Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions

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Cryptococcal immune reconstitution inflammatory syndrome (IRIS) may present as a clinical worsening or new presentation of cryptococcal disease after initiation of antiretroviral therapy (ART), and is thought to be caused by recovery of cryptococcus-specific immune responses. We have reviewed reports of cryptococcal IRIS and have developed a consensus case definition specifically for paradoxical crytopcoccal IRIS in patients with HIV-1 and known cryptococcal disease before ART, and a separate definition for incident cryptococcosis developed during ART (termed ART-associated cryptococcosis), for which a proportion of cases are likely to be unmasking cryptococcal IRIS. These structured case definitions are intended to aid design of future clinical, epidemiological, and immunopathological studies of cryptococcal IRIS, to standardise diagnostic criteria, and to facilitate comparisons between studies. As for definitions of tuberculosis-associated IRIS, definitions for cryptococcal IRIS should be regarded as preliminary until further insights into the immunopathology of IRIS permit their refinement.

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Introduction

Cryptococcal disease is a major cause of morbidity and mortality in people with advanced HIV/AIDS, particularly in Africa and southeast Asia.[1–4] Cryptococcal immune reconstitution inflammatory syndrome (IRIS) presents as a clinical worsening or new presentation of cryptococcal disease after rapid reversal of immune deficiency.[5] In patients with HIV-1 infection, this reversal is driven by antiretroviral therapy (ART), but the syndrome can also occur after solid-organ transplantation (estimated incidence 4·8%),[6] and in pregnancy.[7] Cryptococcal IRIS is thought to be triggered by recovery of immune responses to *Cryptococcus* spp, resulting in exaggerated host inflammatory responses.

The International Network for the Study of HIV-associated IRIS (INSHI) was established in 2006, to promote research collaboration and standardisation of practices and terminology among IRIS researchers worldwide. Generic definitions of IRIS are limited in their application because of the highly heterogeneous spectrum of underlying disease and clinical features. Here we review the clinical and diagnostic features of cryptococcal IRIS reported in cohort and case-control studies (table 1)[8–25] and case series and case reports (table 2)[26–52] and put forward consensus case definitions for the syndrome that can be used in resource-limited and resource-rich settings.

Classification and terminology

Similar to the INSHI case definition of tuberculosis-associated IRIS,[53] two distinct modes of presentation of cryptococcal IRIS are recognised. First, in up to a third of patients with cryptococcosis diagnosed before the initiation of ART, so-called paradoxical cryptococcal IRIS occurs during treatment. This form presents as a worsening of disease or as recurrent disease in the same or new anatomical sites, despite microbiological evidence of effective antifungal treatment.[8–11] Second, new-onset cryptococcosis occurs after ART is started in up to 1% of patients in whom cryptococcosis was not recognised before treatment.[12–15,54]

Paradoxical cryptococcal IRIS

In 12 studies involving a total of 598 patients with known cryptococcal disease before ART, cryptococcal IRIS developed in 8–49% of patients (table 1).[8–12,18,21–23,24,25,54] Of 171 cases in which the sites and modes of presentation were both reported, 126 (74%) involved mainly meningeal disease (tables 1 and 2).[8–16,19–27,29,31,32,34,38–40,42,46] Other common presentations were complications of CNS disease (19 cases, 11%),[12,19,21,22,35–37,41,45] lymphadenopathy (19 cases, 11%),[8–11,19,21,24,28,36,30,33,34,43,44] pneumonitis (nine cases, 5%),[8–11,24–26,34] multifocal disease (seven cases, 4%),[19,25,28,40] and soft-tissue disease (two cases, 2%).[29,34] Specific CNS features included intracranial cryptococcoma or abscess,[20,21,35,37] spinal cord abscess,[36] recalcitrant raised intracranial pressure,[20,31,39] optic disc swelling,[45] cranial nerve lesions,[22,41] dysarthria,[19] hemiparesis,[22] and paraparesis.[12,50] Non-CNS manifestations of paradoxical cryptococcal IRIS included fever,[27,28,43] eye disease,[8] suppurating soft-tissue lesions,[28,29,34] hypercalcaemia,[34] and pulmonary disease, including cavitating or nodular lesions.[8,10,19,20,26,34]

The reported time of onset of paradoxical cryptococcal IRIS after the initiation of ART has varied widely, from 4 days to around 3 years,[11,27,36] with reported median times ranging from 1 month to 10 months in cohort studies.[8–12,16,18,21,22,54]

Reported CD4 cell counts before ART are typically below 50 cells/μL (table 1), but HIV viral loads before ART, virological outcomes, and follow-up CD4 cell counts are inconsistently reported. In case reports, individual data were generally reported, giving median baseline

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values for CD4 cell count and viral load of 28 cells/μL and 5·6 log_{10} copies/mL, respectively, and median event values of 162 cells/μL and 2·4 log_{10} copies/mL, respectively.[12,24–43,45–48,50–52] No study has reported complete data and, therefore, comparison between cryptococcal IRIS cases and appropriate controls receiving ART is not possible. In a South African study the median baseline CD4 cell count in six patients with cryptococcal IRIS cases was 28 cells/μL, rising to 164 cells/μL after 1 month of ART and 240 cells/μL after 6 months, compared with

