Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis

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In patients with HIV-1 infection who are starting combination antiretroviral therapy (ART), the incidence of immune reconstitution inflammatory syndrome (IRIS) is not well defined. We did a meta-analysis to establish the incidence and lethality of the syndrome in patients with a range of previously diagnosed opportunistic infections, and examined the relation between occurrence and the degree of immunodeficiency. Systematic review identified 54 cohort studies of 13 103 patients starting ART, of whom 1699 developed IRIS. We calculated pooled cumulative incidences with 95% credibility intervals (CrI) by Bayesian methods and did a random-effects metaregression to analyse the relation between CD4 cell count and incidence of IRIS. In patients with previously diagnosed AIDS-defining illnesses, IRIS developed in 37·7% (95% CrI 26·6–49·4) of those with cytomegalovirus retinitis, 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 6·4% (1·2–24·7) of those with Kaposi's sarcoma, and 12·2% (6·8–19·6) of those with herpes zoster. 16·1% (11·1–22·9) of unselected patients starting ART developed any type of IRIS. 4·5% (2·1–8·6) of patients with any type of IRIS died, 3·2% (0·7–9·2) of those with tuberculosis-associated IRIS died, and 20·8% (5·0–52·7) of those with cryptococcal meningitis died. Metaregression analyses showed that the risk of IRIS is associated with CD4 cell count at the start of ART, with a high risk in patients with fewer than 50 cells per µL. Occurrence of IRIS might therefore be reduced by initiation of ART before immunodeficiency becomes advanced.

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Introduction

Combination antiretroviral therapy (ART) substantially reduces the occurrence of opportunistic events and mortality in patients with HIV.[1] The beneficial effects of ART result from gradual restoration of pathogen-specific immune responses, mediated by suppressed HIV-1 replication and increased CD4 cell count.[2,3] WHO estimates that by the end of 2008 about 4 million people were receiving ART in countries of low and middle income—ten-times more than at the end of 2003.[4] However, many patients in resource-poor settings start ART at a late stage when they already have advanced immunodeficiency.[5,6]

Complications related to ART-induced immune reconstitution include paradoxical worsening of treated opportunistic infections or the unmasking of previously subclinical, untreated infections—so-called immune reconstitution inflammatory syndrome (IRIS), also known as immune reconstitution disease.[7–10] The panel summarises common definitions for IRIS. The syndrome is usually a consequence of exaggerated activation of the immune system against persistent antigen (paradoxical IRIS) or viable pathogens (unmasking IRIS), but it can also develop as progression of proliferative disease in patients with cancers.[14] IRIS has been associated with a wide range of pathologies, including mycobacterial and cryptococcal infections, Kaposi's sarcoma, non-Hodgkin lymphoma, and progressive multifocal leukoencephalopathy.[8–10,15–17] Non-AIDS-defining illnesses such as sarcoidosis[18] and rheumatic diseases[19] can also transiently deteriorate after starting of ART.

The proportion of patients starting ART who develop IRIS is not well known, with estimates ranging from less than 10% to more than 50%.[20–24] Several studies,[10,17,25–27] but not all,[21,28,29] have reported an increased risk of the syndrome in patients starting ART who have advanced immunodeficiency. We did a systematic review and meta-analysis of cohort studies to better define the incidence and lethality of IRIS in patients starting ART in countries of low, middle, and high income.

Methods

Search strategy and selection criteria

We searched Medline and Embase from January, 1996, to October, 2009, for published reports with the terms "immune reconstitution syndrome", "immune reconstitution disease", "immune restitution syndrome", "immune restitution disease", "immune reconstitution inflammatory syndrome", and "immune recovery uveitis". No language restrictions were used. Articles, brief reports, and letters to editors were included. Reference lists of relevant papers were screened. We also searched abstracts from conferences of the International AIDS Society (International AIDS Conference, and Conference on HIV Pathogenesis, Treatment and Prevention) and the Conference on Retroviruses and Opportunistic Infections from 2000 to 2009. We included longitudinal studies of patients starting ART. Studies were eligible for inclusion in our analysis if the cohort contained at least ten adults starting ART, and they systematically reported IRIS events or mortality.

