis despite immune restoration in a patient with AIDS. J Infect 2002;44(3):185–188. [PubMed: 12099747]
39. Trevenzoli M, Cattelan AM, Rea F, Sasset L, Semisa M, Lanzafame M. Mediastinitus due to cryptococcal infection: a new clinical entity in the HAART era. J Infect 2002;45:173–179. [PubMed: 12387774]
40. Boelaert JR, Goddeeris KH, Vanopdenbosch LJ, Casselman JW. Relapsing meningitis caused by persistent cryptococcal antigens and immune reconstitution after the initiation of highly active antiretroviral therapy. AIDS 2004;18:1223–1224. [PubMed: 15166545]
41. Cattelan AM, Trevenzoli M, Sasset L, Lanzafame M, Marchioro U, Meneghetti F. Multiple cerebral cryptococcomas associated with immune reconstitution in HIV-1 infection. AIDS 2004;18(2):349–351. [PubMed: 15075562]
42. Skiest DJ, Hester LJ, Hardy RD. Cryptococcal immune reconstitution inflammatory syndrome: report of four cases in three patients and review of the literature. J Infect 2005;51(5):289–297.
43. York J, Bodi I, Reeves I, Riordan-Eva P, Easterbrook PJ. Raised intracranial pressure complicating cryptococcal meningitis: immune reconstitution inflammatory syndrome or recurrent cryptococcal disease? J Infect 2005;51(2):165–171. [PubMed: 15961162]
44. Broom J, Woods ML, Allworth AM. Immune reconstitution inflammatory syndrome producing atypical presentations of cryptococcal meningitis: case report and a review of immune reconstitution-associated cryptococcal infections. Scand J Infect Dis 2006;38(3):219–221. [PubMed: 16500787]
45. Khanna N, Nuesch R, Buitrago-Tellez C, Battegay M, Hirsch HH. Hearing loss after discontinuing secondary prophylaxis for cryptococcal meningitis: relapse or immune reconstitution? Infection 2006;34(3):163–168. [PubMed: 16804661]
46. Haddow LJ, Sahid F, Moosa MY. Cryptococcal breast abscess in an HIV-positive patient: arguments for reviewing the definition of immune reconstitution inflammatory syndrome. J Infect 2007;57(1):82–84. [PubMed: 18308398]
47. Huits RM, Bremmer R, Enting RH, Sprenger HG, van Assen S. Return of meningeal symptoms in a patient treated for cryptococcal meningitis. Journal of Neurology 2007;254(10):1443–1444. [PubMed: 17401736]
48. Tahir M, Sharma SK, Sinha S, Das CJ. Immune reconstitution inflammatory syndrome in a patient with cryptococcal lymphadenitis as the first presentation of acquired immunodeficiency syndrome. Journal of Postgraduate Medicine 2007;53(4):250–252. [PubMed: 18097114]
49. Gąsiorowski J, Knysz B, Szetela B, Gładysz A. Cutaneous cryptococcosis as a rare manifestation of the immune reconstitution syndrome in an HIV-1-infected patient. Postepy Hig Med Dosw (Online) 2008;62:1–3. [PubMed: 18202595]
50. Khurana RN, Javaheri M, Rao N. Ophthalmic manifestations of immune reconstitution inflammatory syndrome associated with Cryptococcus neoformans. Ocular immunology and inflammation 2008;16(4):185–190. [PubMed: 18716955]