	Study design and country	Number of cases/ total patients	C-IRIS incidence	Clinical features	ART duration at C-IRIS onset	Criteria for case definition	CD4 cell count (cells/μL)	HIV-1 viral load (log_{10} copies/mL)
Paradoxical C-IRIS in HIV-1-infected individuals with known cryptococcosis at ART initiation								
Lawn et al[12]	Retrospective cohort study, South Africa	6/18	33%	5 CM, 1 paraparesis	1–8 weeks	Any cryptococcosis on ART; negative CSF cultures not required	Pre-ART 22–73/ event NR	Pre-ART4·65–5·70/ event NR
Shelburne et al[9,10]	Retrospective cohort study, USA*	15–17/59*	25–29%	14 CM, 1 LN, 1 lung, 1 not specified*	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 cell count or decrease in viral load	Pre-ART 54–133/ event median 93 increase from baseline	–2·27 decrease from before ART to event
Lortholary et al[11]	Retrospective cohort study, France	7–10/120†	8%	CM +/- lung, LN and CNS complications	Median 8 months	New inflammatory process, no new OI, neoplasia, or drug-related disorder, negative fungal culture, immunological response, virological response, or both, to ART	Pre-ART 0–52/ event 43–640	Pre-ART 3·1–6·2/ event 1·7–3·8 (58% of cases had viral load <50)
Bicanic et al[16]	Prospective cohort study, South Africa	13/32	Total at risk not reported	13 CM	Median 27 days	Meningitis during ART, negative CSF culture	Pre-ART median 27 (IQR 14–44)	Pre-ART median 5·4 (IQR 4·8–5·7)
Robertson et al[37]	Case-control study, USA	3/not specified	n/a	2 CM, 1 LN (mode of presentation not specified)	Not specified	New or worsening disease not explained by newly acquired infection, predicted course of known infection or drug effect, decrease in viral load >1·0 log_{10} copies/mL	NR	NR
Sungkanuparph et al[18]	Retrospective cohort study, Thailand	10/52	19%	10 CM	Median 9.9 months	Cryptococcosis after immunological response to ART, negative culture	Pre-ART median 26 (range 1–93)/ event median 121 (range 59–203)	NR
Manabe et al[19]	Case-control study, USA	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 ART side-effects, OI confirmed by microbiology or histology, decrease in viral load >1·0 log_{10} copies/mL	NR	NR
Kambugu et al[8] and Boulware et al[20]	Prospective cohort study, Uganda	42/85	49%	29 CM,4 CNS mass, 9 non-CNS	Median 8 weeks (IQR 4–17)	Atypical or exaggerated infection not explained by alternative infection, malignancy, OI treatment failure, drug reaction, or non-adherence to ART, negative CSF culture	Pre-ART median patients 21 (range 2–109), controls 19 (1–179)/event median 61 (range 2–264)	NR
Antinori et al[21]	Retrospective cohort study, Italy	5/26	19%	3 CM, 1 LN and abscess, 1 cerebral	Median 15 weeks	Negative CSF or other relevant culture; clinical criteria not specified	Pre-ART median 22/event median 95	
Bicanic et al[22]	Prospective cohort study, South Africa	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, virological, or both, response to ART, confirmed negative or positive CSF culture	Pre-ART median patients, 28 controls 41/ event median patients 162, controls 187	Pre-ART median 5·0/event median decrease 1·6
Sungkanuparph et al[23]	Prospective cohort, study, Thailand	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, negative culture for CM after immunological response to ART	NR	NR
da Cunha et al[24]	Prospective cohort study, Brazil	9/40	22·5%	7 CM, 1 mass, 2 LN, 1 pneumonia	Median 10 weeks (range 4–17 weeks)	Previous clinical improvement, relapse of CM, culture negative or enlarged inflammatory lymph nodes	Pre-ART 6–84/ event 33–287	Pre-ART4·5–5·7/ event 1·7–3·1
Haddow et al[25]	Prospective cohort study, South Africa	2/8	25%	1 CM, 1 disseminated disease	1–2 weeks	Consensus expert opinion	Event 54 increase from baseline (one case)	2·9 decrease from baseline

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41 cells/μL at baseline and 187 cells/μL after 6 months in other patients treated with ART.[22] Baseline median viral load in cryptococcal IRIS cases was 5·0 log_{10} copies/mL, with a minimum fall of 1·6 log_{10} copies/mL after 1 month of ART. In other patients receiving ART, median baseline viral load was 5·2 log_{10} copies/mL but no viral load results at similar time points were reported.

Reported mortality from paradoxical cryptococcal IRIS and ART-associated cryptococcosis has ranged from 27% to 83% in Africa[8,12,13,20,22] and from 0 to 20% in North America, Europe, and southeast Asia.[9,11,18,21,23] In sub-Saharan Africa, paradoxical cryptococcal IRIS is an important contributor to early mortality in patients receiving ART.[8,12,16,20]

Risk factors for paradoxical cryptococcal IRIS have been reported in six studies.[9–11,20,22,23] Retrospective cohort studies indicated risk factors might include high viral load before the start of ART (in a study including ART-experienced and ART-naive patients),[9] early initiation of ART within 1–2 months of initiation of antifungal therapy[9,11] and substantial CD4 cell count increase in the first 6 months of ART (median 220 cells/μL *vs* 124 cells/μL).[22] However, in three prospective cohorts, viral load before treatment, time to start of ART, and baseline CD4 cell counts were not risk factors for cryptococcal IRIS.[20,22,23] Fungaemia and raised serum cryptococcal antigen titres at diagnosis might also be risk factors.[22] However, two studies examining markers of fungal burden found no association between number of colony-forming units in cerebrospinal fluid and IRIS.[20,22] In another prospective cohort, lack of initial cerebrospinal fluid inflammation (cerebrospinal fluid protein <50 mg/dL and white blood cell count <0.025×10⁹/L) before ART was associated with a seven times increase in IRIS risk.[20]

ART-associated cryptococcosis

Infection with *Cryptococcus neoformans* can remain latent for years after initial exposure[55] and active disease may remain subclinical for some time in patients with advanced immunodeficiency. Unsurprisingly, therefore, clinical cryptococcosis may emerge for the first time after ART is started. The incidence of ART-associated

