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Central nervous system–immune reconstitution inflammatory syndrome in resource-limited settings: current burden and future needs

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The current global burden of central nervous system (CNS)–immune reconstitution inflammatory syndrome (CNS-IRIS) in HIV/AIDS has not been estimated. A large number of people are at risk of CNS-IRIS, particularly in low-income and middle-income countries. Of the more than 2.6 million people newly affected with HIV/AIDS in 2010 [1], the ultimate goal is to achieve antiretroviral treatment (ART) access for all. However, just 5.2 million of the estimated 15 million people living with HIV/AIDS in low-income and middle-income countries had access to treatment in 2010 [1]. This treatment gap has implications both for the survival of people with untreated HIV/AIDS and the eventual consequences of treatment when ART is initiated.

CNS-IRIS is a paradoxical worsening of neurological status during immune recovery in a patient with a CNS infection [2]. In the setting of HIV/AIDS, CNS-IRIS is marked by unexpected, new or recurrent neurological decline following the initiation of ART alongside a decrease in HIV viral load and a corresponding increase in CD4 T lymphocytes [3]. This exuberant response of the recovering immune system likely represents trafficking of activated T lymphocytes into the CNS following recognition of pathogenic or self-antigens. Although CNS-IRIS is less common than IRIS outside of the nervous system, CNS-IRIS has a high morbidity and mortality [4–7]. Important opportunistic infections leading to CNS-IRIS include cryptococcal meningitis, CNS tuberculosis, progressive multifocal leukoencephalopathy (PML) due to JC virus and, more rarely, *Candida* meningitis,

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Conflicts of interest

There are no conflicts of interest.

Mycobacterium avium complex meningoencephalitis, *Toxoplasma* encephalitis and varicella zoster meningoencephalitis [8–14]. In some cases, CNS-IRIS may occur in the absence of an opportunistic infection.

CNS-IRIS has received increasing attention in recent years. The population at risk for CNS-IRIS has grown as ART has become increasingly available worldwide, including in settings with limited healthcare workers and diagnostic equipment. Meningitis due to *Cryptococcus neoformans* is a leading cause of fatality among adults with HIV/AIDS, particularly in sub-Saharan Africa, affecting nearly 1 million people worldwide each year [4]. In high-income and middle-income countries, approximately 16% of people diagnosed with cryptococcal meningitis experience CNS-IRIS with an average fatality of 20% after diagnosis of CNS-IRIS [5]. There are no large studies on CNS-IRIS from low-income countries. However, as ART is not as readily available in most low-income countries, it is often reserved for patients with the lowest CD4 cell counts. Patients with the lowest CD4 cell counts are at greater risk for opportunistic infections and have a greater reservoir of HIV in the brain. These factors would be expected to predispose them to developing CNS-IRIS. Thus, the incidence of CNS-IRIS is likely much greater in low-income countries.

In retrospect, early description of disparities in survival between low-income and high-income countries among newly ART-treated individuals [15] may be partly explained by IRIS, including CNS-IRIS. Although IRIS outside of the nervous system may be recognized by clinical examination in resource-limited settings through affordable diagnostic tests (e.g. sputum sample for tuberculosis), available imaging techniques (e.g. chest radiograph), but even direct observation (e.g. Kaposi sarcoma), and diagnosis of neurological infection requires more sophisticated diagnostic techniques, such as neuroimaging and cerebrospinal fluid analysis to rule out alternative diagnoses. Case definitions have been proposed for IRIS in the setting of cryptococcal meningitis, including meningitis after initiation of ART [16]. The precise diagnosis of CNS-IRIS may be difficult to achieve.

Treatment of cryptococcal meningitis in HIV-infected patients poses unique challenges. Even with adequate treatment with antifungal agents, the dead organisms and antigen may persist in the CNS for several months. Hence, patients are at risk of developing IRIS for that duration whenever ART is initiated. Patients with cryptococcal meningitis may deteriorate subacutely due to the development of a communicating hydrocephalus even with adequate treatment. Development of IRIS involving the posterior fossa may lead to a similar change in neurological status due to obstructive hydrocephalus. The two may be difficult to differentiate clinically, requiring neuroimaging [17]. This is critical, as communicating hydrocephalus would be treated with repeated lumbar punctures to drain the cerebrospinal fluid; however, a lumbar puncture in a patient with obstructive hydrocephalus could be catastrophic. Treatment of IRIS in this setting requires use of high-dose corticosteroids. However, most physicians would be hesitant to use corticosteroids in an immunosuppressed patient with an opportunistic infection without a final diagnosis. There are no controlled trials to recommend corticosteroid treatment in CNS-IRIS in any setting, although retrospective studies and anecdotal cases support the use of corticosteroids [17]. In resource-limited settings, steroids for CNS-IRIS carry additional risks of exacerbating other

underlying infections and prophylactic drugs for such infections may not be readily available.