Data extraction and outcome measures

Two reviewers (MM and SA) used a standardised form to extract data in duplicate for eligibility criteria,

Panel: **Definitions of immune reconstitution inflammatory syndrome**

French et al (2004):[10] any cases
- Diagnosis requires both major criteria or one major criterion plus two minor criteria

Major criteria
- Atypical presentation of opportunistic infections or tumours in patients responding to ART: exaggerated and atypical inflammatory reaction; progressive organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy before starting of ART; or exclusion of alternative causes (toxic effects of drug treatment, newly acquired infection or tumour, or treatment failure)
- Decrease in plasma HIV RNA concentration by >1 log copies per mL

Minor criteria
- Increase in blood CD4 cell count after ART
- Increase in an immune response specific to the relevant pathogen—eg, delayed type hypersensitivity response to mycobacterial antigens
- Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of ART

Shelburne et al (2002):[9] any cases

Criteria for diagnosis
- HIV-infected patient
- Receipt of effective ART as shown by a decrease in HIV RNA concentration from baseline or an increase in CD4 cell count from baseline
- Clinical symptoms consistent with inflammatory process
- Clinical course not consistent with expected course of previously or newly diagnosed opportunistic infection, or with toxic effects of drug treatment

Additional criteria for cryptococcal meningitis
- Decrease in CSF antigen concentration
- Negative CSF fungal cultures
- Inflammatory reaction in CSF (increased white blood cell count)

Meintjes et al (2008):[27] tuberculosis-associated cases in resource-poor settings

Antecedents
- Tuberculosis diagnosis according to WHO guidelines before starting of ART
- Tuberculosis should have stabilised or improved before starting of ART

Clinical criteria
- New enlarging lymph nodes, cold abscesses, or other focal tissue involvement
- New or worsening radiological features of tuberculosis
- New or worsening CNS tuberculosis
- New or worsening serositis

Exclusion of alternative causes
- Failure of tuberculosis treatment (non-compliance or resistance)
- Other opportunistic infection or neoplasm
- Reaction to toxic effects of drug treatment

Wendel et al (2001):[28] paradoxical worsening of tuberculosis
- Documented worsening of signs or symptoms of tuberculosis (fever, cough, or adenopathy) or exacerbation of disease at other extrapulmonary sites during appropriate treatment
- Worsening of pulmonary infiltrates on chest radiograph or CT without other aetiology

Karavellas et al (2001):[29] immune reconstitution uveitis
- Patients with symptomatic onset of vitreous inflammation in the setting of inactive cytomegalovirus retinitis—ie, vitritis of 1 or greater severity; clinically significant floaters or decrease in vision of one or more lines, or both
- With or without papillitis or macula changes

ART=antiretroviral therapy. CSF=cerebrospinal fluid.

characteristics of the studies and patients, IRIS events (type, number of patients affected, number of deaths), and length of follow-up. Disagreements were resolved by discussion with a third reviewer (ME). We used the 2008 World Bank country classification to separate study settings into countries of high income, high-middle income, low-middle income, and low income.[30]

The primary outcome measures were the proportion of patients starting ART who developed IRIS, and of those who developed IRIS, the proportion of patients who died. We separated the studies by the previously diagnosed opportunistic infections. We also analysed the relation of cumulative incidence with baseline CD4 cell count, study setting, and type of publication (full article, letter, abstract).

Statistical analysis

To address substantial heterogeneity between the results of individual studies, we used a fully probabilistic (Bayesian) approach for meta-analysis, which provides a flexible framework for hierarchical modelling with random effects at the study level.[31,32] For every study in the meta-analysis, the number of events was assumed to follow a binominal distribution with unknown underlying risk p. We modelled the baseline log odds of an event—ie, logit (p)—as a normal random variable drawn from a common normal distribution, with the mean equal to the baseline log odds in the population of possible studies, and variance representing the variability across studies. Analyses were based on non-informative prior distributions (mean 0, variance 1000), and a uniform distribution of range 0–2 for the SD of the random effects.[32] Results are based on 30 000 iterations after a burn-in period of 50 000 iterations. Between-trial heterogeneity was assessed with an approximate I^2 for Bayesian meta-analysis. Further details on the Bayesian model, the choice of prior distributions, and the implementation in WinBugs are provided in webappendix p 1–6.