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	Study design and country	Number of cases/ total patients	C-IRIS incidence	Clinical features	ART duration at C-IRIS onset	Criteria for case definition	CD4 cell count (cells/μL)	HIV-1 viral load (log_{10} copies/mL)
(Continued from previous page)								
ART-associated cryptococcosis reported as unmasking presentations								
Michelet et al[14]	Retrospective cohort study, France	3/486	0·2%	1 CM, 2 site not specified	Not specified	Development or recurrence of any AIDS-defining event during ART	Event mean 153 increase from baseline	1·7 decrease from baseline
Lawn et al[12]	Retrospective cohort study, South Africa	3/416	0·7%	3 CM	1–23 weeks	Any cryptococcosis during ART; negative CSF cultures not required	Pre-ART 9–58	Pre-ART 4·2–5·6
Shelburne et al[9,10]	Retrospective cohort study, USA	3/not specified*	Not known	2 CM, 1 LN	Median 30 days	New symptoms, elevated CSF protein, high opening pressure, negative CSF cultures, low or decreased CrAg, CSF WBC >0·05×10⁹/L (in unmasking cases), increase in CD4 cell count or decrease in viral load	Pre-ART 54–133/ event median 93 increase from baseline	–2·27 decrease from before ART to event
Lortholary et al[11]	Retrospective cohort study, France	3/not specified†	Not known	Mixed CM, lung and LN†	Median 8 months	New inflammatory process, no new OI, neoplasia, or drug-related disorder, negative fungal culture, immunological, virological, or both, 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 viral load <50)
Manabe et al[19]	Case-control study, USA	2/not specified	n/a	1 CM, 1 disseminated disease	4 and 9 days	Atypical presentation of OI, symptoms not due to ART side-effects, OI confirmed by microbiology or histology, decrease in viral load >1·0 log_{10} copies/mL	NR	NR
Murdoch et al[13]	Prospective cohort study, South Africa	3/423	0·7%	3 CM	14–80 days	New focal infection, exclusion of ART non-adherence, exclusion of virological failure or CD4 cell count decline (if >3 months after start of ART)	NR	NR
Meya et al[15]	Prospective cohort study, Uganda	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	NR	NR
Haddow et al[15]	Prospective cohort study, South Africa	2/490	0·4%	1 CM, 1 pneumonitis	4–7 weeks	Consensus expert opinion	Event 56 and 86 increase from baseline	3·1 and 3·9 decrease from baseline

C-IRIS=cryptococcal immune reconstitution inflammatory syndrome. ART=antiretroviral therapy. CM=cryptococcal meningitis. CSF=cerebrospinal fluid. NR=not reported. LN=lymph node disease. CrAg=cryptococcal antigen. OI=opportunistic infection. WBC=white blood cell count. *Some patients in this cohort were included in two separate publications. †The study reported a cohort of 120 patients, of whom ten developed cryptococcal immune reconstitution inflammatory syndrome, and an additional two cases from other datasets. Of these 12 cases, three (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.

Table 1: **Cohort and case-control studies reporting cases of HIV-1-associated cryptococcal immune reconstitution inflammatory syndrome**