51. Putignani L, Antonucci G, Paglia MG, Vincenzi L, Festa A, De Mori P, et al. Cryptococcal lymphadenitis as a manifestation of immune reconstitution inflammatory syndrome in an HIV-positive patient: a case report and review of the literature. International Journal of Immunopathology and Pharmacology 2008;21(3):751–756. [PubMed: 18831914]
52. Shelburne SA 3rd, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DW, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine (Baltimore) 2002 May;81(3):213–227. [PubMed: 11997718]
53. Jongwutiwes U, Malathum K, Sungkanuparph S. Cryptococcal meningoradiculitis: an atypical presentation after initiation of antiretroviral therapy. J Med Assoc Thai 2007;90 Suppl 2:85–88. [PubMed: 19230429]
54. Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin 2006;24:549–570. [PubMed: 17010783]
55. Boulware, DR.; Meya, DB.; Bergemann, TL.; Wiesner, D.; Bonham, S.; Kambugu, A., et al. Serum inflammatory biomarkers predict HIV immune reconstitution inflammatory syndrome and death after cryptococcal meningitis. Abstract 774. 16th Conference on Retroviruses and Opportunistic Infections (CROI); Montreal, Canada. 2009.
56. Garcia-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant *Cryptococcus neoformans* infection. J Clin Micro 1999;37(10):3204–3209.
57. 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. Clinical Infectious Diseases 2009;48:856–862. [PubMed: 19222372]
58. Pongsai P, Atamasirikul K, Sungkanuparph S. The role of serum cryptococcal antigen screening for the early diagnosis of cryptococcosis in HIV-infected patients with different ranges of CD4 cell counts. J Infect 2010 Jun;60(6):474–477. [PubMed: 20347868]
59. Graybill JR, Sobel J, Saag M, van Der Horst C, Powderly W, Cloud G, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis 2000 Jan;30(1):47–54. [PubMed: 10619732]
60. French MA. Immune reconstitution inflammatory syndrome: a reappraisal. Clin Infect Dis 2009;48(1):101–107. [PubMed: 19025493]
61. Lawn SD, Wilkinson RJ, Lipman MC, Wood R. Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. Am J Respir Crit Care Med 2008;177:680–685. [PubMed: 18202347]
62. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004 Aug 20;18(12):1615–1627. [PubMed: 15280772]
63. Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. AIDS 2009;23(1): 143–145. [PubMed: 19050399]
64. Manabe YC, Breen RAM, Perti T, Girardi E, Sterling TR. Unmasking tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. J Infect Dis 2009;199:437–444. [PubMed: 19090776]
65. Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. Sex Transm Infect 2003;79(4):337–338. [PubMed: 12902592]
66. Powderly WG. Cryptococcal meningitis and AIDS. Clin Infect Dis 1993;17:837–842. [PubMed: 8286622]
67. Boulware, DR.; Meya, DB.; Bonham, S.; Janoff, EN.; Kambugu, A.; Bohjanen, PR. Clinical manifestations and cytokine profiles in HIV-infected Ugandans who develop immune reconstitution inflammatory syndrome (IRIS). Infectious Diseases Society of America 46th Annual Meeting; Washington D.C.. 2008.
68. Boulware, DR.; Meya, DB.; Bonham, S.; Janoff, EN.; Kambugu, A.; Bohjanen, PR. Clinical manifestations and cytokine profiles in HIV-infected Ugandans who develop immune

reconstitution inflammatory syndrome (IRIS). Infectious Diseases Society of America 46th Annual Meeting; Washington D.C.. 2008.