We used random-effects metaregression with inverse variance weights to examine the relation between median CD4 cell count and incidence of IRIS, and to investigate the importance of the study setting and the type of publication. In some instances we converted median age to mean age with the method proposed by Hozo and colleagues.[33] Analyses were done with WinBUGS (version 1.4.3) and Stata (version 10.0). Data are presented as the proportion of patients developing IRIS with 95% credibility intervals (CrIs) for combined estimates from the meta-analysis and 95% CIs for study-specific estimates, and for metaregression models as coefficients that can be interpreted as risk ratios.

Results

The search identified 856 reports and 118 abstracts, of which 54 cohort studies from 22 countries were eligible for analysis: 22 (41%) were full-text reports, 21 (39%) were

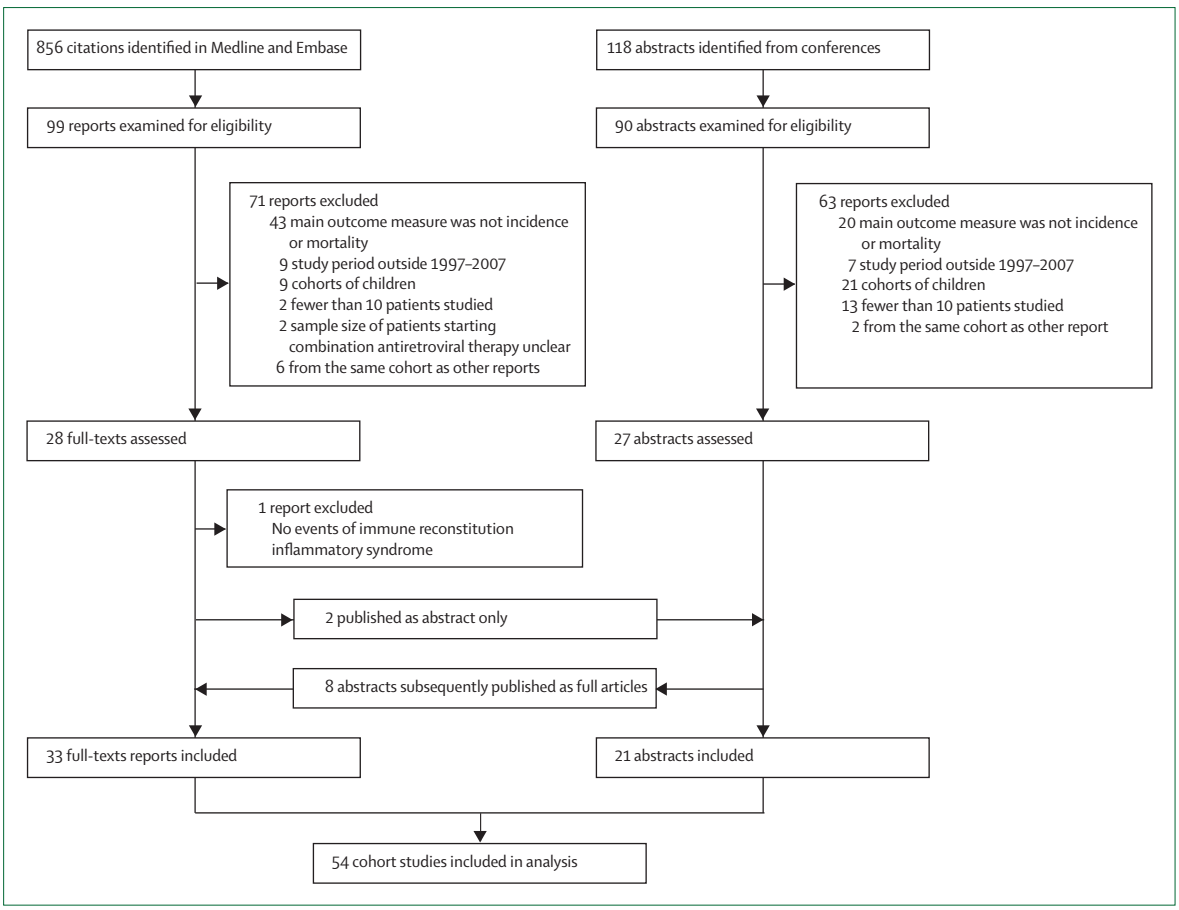

Figure 1: **Selection of eligible cohort studies of patients starting combination antiretroviral therapy for HIV infection**