	Country	Clinical presentations	ART duration at onset	Cryptococcal antigen site and titre	Fungal microscopy/culture/histology	CSF opening pressure (cm)/leucocytes (cells/μL)	CD4 cell count (cells/μL)	HIV-1 viral load (log_{10} copies/mL)
Shelburne et al[26]	USA	3 CM, 1 pneumonia and ARDS	8/11/58 days	CSF 1:2048	NR/negative/NR	NR/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
Woods et al[27]	Australia	1 CM	10 days	CSF 1:200	NR/negative/NR	NR/10	Pre-ART 40/event 240	Pre-ART 5·7/event 3·1
Blanche et al[28]	France	2 LN +/- fever & retropharyngeal abscess	8/15 months	Serum, unchanged	NR/negative/NR	NR	Pre-ART 6, 28/event 63, 251	Pre-ART 5·6/event 3·7, 3·8
Manfredi et al[29]	Italy	1 recurrent CM; 1 multiple abscesses	3/5 months	Serum, CSF, lymph-node aspirate	Positive/positive in CSF of CM case/NR	NR	Pre-ART 98, 7/event 78, 186	Pre-ART 4·8, 4·9/event <1·7
Lanzafame et al[30]	Italy	1 mediastinal LN	6 months	Serum 1:16	NR/NR/positive	NR	Event 137	Event <2·7
Cinti et al[31]	USA	1 CM with raised ICP	3 weeks	CSF 1:8000	Positive/negative/NR	33/500	Pre-ART 67/event 370	Pre-ART 5·8/event 2·7
King et al[32]	USA	1 CM	4 weeks	CSF 1:32	NR/negative/NR	NR/10	Pre-ART 41/event 44	Pre-ART 5·9/event <2·6
Trevenzoli et al[33]	Italy	3 mediastinal LN	2–4 months	NR	NR/negative/positive	NR	Pre-ART 17, 64, 120/event 48, 329, 200	Pre-ART 6·0/event <1·7
Jenny-Avital and Abadi[34]	USA	2 CM, 1 LN, 1 lung, 1 soft tissue mass	2–11 months	CSF 1:32, 1:1	Negative/negative/negative	34, 39/17, 149	Pre-ART 10–102/event 57–306	Pre-ART 4·7–5·9/event <2·7
Breton et al[35]	France	1 cerebral cryptococcoma	3 months	CSF 1:10	NR/negative/positive	NR/1	Pre-ART 3/event 485	Event <2·6
Rambeloarisoa et al[36]	France	1 LN, 1 spinal cord abscess (same patient)	10/34 months	NR	NR/negative/positive	NR/1	Pre-ART 3/event 175	Event <2·6
Cattelan et al[37]	Italy	2 cerebral cryptococcomas	6/7 months	CSF 1:16, 1:1	NR/NR/NR	NR/20, 50	Pre-ART 17, 27/event 220, 205	Pre-ART 5·6, 5·0/event <1·7
Boelaert et al[38]	Belgium	1 CM	8 days	CSF positive	Negative/negative/NR	NR/35	Pre-ART 16/event 38	Pre-ART 5·0/event 2·2
York et al[39]	UK	1 raised ICP	10 days	CSF 1:1	Negative/negative/NR	>40/<5	Pre-ART 9/event 59	Pre-ART >5·7/event <1·7
Skiest et al[40]	USA	3 CM +/- LN	2–18 months	CSF 1:16, 1:2	Positive/negative/positive	NR	Pre-ART 1–4/event 180–409	Pre-ART 4·7–5·7/event 2·1–2·9
Khanna et al[41]	Switzerland	1 CM + hearing loss and LN	17 months	NR	NR/negative/NR	NR/16	Pre-ART 32/event 234	Pre-ART 4·9/event <2·9
Huits et al[42]	Netherlands	1 CM	320 days	CSF "low"	Negative/negative/NR	>50/272	Pre-ART 0/event 120	Event <1·7
Tahir et al[43]	India	1 LN and fever	2 weeks	NR	NR/positive/positive	NR	Pre-ART 13	NR
Putignani et al[44]	Italy	1 LN	NR	NR	NR/positive (enrichment cultures)/positive on PCR	NR	NR	NR
Khurana et al[45]	USA	4 raised ICP with optic disc swelling	17–33 days	CSF 1:128 to 1:256	NR/negative/NR	25, 44, 55, 55/0, 6, 8, 8	Pre-ART mean 20/event mean 65	Pre-ART mean 5·2/event mean 3·5
McCombe et al[46]	Canada	1 CM	6 months	NR	NR/negative/NR	NR/150	NR	NR
Woods et al[27]	Australia	2 CM	4 days, 39 days	NR	NR/positive/NR	28/0·3, 14	Pre-ART 5, 30/event 70, 110	Pre-ART 6·4/event <2·3
Lanzafame et al[30]	Italy	1 mediastinal LN	6 months	Serum 1:2048	NR/NR/positive	NR	Event 110	Event 3·8
Legendre et al[47]	Switzerland	1 pulmonary lesion	4 weeks	CSF 1:16	Positive/NR/NR	NR	Pre-ART 38/event 54	Pre-ART 4·9/event 2·5
Broom et al[48]	Australia	1 CM	10 weeks	CSF 1:256	NR/negative/NR	NR/77	Pre-ART 20/event 70	Event 3·5
Lehloenya and Meintjes[49]	South Africa	1 cutaneous ulceration	1 month	NR	NR/positive/positive	NR	NR	NR
Jongwutiwes et al[50]	Thailand	1 meningo-radiculitis	2 weeks	Serum and CSF positive	Positive/postive/NR	NR/0	Pre-ART 17/event 24	Event <2·6
Haddow et al[51]	South Africa	1 breast abscess	11 months	Serum >1:8	Positive/positive/NR	NR	Pre-ART 89/event 59	Event <1·5
Gąsiorowski et al[52]	Poland	1 cutaneous ulceration	4 weeks	Serum positive	Positive/positive (skin and blood)/positive	NR	Pre-ART 4/event 31	Pre-ART 6·3/event 4·1
McCombe et al[46]	Canada	1 CM	2 months	NR	NR/NR/NR	NR	Pre-ART 8	Pre-ART 5·5

ART=antiretroviral therapy. CM=cryptococcal meningitis. CSF=cerebrospinal fluid. NR=not reported. LN=lymph node disease. ICP=intracranial pressure.

Table 2: **Case reports and case series of HIV-1-associated cryptococcal immune reconstitution inflammatory syndrome**

cryptococcosis ranged from 0·2% to 1·6% in six studies involving more than 2000 patients without evidence of cryptococcosis before starting ART.[12–15,25,54] However, the incidence could be as high as 33% in individuals with subclinical cryptococcal antigenaemia without pre-emptive therapy with fluconazole.[56,57] Subclinical antigenaemia is, therefore, the overwhelming risk factor for ART-associated cryptococcosis.[15,56]

Among 25 patients with ART-associated cryptococcosis in whom clinical features were described, the clinical characteristics were similar to those reported in paradoxical cryptococcal IRIS. Meningitis, CNS complications, or both occurred in 17 (68%) patients,[9,10,12–16,19,25,27,46,48,50] skin or soft-tissue lesions in three (12%),[49,51,52] lymphadenopathy in two (8%),[11,30] lung disease in two (8%),[25,47] and disseminated disease in one (4%).[19] In 13 patients for whom individual values were reported, the median CD4 cell count at baseline was 19 cells/μL and viral load was 5·5 $\log_{10}$ copies/mL, and values at clinical event (range 4 days to 11 months) were 65 cells/μL and 2·6 $\log_{10}$ copies/mL, respectively.

One feature of ART-associated cryptococcal meningitis is the rapid development of severe illness, which develops over a few days from the onset of symptoms,[12,15,27,50] compared with the 1–2-week subacute course typically seen with cryptococcal meningitis in patients not receiving ART.[8,58] From individually reported times of symptom onset, the median time after the start of ART was 9 weeks (IQR 2–26 weeks) in patients with paradoxical cryptococcal IRIS (n=54) and 4 weeks (IQR 2–10 weeks) in those with ART-associated cryptococcosis (n=19), although the difference was not significant (p=0.12).