Autopsy studies suggest that PML and PML-IRIS are under diagnosed in low-income and middle-income countries [18]. The diagnosis of PML requires neuroimaging and the demonstration of JC virus in the cerebrospinal fluid by PCR. As there is no effective antiviral treatment for PML, the best treatment is the reconstitution of the immune system following ART. This carries the risk of development of IRIS, which needs to be differentiated from the progression of PML in a patient who may be clinically deteriorating. This can only be achieved by repeated MRI. Corticosteroids may be beneficial in treatment of PML-IRIS, particularly in individuals who develop massive edema [19].

In IRIS associated with tuberculous meningitis or tuberculoma, adjunctive corticosteroid therapy is often used as treatment despite a lack of clinical trials to determine its usefulness. Inappropriate adjunctive corticosteroid therapy for immunosuppressed individuals who have suboptimally treated tuberculosis or other untreated opportunistic infections may lead to rapid progression of the infection and can be fatal. All the same, if treatment with corticosteroids is effective, then failure to administer them may have severe consequences. Proper diagnosis and management requires access to drug susceptibility testing, neuroimaging and analysis of cerebrospinal fluid.

In one prospective study on IRIS associated with tuberculosis from South Africa, it was found that 19% of individuals with tuberculous-IRIS had neurological involvement with 91% ($n = 21$) of them treated with corticosteroids for a mean duration of 2 months. At 6 months from initial presentation, 70% ($n = 16$) were alive and 10 of these patients had full recovery [20].

A review [5] of 54 cohort studies from 22 countries of 13 103 patients starting ART identified 1699 with IRIS. Meta-analysis showed that in patients with previously diagnosed AIDS-defining illnesses, IRIS developed in 19.5% (6.7–44.8) of those with cryptococcal meningitis, 15.7% (9.7–24.5) of those with tuberculosis, 16.7% (2.3–50.7) of those with progressive multifocal leukoencephalopathy and 12.2% (6.8–19.6) of those with herpes zoster [5].

Table 1 [4,5] proposes an estimated global burden of CNS-IRIS in the setting of cryptococcal meningitis. This estimate is based on published data on the global burden on cryptococcal meningitis in AIDS by world region [4] multiplied by the incidence of CNS-IRIS in HIV-associated cryptococcal meningitis (19.5%) among all people with cryptococcal meningitis started on ART [5]. All people with HIV and cryptococcal meningitis globally were assumed to have received ART. Further assumptions included steady-state underlying regional population structures, relatively stable regional populations of cryptococcal meningitis-afflicted AIDS patients and constant and comparable incidence rates of CNS-IRIS in these populations over time. Notably, these estimates do not include the complete burden of CNS-IRIS, as other opportunistic infections, notably including tuberculosis of the CNS, have not been estimated and incorporated into the global estimation.

The value of delaying ART until antimicrobial treatment has been initiated must be carefully weighed against the increased risk of death when ART is delayed. The WHO released *Rapid Advice* on the diagnosis, prevention and management in HIV-associated cryptococcal disease in December 2011. A conditional recommendation, based on a ‘low quality of evidence,’ is ‘immediate ART is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening’ [21]. Therefore, the optimal timing to initiate ART to promote international guidelines related to CNS-IRIS, is problematic. CNS-IRIS may occur up to 1 year after initiation of ART. It is unclear whether delay in ART initiation for 2 or 4 weeks or 6 or more weeks would substantially reduce the number of CNS-IRIS cases in resource-limited settings without more data from these settings (Table 2) [7–9,19,22–28]. As the severity of IRIS is associated with a rapid decline in viral load, the possibility of gradual introduction of combination ART may need to be investigated in severely immunosuppressed individuals. The benefit of such an approach would need to be weighed against the possibility of development of drug resistance.

There are major, persistent gaps in the current knowledge in CNS-IRIS. Depiction of the relative burden of opportunistic infections related to CNS-IRIS in multiple settings would help direct guidelines for management at a regional level. The establishment of a biomarker for CNS-IRIS, ideally from the serum rather than the cerebrospinal fluid, would be among the best possible advances. Better neuroimaging availability would also help diagnose this disorder in settings in which incidence is likely high.

Improved treatment modalities apart from corticosteroids also need to be developed for IRIS. CNS-IRIS demonstrates point-of-care HIV testing does not remove the healthcare worker from the treatment of HIV/AIDS. Initiating ART earlier in the course of the illness before CD4 cell counts fall would likely decrease the global incidence of all forms of IRIS.