69. Meintjes G, Wilkinson KA, Rangaka MX, Skolimowska K, van Veen K, Abrahams M, et al. Th1 and FoxP3 positive T cells and the HIV-tuberculosis immune reconstitution inflammatory syndrome. Am J Respir Crit Care Med. 2008
70. Seddiki N, Sasson SC, Santner-Nanan B, Munier M, van Bockel D, Ip S, et al. Proliferation of weakly suppressive regulatory CD4+ T cells is associated with over-active CD4+ T-cell responses in HIV-positive patients with mycobacterial immune restoration disease. Eur J Immunol 2009;39:391–403. [PubMed: 19180462]
71. Ruhwald M, Ravn P. Immune reconstitution syndrome in tuberculosis and HIV-co-infected patients: Th1 explosion or cytokine storm? AIDS 2007;21(7):882–883. [PubMed: 17415049]
72. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis 2007;7:395–401. [PubMed: 17521592]
73. Bourgarit A, Carcelain G, Martinez V, Lascoux C, Delcey V, Gicquel B, et al. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. AIDS 2006;20(2):F1–F7. [PubMed: 16511406]
74. Lawn SD, Bekker L-G, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005;5(6):361–373. [PubMed: 15919622]
75. 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]
76. Manosuthi W, Van Tieu H, Mankatitham W, Lueangniyomkul A, Ananworanich J, Avihingsanon A, et al. Clinical case definition and manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 2009 Nov 27;23(18):2467–2471. [PubMed: 19898217]
77. Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 2010;24:103–108. [PubMed: 19926965]
78. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis 2006;42(3):418–427. [PubMed: 16392092]
79. Kumarasamy N, Chaguturu S, Mayer KH, Solomon S, Yepthomi HT, Balakrishnan P, et al. Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. J Acquir Immune Defic Syndr 2004;37(5): 1574–1576. [PubMed: 15577411]
80. Breton G, Duval X, Estellat C, Poaletti X, Bonnet D, Mvondo Mvondo D, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 2004;39(11):1709–1712. [PubMed: 15578375]
81. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. AIDS 2005;19:2109–2116. [PubMed: 16284460]
82. French MA, Mallal SA, Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. AIDS 1992;6(11):1293–1297. [PubMed: 1472334]
83. Kamya MR, Mayanja B, Kambugu A, Bakeera-Kitaka S, Semitala F, Mwebaze-Songa P, et al. Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy. J Acquir Immune Defic Syndr 2007;46(2):187–193. [PubMed: 17693883]
84. Phillips P, Bonner S, Gataric N, Bai T, Wilcox P, Hogg R, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005;41:1483–1497. [PubMed: 16231262]
85. Liu PY, Yang Y, Shi ZY. Cryptococcal liver abscess: a case report of successful treatment with amphotericin-B and literature review. Jpn J Infect Dis 2009;62(1):59–60. [PubMed: 19168962]

86. Jurado R, Carpenter SL, Rimland D. Case reports: trimethoprim-sulfamethoxazole-induced meningitis in patients with HIV infection. Am J Med Sci 1996;312(1):27–29. [PubMed: 8686726]
87. Longley N, Muzoora C, Taseera K, Mwesigye J, Rwebembera J, Chakera A, et al. Dose Response Effect of High-Dose Fluconazole for HIV-Associated Cryptococcal Meningitis in Southwestern Uganda. Clin Infect Dis 2008;47(12):1556–1561. [PubMed: 18990067]
88. Saag MS, Powderly WG, Cloud GA, Robinson P, Grieco MH, Sharkey PK, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. New England Journal of Medicine 1992;326(2):83–89. [PubMed: 1727236]
89. van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. New England Journal of Medicine 1997;337(1):15–21. [PubMed: 9203426]
90. Brouwer AE, Rajanuwong A, Chierakul W, Griffin GE, Larsen RA, White NJ. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet 2004;363:1764–1767. [PubMed: 15172774]
91. Pappas PG, Chetchotisakd P, Larsen RA, Manosuthi W, Morris MI, Anekthananon T, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis 2009;48:1775–1783. [PubMed: 19441980]
92. Hamill RJ. Free fluconazole for cryptococcal meningitis: too little of a good thing? Clin Infect Dis 2006;43:1074–1076. [PubMed: 16983623]
93. Antinori S. Cryptococcosis: we should do better! Clin Infect Dis 2006;43:948–949. [PubMed: 16941382]
94. McCarthy KM, Morgan J, Wannemuehler KA, Mirza SA, Gould SM, Mhlongo N, et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS 2006;20(17):2199–2206. [PubMed: 17086060]
95. Moosa MY, Coovadia YM. Cryptococcal meningitis in Durban, South Africa: a comparison of clinical features, laboratory findings, and outcome for human immunodeficiency virus (HIV)-positive and HIV-negative patients. Clin Infect Dis 1997;24(2):131–134. [PubMed: 9114135]
96. Menichetti F, Fiorio M, Tosti A, Gatti G, Pasticci MB, Miletich F, et al. High-dose fluconazole therapy for cryptococcal meningitis in patients with AIDS. Clin Infect Dis 1996;22:838–840. [PubMed: 8722942]
97. Haubrich RH, Haghighat D, Bozzette SA, Tilles J, McCutchan JA. High dose fluconazole for treatment of cryptococcal disease in patients with human immunodeficiency virus infection. The California Collaborative Treatment Group. J Infect Dis 1994;170:238–242. [PubMed: 8014509]
98. Meintjes G, Rangaka MX, Maartens G, Rebe K, Morroni C, Pepper DJ, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. Clin Infect Dis 2009;48(5):667–676. [PubMed: 19191655]
99. Liechty CA, Solberg P, Were W, Ekwaru JP, Ransom RL, Weidle PJ, et al. Asymptomatic serum cryptococcal antigenaemia and early mortality during antiretroviral therapy in rural Uganda. Tropical Medicine and International Health 2007;12(8):929–935. [PubMed: 17697087]
100. French N, Gray K, Watera C, Nakiyingi J, Lugada E, Moore M, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS 2002;16(7):1031–1038. [PubMed: 11953469]
101. Micol R, Lortholary O, Sar B, Laureillard D, Ngeth C, Dousset JP, et al. Prevalence, determinants of positivity, and clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients. J Acquir Immune Defic Syndr 2007;45(5):555–559. [PubMed: 17577124]
102. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One 2009;4(5):e5575. [PubMed: 19440326]
103. Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in Sub-Saharan Africa. Clin Infect Dis 2010 Apr 23;50(11):1532–1538. [PubMed: 20415574]