In patients who develop clinical cryptococcosis only after the start of ART, differentiation between IRIS-associated disease (caused by restoration of specific immune responses to previously subclinical disease and termed unmasking cryptococcal IRIS) and progression of untreated occult cryptococcosis in the context of persisting immunodeficiency might be difficult.[59] Therefore, we favour the term ART-associated cryptococcosis for both. The analogous situation in ART-associated tuberculosis is that the classification of unmasking IRIS is reserved for a subset of cases with heightened intensity of clinical manifestations or rapid, destructive, necrotic inflammation.[53,60–64] ART-associated cryptococcosis with florid inflammatory features might, therefore, be more likely to occur with unmasking IRIS than to be associated with persistent immunodeficiency.

The clinical spectrum of ART-associated cryptococcosis does not seem to differ notably from that for disease arising before treatment, when 75–90% of cases present as meningitis, encephalitis, or both, and the remainder present mainly as pneumonitis, lymphadenopathy, or cutaneous lesions.[65] Therefore, although we acknowledge that most cases of cryptococcosis arising during ART might be suspected unmasking cryptococcal IRIS, we propose that such cases should be reported only as ART-associated cryptococcosis until further evidence becomes available to support meaningful clinical discrimination between cryptococcal IRIS and illness progressing owing to immunodeficiency.

Proposed case definitions for cryptococcal IRIS

We have developed case definitions for paradoxical cryptococcal IRIS and ART-associated cryptococcosis in patients with HIV that are based on published data on clinical and diagnostic features. The case definition for paradoxical cryptococcal IRIS (panel 1) applies to patients who have cryptococcal disease that was recognised before initiation of ART and worsens during treatment. The definition of ART-associated cryptococcosis (panel 2) applies to patients without recognised cryptococcosis at the start of ART and who develop the disease during treatment. Although these definitions are focused on HIV-1-related IRIS, we anticipate that they could be modified for use in IRIS related to non-HIV disorders or conditions (eg, pregnancy) in which immunosuppression is reversed.[5–7]

Paradoxical cryptococcal IRIS

Clinical features

From the available reports, we have identified six main clinical syndromes in paradoxical IRIS and ART-associated cryptococcosis: meningitis, accounting for

Panel 1: **Case definition for paradoxical cryptococcal immune reconstitution inflammatory syndrome in patients HIV-1**

Antecedent requirements

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

Clinical criteria

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

Other explanations for clinical deterioration to be excluded

- Non-adherence or suboptimum antifungal therapy, indicated by an increase in quantitative culture or antigen titre, or any positive cryptococcal culture after 3 months of antifungal therapy
- Alternative infection or malignant disease in the affected site
- Failure of ART excluded if possible (eg, failure to achieve ≥1 $\log_{10}$ copies/mL decrease in viral load by 8 weeks of ART)

ART=antiretroviral therapy. CSF=cerebrospinal fluid.

around 70% of cases; lymphadenopathy, typically necrotic; space-occupying CNS lesions; multifocal disease; soft-tissue or subcutaneous mass lesions, typically suppurative; and pneumonitis (panel 1). Other localised sites, such as bone, prostate, and peritoneum, have been described in individuals not infected with HIV and might be sites of cryptococcal IRIS disease, but have not been reported in ART-treated individuals.

Vigorous inflammatory signs with granulomatous lesions, evidence of necrosis with or without organisms on fungal staining and culture, or both might be seen.[28–30,33,36,40,51] In patients treated with ART who develop cryptococcal IRIS, concentrations of C-reactive protein and interleukin 6 might be higher before the development of the syndrome than those in patients who do not.[66] A central pathogenic role for a change in the T-helper-1 (Th-1) and T-helper-2 (Th-2) balance has been proposed.[5,67] At the time of cryptococcal IRIS onset, a marked Th-1 response is present in serum and cerebrospinal fluid.[20,68] Findings for tuberculosis-associated IRIS indicate that some patients do not have a swing from a Th-2 to a Th-1 response, but that innate immune responses are involved.[69] Before ART, people with increased Th-2 responses (eg, secretion of interleukin 4) might be at increased risk of subsequent cryptococcal IRIS (Boulware DR, unpublished). People at risk of cryptococcal IRIS have a paucity of inflammation and ineffective antigen clearance before ART,[20] followed by antigen presentation after ART is started, and robust and probably dysregulated antigen-specific and generalised proinflammatory responses.[55,60,67,70–72]

Cerebrospinal fluid profiles of many patients with paradoxical cryptococcal IRIS frequently show increased white blood cell counts and opening pressures of at least 25 cm, but the range of values overlaps greatly with those seen in patients with cryptococcal meningitis before ART is started or with non-IRIS relapses of cryptococcal meningitis due to therapeutic failure.[20,21] In one series of 14 patients with paradoxical cryptococcal IRIS and 45 controls with non-IRIS cryptococcal meningitis, patients with cryptococcal IRIS had higher median cerebrospinal fluid opening pressures (45 cm *vs* 31 cm) and white blood cell counts (56 cells × 10^6/L *vs* 12 cells × 10^6/L).[9] However, the interpretation of these findings is limited because the control group included cases of cryptococcal meningitis present before and after the start of ART, and high cerebrospinal fluid opening pressures and white blood cell counts formed part of the diagnostic criteria for IRIS. In addition, these findings were not confirmed in three other studies of similar or larger sizes.[16,20,21] Therefore, we recommend caution in the adoption of a predefined threshold in cerebrospinal fluid opening pressure or white blood cell counts to distinguish IRIS from non-IRIS cryptococcal meningitis, until further studies are done. Assessment of cytokine profiles as disease worsens might help to distinguish cryptococcal IRIS from cryptococcal meningitis relapse, with increased proinflammatory cytokines (eg, interferon γ, tumour necrosis factor α, and interleukins 12 and 17) being present in the cerebrospinal fluid of patients with cryptococcal IRIS but not cryptococcal meningitis.[20]