abstracts, and 11 (20%) were letters to the editor (figure 1, table 1). 17 cohorts (31%) were in unselected groups of people that included patients with and without AIDS, and studied any type of IRIS (table 1). The remaining studies were in patients with previously diagnosed opportunistic infections and examined paradoxical worsening of these after starting ART: tuberculosis (16 studies, 30%), cryptococcal meningitis (six studies, 11%), cytomegalovirus retinitis (ten studies, 19%), herpes zoster (one study, 2%), Kaposi's sarcoma (two studies, 4%), and progressive multifocal leukoencephalopathy (two studies, 4%). 20 studies (37%) used one of the definitions listed in the panel, 14 (26%) used another definition, and in 20 studies (37%) the definition was unclear (table 1).

Overall 13 103 patients were included in our analysis; the number of patients included in the studies ranged from ten to 2330 (median 75 patients, IQR 30–200) per study. Length of follow-up reported by 17 studies (31%) was from 5 to 37 months (median 12 months, IQR 6–21). 20 studies (37%) were from countries of high income (Australia, France, Ireland, Japan, South Korea, Spain, UK, Germany, Taiwan, and USA), 17 (31%) were from countries of high-middle income (Argentina, Brazil, Mexico, Poland, Serbia, South Africa, and Venezuela), 14 (26%) were from countries of low-middle income (India and Thailand), and three (6%) were from countries of low income (Cambodia, Mozambique, and Senegal; table 1). 19 cohorts (35%) were from the Asia-Pacific region, 13 (24%) from Europe, nine (17%) from North America, four (7%) from South America, and nine (17%) from Africa (table 1). Mean age was available for 21 studies (39%); patients' ages ranged from 34 to 41 years (median 36·3 years, IQR 35·0–38·0). CD4 cell count at the start of ART ranged from 17 to 174 cells per μL (median 57 cells per μL, IQR 33–106), as reported by 22 studies (41%).

See Online for webappendix

1699 patients (13%) developed IRIS (table 1). Meta-analysis showed that the lowest to highest incidence of IRIS by previously diagnosed opportunistic illness was in patients with Kaposi's sarcoma (6·4% based on two studies), herpes zoster (12·2%, one study), tuberculosis (15·7%, 16 studies), progressive multifocal leuko-encephalopathy (16·7%, two studies), cryptococcal meningitis (19·5%, six studies), and cytomegalovirus retinitis (37·7%, ten studies; figure 2). From 17 studies of unselected patients starting ART, 16·1% of patients had any type of IRIS. Between-study heterogeneity was moderate to high.

Metaregression analysis of 21 studies for the relation of median CD4 cell count at the start of ART with the incidence of IRIS showed an exponential increase in occurrence as the CD4 cell count declined, which seemed to be independent of previously diagnosed opportunistic illness (figure 3). In univariable analysis the coefficient associated with log median CD4-cell count was –0·61 (95% CI –1·18 to –0·04, p=0·04). The coefficient changed little when adjusting for opportunistic illnesses: –0·80 (95% CI –1·74 to 0·13, p=0·09). Webappendix p 7 gives details.