104. Kaplan J, Benson C, Holmes K, Brooks J, Pau A, Masur H. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2009;58:1–207.

105. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2010 Jan 4;50 *In Press*.

106. Meintjes, G.; Wilkinson, RJ.; Morroni, C.; Pepper, DJ.; Rebe, K.; Rangaka, MX., et al. Randomized placebo-controlled trial of prednisone for TB IRIS; Conference on Retroviruses and Opportunistic Infections; 2009. Abstract 34.

107. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. Clin Infect Dis 2000;30:710–718. [PubMed: 10770733]

108. Bonham S, Meya DB, Bohjanen PR, Boulware DR. Biomarkers of HIV immune reconstitution inflammatory syndrome. Biomarker Medicine 2008;2(4):349–361.

109. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis and Rheumatism 1988;31(3):315–324. [PubMed: 3358796]

110. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis and Rheumatism 1982;25(11):1271–1277. [PubMed: 7138600]

111. HIV Lipodystrophy Case Definition Study Group. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. Lancet 2003;361:726–735. [PubMed: 12620736]

Table 1

Cohort and case-control studies reporting cases of HIV-associated cryptococcal IRIS (C-IRIS)

Ref	Country	Study design	Number of cases / total subjects	Incidence of C-IRIS	Clinical features	Time on ART at onset	Criteria required for case definition	CD4 count pre-ART and at C-IRIS event (cells/mm^3)	VL pre-ART and at C-IRIS event (log_{10} copies/mL)
Paradoxical C-IRIS in HIV-infected individuals (known cryptococcosis at ART initiation)									
(14)	South Africa	Retrospective cohort	6 / 18	33%	5 CM, 1 paraparesis	1–8 weeks	Any cryptococcosis on ART; negative CSF cultures *not* a requirement	Pre-ART: 22–73; event: not reported	Pre-ART: 4.65–5.70; event: not reported
(10,11) [a]	USA	Retrospective cohort	15–17 / 59 *a*	25–29%	14 CM, 1 LN, 1 lung, 1 not specified [a]	Median 30 days	New or worsening symptoms; initial clinical response; elevated CSF protein; high opening pressure; negative CSF cultures; low or decreased CrAg; increase in CD4 *or* decrease in VL	Pre-ART: 54–133; event: median +93 compared to baseline	−2.27 decrease between pre-ART and event
(12)	France	Retrospective cohort	7–10 / 120 *b*	8%	CM +/− lung, LN and CNS complications	Median 8 months	New inflammatory process; no new OI, neoplasia or drug-related disorder; fungal culture negative; immunological and/or virological response to ART	Pre-ART: 0–52; event: 43–640	Pre-ART: 3.1–6.2; event: 1.7–3.8 (58% of cases had VL<50)
(18)	South Africa	Prospective cohort	13 / 32	Total at risk not reported	13 CM	Median 27 days	Meningitis on ART; CSF culture negative	Pre-ART median 27 (IQR 14–44)	Pre-ART median 5.4 (IQR 4.8–5.7)
(25)	USA	Case-control	3 / not specified	n/a	2 CM, 1 LN (mode of presentation not specified)	Not specified	New or worsening infection; not explained by newly-acquired infection, predicted course of known infection or drug effect; decrease in VL >1 log	Not reported	Not reported
(19)	Thailand	Retrospective cohort	10 / 52	19%	10 CM	Median 9.9 months	Cryptococcosis after immunological response to ART; culture-negative	Pre-ART: median 26 (range 1–93); event: median 121 (range 59–203)	Not reported
(26)	USA	Case-control	8 / not specified	n/a	4 CM, 2 LN, 1 cerebral mass, 1 CM and lung	8 days to 6 months	Atypical presentation of OI; symptoms not due to side effect of ART; OI confirmed by microbiology or histology; decrease in VL >1 log	Not reported	Not reported
(9,22) [a]	Uganda	Prospective cohort	42 / 85	49%	29 CM,4 CNS mass, 9 non-CNS	Median 8 weeks (IQR 4–17)	Atypical or exaggerated infection; not explained by	Pre-ART: median 21, range 2–109	Not reported