Panel 2: **Proposed case definitions for antiretroviral-therapy-associated cryptococcosis and unmasking cryptococcal immune reconstitution inflammatory syndrome**

ART-associated cryptococcosis

- Patient taking ART
- No recognised cryptococcal disease at ART initiation
- Clinical disease worsening caused by cryptococcosis occurs after initiation, re-introduction, or regimen switch after previous failure (supported by microbiological, histological, or serological evidence)
- Cryptococcal infection characterised by meningitis, CNS complications, skin or soft-tissue lesions, lymphadenopathy, lung disease, or disseminated disease

Unmasking cryptococcal IRIS (provisional)

- Criteria for ART-associated cryptococcosis are met
- Unusual, exaggerated, or heightened inflammatory manifestations, such as the following:
  - Meningitis with CSF WBC >50×10^6/L or CSF opening pressure >20 cm that is refractory to therapy
  - Painful or suppurating lymphadenopathy
  - Rapidly expanding CNS lesions, cryptococcomas
  - Unusual focal site (ie, 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 (eg, ≥1·0 $\log_{10}$ copies/mL decrease in HIV-1 viral load by 8 weeks treatment)

ART=antiretroviral therapy. IRIS=immune reconstitution inflammatory syndrome. CSF=cerebrospinal fluid. WBC=white blood cell count. *No specific time limit is proposed for unmasking cryptococcal IRIS, pending further research. Typically, onset within 3 months of starting ART could be assumed to support a diagnosis of IRIS owing to early and rapid changes in immune function. However, late presentations of cryptococcal IRIS have been reported in patients with good responses to therapy assessed by CD4 cell counts.

Timing of onset of symptoms

We propose a cutoff time of 12 months after ART initiation for development of cryptococcal IRIS symptoms. This upper limit is based on the reported time of onset in published studies; the onset range seems to be 1–10 months,[8–12,16,18,21,22,54] which is later than IRIS associated with other diseases, such as tuberculosis, in which the median onset of paradoxical IRIS is as early as 2–4 weeks after ART is started.[73,74] Rare late presentations of cryptococcal disease can occur,[11,18,36,40,41] and in these cases exclusion of ART failure and relapse caused by fluconazole-resistant organisms is crucial. We acknowledge that any cutoff time for diagnosis is arbitrary and would probably exclude occasional cases, but should improve the specificity and practical usefulness of the case definition without substantially diminishing sensitivity.

Confirmation of a therapeutic response to ART

Confirmation of a virological response to ART is recommended, but not essential, to make a diagnosis of cryptococcal IRIS. A specific threshold for a reduction in

viral load of less than 1·0 log_{10} copies/mL at the time of clinical event has been suggested as an exclusion criterion for IRIS.[13,17,26,60] However, the best time to do viral load assays or the best threshold value or values have not been experimentally validated. Studies of the INSHI tuberculosis-associated IRIS clinical case definition[53] have shown that the absence of CD4 cell counts and viral load measurement does not significantly affect the case definition's performance.[75,76] Several other major studies examining the epidemiology of IRIS have also omitted these assessments from case definitions.[13,17,19,74,77–79]

Although the lack of a virological response to ART might support a diagnosis of treatment failure, suboptimum responses to combination ART could still be consistent with IRIS; notably, the syndrome was originally described during zidovudine monotherapy.[80] ART-naive patients with good adherence typically have excellent virological responses to ART in the first 6 months of therapy.[81] In the largest prospective cohort study of IRIS to date, virological failure was present in only five (3·5%) of 144 probable IRIS events.[25] Similarly, in a large prospective cohort of Ugandan patients with cryptococcosis (n=101), 57 (97%) of 59 individuals with suspected cryptococcal IRIS who had viral loads measured had a decrease in viral load of more than 1·0 log_{10} copies/mL at the time of cryptococcal IRIS event or by 12 weeks of ART.[20] Therefore, ART-naive individuals who report good adherence may, in the absence of another reason, be assumed to have an early virological response and partial immune reconstitution within days or weeks of starting ART, and the lack of a viral load assay does not exclude IRIS. In settings where viral load assays are readily available, a reduction threshold of 1·0 log_{10} copies/mL by 8 weeks of therapy or at the time of clinical worsening of disease may be used. In all settings, an assessment of adherence to ART is essential in patients presenting with suspected cryptococcal IRIS.

Our case definitions do not include any criteria based on patients' CD4 cell counts. As with changes in viral load, some diagnostic criteria for IRIS have incorporated a rise in CD4 cell count,[13,26,60] but several major studies have omitted this assessment.[13,17,19,74,77–79] The main arguments for this omission have been presented above and in a review.[53] The number of CD4 cells measured in peripheral blood does not necessarily reflect function or how many CD4 cells are actually present at the site of an opportunistic infection. In addition, there might be functional immunological improvements even in the absence of a rise in CD4 cell count. In one prospective cohort study of cryptococcal IRIS, 11 (30%) of 36 patients with sterile cerebrospinal fluid cultures and virological responses had increases in CD4 cell counts of less than 25 cells/μL from before ART.[20] Furthermore, data from cohort studies on IRIS associated with non-tuberculous mycobacterial infection suggest that restoration of a pathogen-specific cellular immune response occurs without an increase in the circulating CD4 cell count.[82]