In analyses stratified by median CD4 cell count at the start of ART, IRIS developed in 20·7% (95% CrI 9·0–45·7) of patients with tuberculosis in studies with a

	Definition of IRIS*	Type of publication	Country	Study period	Mean age (years)	Median CD4 cell count (cells per μL)	Number of patients	Patients with AIDS at enrolment	Patients developing IRIS	Deaths from IRIS
Tuberculosis (pulmonary and extrapulmonary)										
Narita et al (1998)[22]	Wendel et al[12]	Full-text report	USA	1996–97	..	..	33	33 (100%)	12 (36%)	..
Wendel et al (2001)[12]	Wendel et al[12]	Full-text report	USA	1996–2000	..	..	24	24 (100%)	3 (13%)	..
Navas et al (2002)[34]	Other	Letter	Spain	1995–98	36·3 (..)	35 (18–215)	17	17 (100%)	6 (35%)	0
Breton et al (2004)[28]	Shelburne et al[9]	Letter	France	1996–2001	35·0 (..)	100 (..)	37	37 (100%)	16 (43%)	..
Kumarasamy et al (2004)[21]	Other	Letter	India	2000–03	34·0 (..)	122 (..)	144	144 (100%)	11 (8%)	..
Michailidis et al (2005)[35]	Other	Full-text report	UK	2001–03	37·4 (..)	..	55	55 (100%)	14 (25%)	..
Bourgarit et al (2006)[27]	French et al[10]	Full-text report	France	..	39·1 (10)	32 (15–131)	19	19 (100%)	7 (37%)	..
Chew et al (2006)[36]	..	Abstract	Ireland	2004–06	..	82 (..)	16	16 (100%)	4 (25%)	0
Manosuthi et al (2006)[37]	French et al[10]	Full-text report	Thailand	2003–04	34·5 (..)	36 (15–69)	167	167 (100%)	21 (13%)	2 (1%)
Elliott et al (2007)[38]	..	Abstract	Cambodia	..	..	..	27	27 (100%)	6 (22%)	1 (4%)
Lawn et al (2007)[39]	Other	Full-text report	South Africa	2002–05	..	68 (29–133)	160	160 (100%)	19 (12%)	2 (1%)
Park et al (2007)[40]	Shelburne et al[9]	Letter	South Korea	1998–2005	38·0 (..)	..	482	..	9 (2%)	..
Serra et al (2007)[41]	Wendel et al[12]	Full-text report	Brazil	2000–03	..	..	84	84 (100%)	10 (12%)	0
Eshun-Wilson et al (2009)[42]	Meintjes et al[11]	Abstract	South Africa	2003–08	..	..	337	337 (100%)	56 (17%)	6 (2%)
Kumarasamy et al (2009)[43]	French et al[10]	Abstract	India	1996–2008	..	..	1731	1731 (100%)	95 (5%)	0
Manosuthi et al (2009)[44]	Meintjes et al[11]	Abstract	Thailand	2006–07	35 (..)	43 (..)	126	126 (100%)	21 (17%)	0
Cryptococcal meningitis										
Jenny-Avital et al (2002)[45]	..	Full-text report	USA	1998–2001	..	..	10	10 (100%)	5 (50%)	..
Lawn et al (2005)[23]	..	Letter	South Africa	2002–05	34·0 (..)	86 (46–146)	434	412 (95%)	9 (2%)	6 (1%)
Shelburne et al (2005)[15]	Shelburne et al[9]	Letter	USA	..	..	..	59	..	18 (31%)	1 (2%)
Jenkin and Karstaedt (2006)[46]	Shelburne et al[9]	Abstract	South Africa	2004–05	..	32·5 (..)	59	59 (100%)	23 (39%)	9 (15%)
Sungkanuparph et al (2007)[47]	French et al[10]	Letter	Thailand	..	34·4 (6·9)	26 (..)	52	52 (100%)	10 (19%)	0
Bicanic et al (2009)[48]	Other	Full-text report	South Africa	2005–06	..	..	65	65 (100%)	11 (17%)	3 (5%)
Immune recovery uveitis										
Nguyen et al (2000)[49]	Other	Full-text report	USA	1995–98	..	..	33	33 (100%)	6 (18%)	..
Karavellas et al (2001)[13]	Karavellas et al[13]	Full-text report	USA	1996–98	..	..	30	30 (100%)	19 (63%)	..
Banker and Patel (2002)[50]	Karavellas et al[13]	Full-text report	India	1998–2000	37·3 (11)	36·5 (22–63)	12	12 (100%)	5 (42%)	..
Arevalo et al (2003)[51]	Karavellas et al[13]	Full-text report	Venezuela	1998–2000	..	..	32	32 (100%)	12 (38%)	..
Colombero et al (2004)[52]	French et al[10]	Abstract	Argentina	..	..	32 (..)	30	30 (100%)	9 (30%)	..
Ortega-Larrocea et al (2005)[24]	Other	Letter	Mexico	1996–2003	..	19·7 (..)	43	43 (100%)	23 (53%)	..
Sarkar et al (2006)[53]	..	Abstract	India	2002–04	..	..	20	20 (100%)	8 (40%)	..
Uemura et al (2006)[54]	..	Abstract	Japan	2002–03	..	..	10	10 (100%)	3 (30%)	..
Dujic and Jevtovic (2007)[55]	Karavellas et al[13]	Abstract	Serbia	..	..	..	21	21 (100%)	9 (43%)	..
Lin et al (2008)[56]	Karavellas et al[13]	Full-text report	Taiwan	1995–2006	40·3 (..)	16·6 (..)	41	41 (100%)	10 (24%)	..
Herpes zoster										
Dunic et al (2005)[57]	..	Full-text report	Serbia	2000–01	38·1 (..)	..	115	115 (100%)	14 (12%)	..
Kaposi's sarcoma										
Bower et al (2005)[20]	..	Full-text report	UK	1996–2004	37·9 (..)	..	150	150 (100%)	10 (7%)	..
De Schacht et al (2005)[58]	..	Abstract	Mozambique	2004	..	..	29	29 (100%)	2 (7%)	0
Progressive multifocal leukoencephalopathy										
Vidal et al (2008)[59]	Other	Full-text report	Brazil	2003–04	37·3 (..)	45 (..)	12	12 (100%)	1 (8%)	0
Corral et al (2009)[60]	Other	Abstract	Spain	1996–2008	..	..	53	53 (100%)	12 (23%)	..