Ref	Country	Study design	Number of cases / total subjects	Incidence of C-IRIS	Clinical features	Time on ART at onset	Criteria required for case definition	CD4 count pre-ART and at C-IRIS event (cells/mm^3)	VL pre-ART and at C-IRIS event (log_{10} copies/mL)
							alternate infection, malignancy, OI treatment failure, drug reaction or non-compliance with ART; CSF culture negative	(controls 19, 1–179); event: median 61 (range 2–264)	
(20)	Italy	Retrospective cohort	5 / 26	19%	3 CM, 1 LN and abscess, 1 cerebral	Median 15 weeks	Negative culture of CSF or relevant site (clinical criteria not specified)	Pre-ART: median 22; event: median 95	
(21)	South Africa	Prospective cohort	11 / 65	17%	11 CM (2 with focal neurological signs)	Median 29 days	Resolution of cryptococcosis symptoms before ART; adherence to fluconazole and ART; recurrence of CM on ART; no alternative diagnosis; immunological and/or virological response to ART; cases were categorized as CSF culture-negative or -positive	Pre-ART: median 28 (controls median 41); event: median 162 (controls median 187)	Pre-ART: median 5.0; event: median decrease 1.6
(23)	Thailand	Prospective cohort	13 / 101	13%	13 CM	9 weeks (range 1.7–18.4 weeks:	Atypical manifestations of cryptococcosis; demonstration of virological or immunological response to ART; culture-negative CM after immunological response to ART (62)	Not reported	Not reported
(24)	Brazil	Prospective cohort	9 / 40	22.5%	7 CM, 1 mass, 2 LN, 1 pneumonia	Median 10 weeks (range 4–17 weeks)	Prior clinical improvement; relapse of CM; culture negative, and/or enlarged inflammatory lymph-nodes	Pre-ART: 6–84; event: 33–287	Pre-ART: 4.5–5.7; event: 1.7–3.1
(27)	South Africa	Prospective cohort	2 / 8	25%	1 CM, 1 disseminated disease	1–2 weeks	Consensus expert opinion, based on principles outlined in published article	Event: +54 compared to baseline (1 case)	Event: −2.9 compared to baseline
ART-associated cryptococcosis (reported as "unmasking" presentations)									
(16)	France	Retrospective cohort	3 / 486	0.2%	1 CM, 2 site not specified	Not specified	Development or recurrence of any AIDS-defining event on ART	Event: mean +153 compared to baseline	Event: −1.7 compared to baseline
(14)	South Africa	Retrospective cohort	3 / 416	0.7%	3 CM	1–23 weeks	Any cryptococcosis on ART; negative CSF cultures *not* a requirement	Pre-ART: 9–58; event: not reported	Pre-ART: 4.2–5.6; event: not reported
(10,11) [a]	USA	Retrospective cohort	3 / not specified [a]	Not known	2 CM, 1 LN	Median 30 days	New symptoms; elevated CSF protein; high opening pressure; negative CSF cultures; low or decreased	Included within paradoxical C-IRIS cases above	Included within paradoxical C-IRIS cases above