Exclusion of other causes

Non-adherence to ART or antifungal therapy, no response to ART, and comorbidity, such as other common pathogens or malignant disease, are important to consider. However, in some settings the exclusion of other causes might be problematic because of limited diagnostic capabilities. As a minimum requirement, tuberculosis (tested by staining for acid-fast bacilli) and bacterial disease should be excluded, since IRIS associated with co-infection is possible, and some patients with cryptococcal meningitis before starting ART develop ART-associated tuberculosis.[8]

The distinguishing of cryptococcal IRIS from drug-related toxic effects is not generally problematic, since few drug effects are likely to mimic the syndrome. Two rare but plausible considerations are hepatic cryptococcal lesions mimicking drug-related hepatotoxic effects,[83] and aseptic meningitis induced by co-trimoxazole.[84]

Clinical history before initiation of ART

Paradoxical cryptococcal IRIS can occur after ART is started in treatment-naive individuals, when treatment is restarted, or when the regimen is switched after virological failure. To meet the antecedent criteria of paradoxical cryptococcal IRIS, the diagnosis of cryptococcosis before ART may be defined by locally available diagnostic facilities, such as India ink stain, fungal culture, and cryptococcal antigen detection in cerebrospinal fluid or serum. Two scenarios might fall outside the definition of paradoxical cryptococcal IRIS: patients with known cryptococcosis who have discontinued antifungal therapy before starting ART, and cases where a provisional diagnosis of cryptococcosis before the start of therapy is confirmed after ART initiation.

Fungal culture and antigen detection in diagnosis

In an ideal setting, quantitative cerebrospinal fluid culture should be used to assist the diagnosis of cryptococcal IRIS presenting with meningitis. In contrast to several published definitions,[8–11,16,18] our view is that a negative cryptococcal culture is not an absolute requirement for the diagnosis of paradoxical cryptococcal IRIS. Our reasoning is that the timing of cerebrospinal fluid culture sterility is variable, with around 50% of patients becoming culture negative within 2 weeks, 66% by 4 weeks, and 80% by 6 weeks of starting amphotericin-based therapy.[8,85–89] The reality in sub-Saharan Africa is that many cryptococcus-infected patients only receive oral fluconazole therapy,[16,90–93] and cerebrospinal fluid sterilisation with this drug takes longer than with amphotericin therapy.[87] Even in patients receiving high-dose fluconazole therapy (800–1200 mg daily), up to 20% can have persistent positive cerebrospinal fluid cultures after 12 weeks.[94,95] Thus if patients commence ART shortly after antifungal therapy is started, cerebrospinal fluid might still be culture positive when they present with paradoxical IRIS. In a Ugandan cohort, 32 (97%) of 33 patients with a final diagnosis of meningitis

cryptococcal IRIS had negative cerebrospinal fluid cultures.[20] One person with culture-positive cryptococcal IRIS had a quantitative cerebrospinal fluid culture with only 70 colony-forming units/mL. An association seemed to exist between mycological and virological failure: of five patients who initially had suspected cryptococcal IRIS but who had positive cerebrospinal fluid cultures during ART, two had a viral load increase to more than 4·0 $\log_{10}$ copies/mL.

Although we accept the difficulties in making a diagnosis of cryptococcal IRIS when cultures remain positive, we favour an approach informed by the expected range of therapeutic responses to antifungal therapy. Although the likelihood of a positive fungal culture and the risk of cryptococcal IRIS both decrease over time, we believe a positive fungal culture after 3 months of antifungal therapy is likely to indicate therapeutic failure and, therefore, we propose excluding such events from the paradoxical cryptococcal IRIS definition.

Serum and cerebrospinal fluid cryptococcal antigen titres are unhelpful in the diagnosis of cryptococcal IRIS. In the Ugandan cohort, 25 (25%) of 101 patients had less than four-times decreases in cryptococcal antigen titres in cerebrospinal fluid at the time of their cryptococcal IRIS event.[20]

Recurrence of cryptococcal symptoms might be caused by the host immune response (ie, IRIS), persistent immunosuppression, sequelae of existing disease, or failure of antifungal therapy. Although these mechanisms might be distinct, they can coexist concurrently. For example, suboptimum antifungal therapy or adherence could lessen the decline in pathogen burden before ART and provoke a more vigorous cryptococcus-specific immune response during therapy than would have occurred with more effective antifungal treatment. The development of paradoxical tuberculosis-associated IRIS in cases of undiagnosed drug-resistant tuberculosis has been highlighted.[96] Furthermore, whether the antigen is derived from live organisms, dead intact organisms, or cellular debris, might not be crucial in propagating an immune response leading to IRIS.

ART-associated cryptococcosis

Uncertainty is inherent in the differentiation of ART-associated cryptococcosis caused by restoration of a cryptococcus-specific immune response (ie, unmasking cryptococcal IRIS) from that caused by persistent immunodeficiency while receiving ART. Clinical management could be affected 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 immunodeficiency-related cryptococcosis and unmasking cryptococcal IRIS are provisional. Although specific criteria or clinical thresholds might improve the objectivity of our definition, they introduce unnecessary arbitrariness into the diagnostic process. As with tuberculosis[53] and other opportunistic infections,[59] immunodeficiency-associated cryptococcosis and cryptococcal IRIS might be part of the same continuous spectrum, rather than two distinct entities.