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	Definition of IRIS*	Type of publication	Country	Study period	Mean age (years)	Median CD4 cell count (cells per µL)	Number of patients	Patients with AIDS at enrolment	Patients developing IRIS	Deaths from IRIS
(Continued from previous page)										
Any IRIS										
French et al (2000)[25]	..	Full-text report	Australia	1996–97	..	..	132	..	33 (25%)	..
Wnuk et al (2003)[61]	..	Abstract	Poland	..	..	..	90	..	15 (17%)	..
Thomas (2004)[62]	..	Abstract	India	..	..	..	23	10 (43%)	6 (26%)	..
Jevtovic et al (2005)[26]	..	Full-text report	Serbia	1998–2004	41·0 (10)	108 (..)	389	340 (87%)	65 (17%)	1 (<1%)
Shelburne et al (2005)[63]	Shelburne et al[9]	Full-text report	USA	1997–2003	38·8 (..)	..	180	175 (97%)	57 (32%)	2 (1%)
Bhrushundi and Mishra (2006)[64]	..	Abstract	India	..	..	..	720	..	68 (9%)	2 (<1%)
Chenghat et al (2006)[65]	..	Abstract	India	2004–06	..	..	1342	..	42 (3%)	..
Ratnam (2006)[66]	Other	Full-text report	UK	2000–02	35·0 (..)	174 (82–285)	199	..	44 (22%)	..
Rajasekaran et al (2006)[67]	..	Letter	India	2004–05	..	..	2330	..	302 (13%)	..
Wijeyasangary et al (2006)[68]	..	Abstract	India	..	..	..	200	..	7 (4%)	2 (1%)
Pulimood et al (2007)[29]	Other	Abstract	India	2004–06	..	110·5 (55–192)	212	..	24 (11%)	..
Murdoch et al (2008)[69]	Other	Full-text report	South Africa	2006	34 (..)	115 (51–173)	423	..	43 (10%)	2 (<1%)
Sharma et al (2008)[70]	Other	Letter	India	2004–06	..	..	90	..	20 (22%)	..
Haddow et al (2009)[71]	Other	Abstract	South Africa	2006–07	35 (..)	106 (..)	498	343 (69%)	116 (23%)	5 (1%)
Hoyo-Ulloa et al (2009)[72]	..	Abstract	Mexico	2001–07	35 (..)	87 (..)	390	..	107 (27%)	8 (2%)
Khaykin et al (2009)[73]	..	Abstract	Germany	2001–07	..	..	1014	442 (44%)	181 (18%)	..
Poda et al (2009)[74]	..	Letter	Senegal	2003–06	..	..	102	..	40 (39%)	..