Ref	Country	Study design	Number of cases / total subjects	Incidence of C-IRIS	Clinical features	Time on ART at onset	Criteria required for case definition	CD4 count pre-ART and at C-IRIS event (cells/mm^3)	VL pre-ART and at C-IRIS event (log_{10} copies/mL)
							CrAg; CSF WBC >50 (in unmasking cases); increase in CD4 *or* decrease in VL		
(12)	France	Retrospective cohort	3 / not specified [b]	Not known	Mixed CM, lung and LN †	Median 8 months	New inflammatory process; no new OI, neoplasia or drug-related disorder; fungal culture negative; immunological and/or virological response to ART	Included within paradoxical C-IRIS cases above	Included within paradoxical C-IRIS cases above
(26)	USA	Case-control	2 / not specified	n/a	1 CM, 1 disseminated disease	4 and 9 days	Atypical presentation of OI; symptoms not due to side effect of ART; OI confirmed by microbiology or histology; decrease in VL >1 log	Not reported	Not reported
(15)	South Africa	Prospective cohort	3 / 423	0.7%	3 CM	14–80 days	New focal infection; exclusion of non-adherence; exclusion of virological failure or CD4 decline (if later than 3 months ART)	Not reported	Not reported
(17)	Uganda	Prospective cohort	5 / 295	1.6%	2 CM	1–8 weeks	New CM on ART. All patients were serum CrAg positive pre-ART and did not receive fluconazole therapy	Not reported	Not reported
(27)	South Africa	Prospective cohort	2 / 490	0.4%	1 CM, 1 pneumonitis	4–7 weeks	Consensus expert opinion, based on principles outlined in published article	Event: +56 and +86 compared to baseline	Event: −3.1 and −3.9 compared to baseline

[a] Some patients in this cohort were included in two separate publications.

[b] The study reported a cohort of 120 patients, of whom 10 developed C-IRIS, and an additional 2 cases from other datasets. Of these 12 cases, 3 (25%) were ART-associated cryptococcosis. The study did not provide specific data to calculate the incidence of paradoxical cases and ART-associated cryptococcosis with certainty, or the individual clinical features of the two modes of presentation.

ARDS, adult respiratory distress syndrome; ART, antiretroviral therapy; CM, cryptococcal meningitis; CNS, central nervous system; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; IQR, inter-quartile range; LN, lymph node disease; OI, opportunistic infection; VL, HIV-1 viral load; WBC, white blood cell count

Table 2

Case reports and case series of HIV-associated cryptococcal IRIS (C-IRIS)