The current burden of CNS-IRIS is likely high globally and may reach more than 185 000 cases per year. This may be a conservative estimation given that the number of people treated with ART will likely increase and diagnostic testing for opportunistic infections is improving. The optimal timing of ART initiation is a source of important policy recommendations, but is based on limited evidence. Establishment of a broader knowledge on CNS-IRIS would more clearly inform future policy recommendations and save lives of people who finally have the chance to access ART.

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Table 1

Global estimation of cryptococcal meningitis–immune reconstitution inflammatory syndrome by world region per year.

Region	Annual number of cases of cryptococcal meningitis (2007) (Park <i>et al.</i> [4])	Predicted annual number of cases of cryptococcal CNS-IRIS (2007) ^a
Sub-Saharan Africa	720 000	140 400
South and south-east Asia	120 000	23 400
Latin America	54 400	10 608
Eastern Europe and Central Asia	27 200	5304
East Asia	13 600	2652
North America	7800	1521
Caribbean	7800	1521
North Africa and Middle East	6500	1268
Western and central Europe	500	98
Oceania	1000	20
Global	957 900	186 791

ART, antiretroviral treatment; CNS-IRIS, central nervous system–immune reconstitution inflammatory syndrome.

^aEstimated number of cases of CNS-IRIS established by assuming a 19.5% incidence of CNS-IRIS among ART-initiators with cryptococcal meningitis [5].

Clinical studies (*n* 7 cases) with detailed descriptions of central nervous system–immune reconstitution inflammatory syndrome in the setting of HIV, 2005–2011.

Table 2

References	Study location	Related opportunistic infections	Study design (prospective/retrospective)	Number of people of people observed, <i>n</i>	Number of people diagnosed with CNS-IRIS, <i>n</i>	Number of CNS-IRIS deaths, <i>n</i>	Median initial CD4 cell count, cells/ μ l	Median time to ART initiation	Median time to CNS-IRIS diagnosis	Shortest Time to CNS-IRIS	Longest Time to CNS-IRIS
Low-income and middle-income countries											
da Cunha Colombo <i>et al.</i> [22]	Brazil	Cryptococcus	Prospective	40	7	0	44	2–3 weeks	72 days	27 days	120 days
Asselman <i>et al.</i> [23]	South Africa	TB, Cryptococcus	Prospective	75	21	NP ^a	64	56 days (TB)	16 days (TB); 58 days (crypto)	11 days (25th percentile)	88 days (75th percentile)
Boulware <i>et al.</i> [24]	Uganda	Cryptococcus	Prospective	101	45	16	26	36 days	8.8 weeks	NP	NP
Boulware <i>et al.</i> [25]	Uganda	Cryptococcus	Prospective	85	33	NP	30 ^b	5 weeks	8 weeks	4 weeks (25th percentile)	17 weeks (75th percentile)
Sungkanuparph <i>et al.</i> [8]	Thailand	Cryptococcus	Prospective	101	13	1	NP	NP	NP	NP	NP
Bicanic <i>et al.</i> [9]	South Africa	Cryptococcus	Prospective	65	11	4	28	47 days	29 days	19 days	63 days
Sungkanuparph <i>et al.</i> [26]	Thailand	Cryptococcus	Retrospective	52	10	0	26	2.6 months	NP	3 months	27.3 months
Bicanic <i>et al.</i> [27]	South Africa	Cryptococcus	Prospective	NP	27	9	27	146 days	<2 months ^c	NP	NP
Shelburne <i>et al.</i> [28]	USA	Cryptococcus	Retrospective	84	17	NP ^d	72	NP	59 days	NP	NP
High-income countries											
Tan <i>et al.</i> [19]	Literature review, USA	PML	Retrospective	54	36	19	53	NP	7 weeks	1 weeks	26 months
McCombe <i>et al.</i> [7]	Canada	TB, Cryptococcus, Toxoplasma	Retrospective	461 (total beginning ART)	7	1	30	NP	9 weeks	2 weeks	25 weeks

ART, antiretroviral treatment; CNS-IRIS, central nervous system–immune reconstitution inflammatory syndrome; Crypto, *Cryptococcus neoformans* meningitis; NP, not provided; PML, progressive multifocal leukoencephalopathy; TB, tuberculosis.

^aSeventeen deaths, including non-IRIS-related deaths.

^bMean CD4 cell count, not median.

Twenty-seven days for culture-negative cerebrospinal fluid and 55 days for culture-positive cerebrospinal fluid.
Mortality rate was 9% among IRIS patients still followed at 18 months.

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