Although clinically recognisable cryptococcosis should be absent when ART is started, the presence of mild symptoms should not preclude a diagnosis of ART-associated cryptococcosis if appropriate screening for cryptococcal infection was initially negative. Occult cryptococcal antigenaemia can occur in asymptomatic individuals before ART, particularly in resource-limited settings with high cryptococcal prevalence.[57,97] Although patients with untreated antigenaemia are more likely to develop clinical cryptococcosis than those without,[56,97–99] we have observed ART-associated cryptococcosis in patients negative for cryptococcal antigen in serum before starting ART in South Africa and Uganda, albeit rarely (Haddow L, unpublished). Similarly, a placebo-controlled study of fluconazole as primary prophylaxis in Uganda reported ART-associated cryptococcosis in 1% of individuals receiving placebo or ART, all of whom were negative for cryptococcal antigen in serum at a median of 11 weeks before initiation of ART.[54] Therefore, neither a positive nor negative serum cryptococcal antigen test result before the start of ART is an exclusion criterion for ART-associated cryptococcosis. However, screening for cryptococcal antigenaemia before initiation of ART could 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

Prevention of paradoxical cryptococcal IRIS has been used as a justification for delaying ART, yet the evidence for such a rationale is unclear. In two retrospective studies, ART initiation less than 4–8 weeks after antifungal therapy was started was associated with increased risk of cryptococcal IRIS,[9,11] but in two prospective observational cohorts, timing of ART initiation was not associated with IRIS.[20,22] Two randomised, controlled trials to address the question of when to start ART have been completed, both with a primary outcome of mortality. In the ACTG a5164 trial,[100] incidence of IRIS did not decrease when ART initiation was delayed to 6 weeks compared with when it was started within 2 weeks, but the former approach was associated with increased mortality. Only 35 (12%) of 282 patients in the trial had cryptococcosis, compared with 177 (63%) with pneumocystis, and only aggregated data were reported. In a second trial of 54 patients from Zimbabwe with cryptococcosis, initiation of ART a median of 24 h after starting antifungal therapy was associated with increased mortality compared with a delay of 10 weeks.[101] The causes of death were, however, unclear and cryptococcal IRIS was not assessed. We do not support early or delayed initiation of ART as a

recommendation for clinical practice. A clinical trial is planned to try to definitively answer when to start ART after onset of cryptococcal meningitis, and whether earlier ART is associated with excess risk of cryptococcal IRIS (NCT01075152 on www.ClinicalTrials.gov).

For treatment of cryptococcosis, published expert guidelines do not discuss IRIS in detail.[102,103] Intensification of antifungal therapy is indicated in all cases of severe cryptococcal IRIS (eg, intracranial space-occupying lesions or extracranial disease impinging on vital structures), any with positive culture, and in those in which antifungal therapy is suboptimum.

Case reports have noted beneficial responses of cryptococcal IRIS to immune modulating therapies, including corticosteroids,[11,26,32,42] non-steroidal anti-inflammatory drugs,[29] and thalidomide,[11] and a randomised, controlled trial of high-dose oral prednisone in mild to moderate tuberculosis-associated IRIS reported an overall reduction in the numbers of inpatient days and outpatient therapeutic procedures,[104] but there is no evidence of therapeutic benefit of steroids in either cryptococcal IRIS or non-IRIS cryptococcal meningitis.[105] Potential risks associated with corticosteroid use in immunosuppressed patients include development of *Strongyloides* spp hyperinfection, worsening of Kaposi's sarcoma, or inappropriate administration during culture-positive cryptococcal relapse. Aggressive control of raised intracranial pressure by therapeutic lumbar punctures[58,103] and optimisation of antifungal therapy should take priority, irrespective of whether diagnosis of cryptococcal IRIS can be confirmed or excluded.

Assessment of case definitions

Our structured case definitions for cryptococcal IRIS and ART-associated cryptococcosis provide approaches for future clinical, epidemiological, and immunopathological studies of cryptococcal IRIS in HIV-infected patients, as they enable investigators to standardise diagnostic criteria and facilitate comparison of studies' designs and findings, pooling of data, and meta-analysis. Specifically, we recommend future reports avoid assessing and reporting findings for paradoxical cryptococcal IRIS and ART-associated cryptococcosis together, and instead report each separately.

Assessment of our case definitions will require comparison with expert opinion, given the current absence of an objective gold standard. The use of measurement parameters for cerebrospinal fluid assessments and inflammatory biomarkers in cryptococcal IRIS requires particular attention.[106] Evidence for specific diagnostic cutoff values is conflicting, and the entity of unmasking cryptococcal IRIS remains controversial. Therefore, future alterations to our case definitions are anticipated. In the development of case definitions of rheumatological and other complex syndromes, researchers assessed the sensitivity and specificity of candidate criteria, and used data-mining techniques to identify the best combinations of criteria.[107–109] As with tuberculosis-associated IRIS case definitions, these proposed definitions of cryptococcal IRIS should be viewed as preliminary until they are refined by further insights into the immunopathology of IRIS associated with HIV-1 infection and its various other presentations.

Search strategy and selection criteria

We conducted a Medline search for articles published up to June, 2010, to identify English-language cohort studies, case-control studies, case series, and case reports describing or enumerating cases of cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected patients. The search terms used were ("HIV" OR "HIV infections") AND (["immune reconstitution inflammatory syndrome" OR "immune"] AND ["reconst*" OR "restor*"] AND ["syndrome" OR "disease"]) AND ("cryptococc*" OR "Cryptococcus" OR "cryptococcosis" OR "Cryptococcus neoformans"). We also searched the reference lists of identified articles for further relevant reports. Where possible, the original source data were obtained from authors of cohort reports.

Contributors

RC organised the case definition project for the International Network for the Study of HIV-associated IRIS (INSHI). LJH and DRB conceived the Review, proposed the case definitions, and took primary responsibility for literature review, discussion points, drafting and correction of the article, and submission. All authors contributed to all discussions, according to their areas of expertise, and extensively reviewed all drafts.

Conflict of interest

We declare that we have no conflicts of interest.

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