Ref	Country	Clinical presentations	Time on ART at onset	Cryptococcal antigen (site and titre)	Microscopy for fungi	Fungal culture	Histologic evidence of fungi	CSF opening pressure (cm)	CSF leukocytes cells/μL)	CD4 count pre-ART and at C-IRIS event (cells/mm^3)	VL pre-ART and at C-IRIS event (log_{10} copies/mL)
(52)	USA	3 CM, 1 pneumonia and ARDS	8, 11, 58 days	CSF 1:2048		Negative			71	Pre-ART: 42, 25, 76; event: 140, 55, 138	Pre-ART: 6.2, 5.8, 5.4; event: 2.9, 3.0, 4.0
(31)	Australia	1 CM	10 days	CSF 1:200		Negative			10	Pre-ART: 40, event: 240	Pre-ART: 5.7; event: 3.1
(28)	France	2 LN +/− fever & retropharyngeal abscess	8, 15 months	Serum “unchanged”		Negative				Pre-ART: 6, 28; event: 63, 251	Pre-ART: 5.6; event: 3.7, 3.8
(33)	Italy	1 recurrent CM; 1 multiple abscesses	3, 5 months	Serum, CSF, lymph node aspirate positive	Positive	Positive in CSF of CM case				Pre-ART: 98, 7; event: 78, 186	Pre-ART: 4.8, 4.9; event: <1.7
(32)	Italy	1 mediastinal LN	6 months	Serum 1:16			Positive			Event: 137	Event: <2.7
(34)	USA	1 CM with raised ICP	3 weeks	CSF 1:8000	Positive	Negative		33	500	Pre-ART: 67; event: 370	Pre-ART: 5.8; event: 2.7
(37)	USA	1 CM	4 weeks	CSF 1:32		Negative			10	Pre-ART: 41; event: 44	Pre-ART: 5.9; event: <2.6
(39)	Italy	3 mediastinal LN	2–4 months			Negative	Positive			Pre-ART: 17, 64, 120; event: 48, 329, 200	Pre-ART: 6.0; event: <1.7
(36)	USA	2 CM, 1 LN, 1 lung, 1 soft tissue mass	2–11 months	CSF 1:32, 1:1	Negative	Negative	Positive	34, 39	17, 149	Pre-ART: 10–102; event: 57–306	Pre-ART: 4.7–5.9; event: <2.7
(35)	France	1 cerebral cryptococcoma	3 months	CSF 1:10		Negative	Positive		1	Pre-ART: 3; event: 485	Event: <2.6
(38)	France	1 LN, 1 spinal cord abscess (same patient)	10, 34 months			Negative	Positive		1	Pre-ART: 3; event: 175	Event: <2.6
(41)	Italy	2 cerebral cryptococcomas	6, 7 months	CSF 1:16, 1:1					20, 50	Pre-ART: 17, 27; event: 220, 205	Pre-ART: 5.6, 5.0; event: <1.7
(40)	Belgium	1 CM	8 days	CSF positive	Negative	Negative			35	Pre-ART: 16, event: 38	Pre-ART: 5.0; event: 2.2
(43)	UK	1 raised ICP	10 days	CSF 1:1		Negative		>40	<5	Pre-ART: 9; event: 59	Pre-ART: >5.7; event: <1.7
(42)	USA	3 CM +/− LN	2–18 months	CSF 1:16, 1:2	Positive	Negative	Positive			Pre-ART: 1–4; event: 180–409	Pre-ART: 4.7–5.7; event: 2.1–2.9
(45)	Switzerland	1 CM + hearing loss and LN	17 months			Negative			16	Pre-ART: 32; event: 234	Pre-ART: 4.9; event: <2.9
(47)	Netherlands	1 CM	320 days	CSF “low”	Negative	Negative		>50	272	Pre-ART: 0; event: 120	Event: <1.7
(48)	India	1 LN and fever	2 weeks		Positive	Positive				Pre-ART:13	
(51)	Italy	1 LN	Not known			Positive (enrichment cultures)	Positive using PCR				

Ref	Country	Clinical presentations	Time on ART at onset	Cryptococcal antigen (site and titre)	Microscopy for fungi	Fungal culture	Histologic evidence of fungi	CSF opening pressure (cm)	CSF leukocytes cells/μL)	CD4 count pre-ART and at C-IRIS event (cells/mm^3)	VL pre-ART and at C-IRIS event (log_{10} copies/mL)
(50)	USA	4 raised ICP with optic disk swelling	17–33 days	CSF 1:128 to 1:256		Negative		25, 44, 55, 55	0, 6, 8, 8	Pre-ART: mean 20; event: mean 65	Pre-ART: mean 5.2; event: mean 3.5
(30)	Canada	1 CM	6 months			Negative			150		
(31)	Australia	2 CM	4, 39 days			Positive		28	0.3, 14	Pre-ART: 5, 30; event: 70, 110	Pre-ART: 6.4; event: <2.3
(32)	Italy	1 mediastinal LN	6 months	Serum 1:2048			Positive			Event: 110	Event: 3.8
(29)	Switzerland	1 pulmonary lesion	4 weeks	CSF 1:16	Positive					Pre-ART: 38; event: 54	Pre-ART: 4.9; event: 2.5
(44)	Australia	1 CM	10 weeks	CSF 1:256		Negative			77	Pre-ART: 20; event: 70	Event: 3.5
(54)	South Africa	1 cutaneous ulceration	1 month			Positive	Positive				
(53)	Thailand	1 meningoradiculitis	2 weeks	Serum and CSF positive	Positive	Positive			0	Pre-ART: 17; event: 24	Event: <2.6
(46)	South Africa	1 breast abscess	11 months	Serum >1:8	Positive	Positive				Pre-ART 89: event: 59	Event: <1.5
(49)	Poland	1 cutaneous ulceration	4 weeks	Serum positive	Positive (skin and blood)	Positive				Pre-ART: 4; event: 31	Pre-ART 6.3; event 4.1
(30)	Canada	1 CM	2 months							Pre-ART 8	Pre-ART 5.5