Data are mean (SD), median (IQR), or number (%), unless otherwise indicated. ..=data not reported. *See panel for definitions.

***Table 1*: Characteristics of studies of immune reconstitution inflammatory syndrome (IRIS) in patients starting antiretroviral therapy for HIV infection, by type of study population**

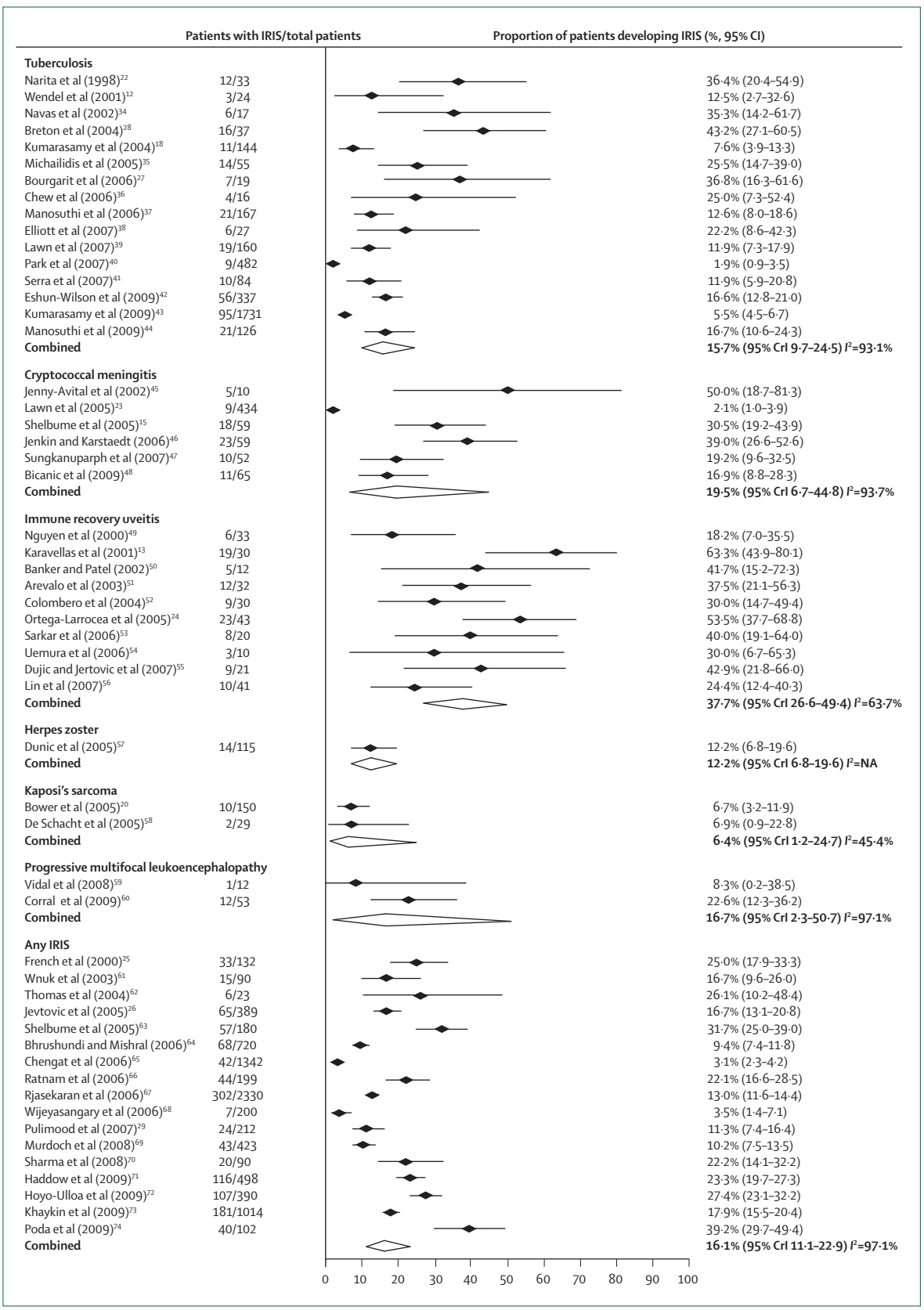
median CD4 cell count of fewer than 50 cells per µL (four studies), and in 17·7% (5·4–54·2) of patients in studies with more 50 cells per µL (four studies). IRIS was recorded in 28·3% (6·1–68·2) of patients with cryptococcal meningitis in studies with fewer than 50 cells per µL (two studies) and 2·0% (0·2–15·5) of those in one study with more than 50 cells per µL. In patients with cytomegalovirus retinitis, IRIS developed in 37·7% (16·8–61·7%) of those in studies with fewer than 50 cells per µL (four studies); no studies had more than 50 cells per µL. For patients with any type of IRIS, CD4 cell count was reported in six studies; all studies had median CD4 cell counts of more than 50 cells per µL, and 17·7% (10·5–27·7) of patients developed IRIS.