Blank cells or missing values indicate data not reported.

CM, cryptococcal meningitis; CSF, cerebrospinal fluid; ICP, intracranial pressure; LN, lymph node disease; PCR, polymerase chain reaction

Table 3

Case definition for paradoxical cryptococcal IRIS in HIV-infected patients

(A) Antecedent requirements

- Taking antiretroviral therapy
- Cryptococcal disease diagnosed pre-ART by positive culture or typical clinical features plus positive India ink staining or antigen detection
- Initial clinical response to antifungal therapy with:
  1. partial or complete resolution of symptoms or signs, fever, or other lesions, or
  2. reduction in CSF cryptococcal antigen or quantitative culture

(B) Clinical criteria

- Event occurs within 12 months of ART initiation, reintroduction, or switching after previous failure
- Clinical deterioration with one of the following inflammatory manifestations of cryptococcosis (see text for possible rarer manifestations):
  - Meningitis
  - Lymphadenopathy
  - Intracranial space-occupying lesion/s
  - Multifocal disease
  - Cutaneous / soft tissue lesions
  - Pneumonitis or pulmonary nodules

(C) Other explanations for clinical deterioration to be excluded:

- Non-adherence or suboptimal antifungal therapy, indicated by an increase in quantitative culture or antigen titer, or any positive cryptococcal culture after 3 months.
- Alternative infection or malignancy in the affected site
- Failure of ART excluded if possible (e.g. failure to achieve ≥1 $\log_{10}$ copies/mL decrease in VL by 8 weeks of ART)

See text for full explanation of diagnostic criteria.

ART, antiretroviral therapy; CSF, cerebrospinal fluid; VL, HIV-1 viral load

Table 4

Working case definitions for ART-associated cryptococcosis and unmasking cryptococcal IRIS

ART-associated cryptococcosis
We propose that ART-associated cryptococcosis (all cases of cryptococcosis that are diagnosed during ART) should be defined as follows:

- Taking antiretroviral therapy (ART)
- No recognized cryptococcal disease at ART initiation
- Clinical deterioration caused by cryptococcosis occurs after initiation, reintroduction, or switch after previous failure (supported by microbiological, histological or serological evidence); see text for possible manifestations

Unmasking cryptococcal IRIS (provisional)
We propose that the following suggest a diagnosis of unmasking cryptococcal IRIS:

- Criteria for ART-associated cryptococcosis (above) are met
- Unusual, exaggerated or heightened inflammatory manifestations, for example:
  - Meningitis with markedly elevated leukocyte count (>50 cells/μL) or elevated opening pressure refractory to therapy
  - Painful or suppurating lymphadenopathy
  - Rapidly-expanding CNS lesions, cryptococcoma(s)
  - Unusual focal site (i.e., not within the CNS, lung, skin or lymph nodes)
  - Granulomatous inflammation on histology
- Pneumonitis, particularly if cavitating or necrotic
- Event occurs early after ART initiation [*]
- Failure of ART excluded if possible (e.g. ≥1 $\log_{10}$ copies/mL decrease in VL by 8 weeks of ART)

[a] No specific time limit is proposed for unmasking cryptococcal IRIS, pending further research. Onset within 1 month of initiation of ART is supportive of IRIS, rather than immunodeficiency-related disease.

See text for full explanation of diagnostic criteria.

ART, antiretroviral therapy; CNS, central nervous system; VL, HIV-1 viral load