In a model to establish the relation of IRIS with previously diagnosed opportunistic infection and study setting, we recorded decreasing risk of IRIS with lower income of countries. Overall, the risk ratio per change in country classification from higher to lower income was 0·76 (95% CI 0·59–0·97; p=0·03). Table 2 shows the incidence of IRIS stratified by type of opportunistic illness and countries' income. IRIS was most common in patients with tuberculosis from high-income and low-income countries. For cryptococcal meningitis, the proportion of patients with IRIS was greater in high-income than in low-income countries. In patients with immune recovery uveitis, the proportion with IRIS was about the same irrespective of countries' income. For herpes zoster, Kaposi's sarcoma, and progressive multifocal leukoencephalopathy, no more than one study was available for every country classification and the association could not be assessed. In the same model, publication type did not seem to be associated with occurrence of IRIS (p=0·40).

Data for deaths in patients developing IRIS were available from 23 cohorts (table 1). 52 deaths were explicitly attributed to the syndrome. 4·5% (95% CrI 2·1–8·6) of patients with any type of IRIS died, 3·2% (0·7–9·2) of those with tuberculosis died, and 20·8% (5·0–52·7) of those with cryptococcal meningitis died. 11 cohorts reported the number of deaths in total and those attributable to IRIS: 33 (21%) of 158 deaths were attributable to IRIS, including three studies with zero deaths from IRIS. Restriction of the analysis to the four studies in any type of IRIS, showed that 17 (22%) of 78 deaths were attributable to IRIS.

Discussion

The incidence of IRIS among people starting ART varies with the AIDS-defining illness. The proportion of patients developing IRIS was highest in those with cytomegalovirus retinitis, high in those with cryptococcal meningitis, progressive multifocal leukoencephalopathy, or tuberculosis, and least common in those with Kaposi's sarcoma or herpes zoster. Differences in the incidence of IRIS between these opportunistic infections seem to be related to CD4 cell counts at baseline. In unselected patients with and without a history of AIDS, about a sixth of patients developed IRIS, but the results from these studies were highly heterogeneous. Overall, about


Patients with IRIS/total patients
Proportion of patients developing IRIS (%, 95% CI)
Tuberculosis
Narita et al (1998)[22] 12/33 36·4% (20·4–54·9)
Wendel et al (2001)[12] 3/24 12·5% (2·7–32·6)
Navas et al (2002)[34] 6/17 35·3% (14·2–61·7)
Breton et al (2004)[28] 16/37 43·2% (27·1–60·5)
Kumarasamy et al (2004)[18] 11/144 7·6% (3·9–13·3)
Michailidis et al (2005)[35] 14/55 25·5% (14·7–39·0)
Bourgarit et al (2006)[27] 7/19 36·8% (16·3–61·6)
Chew et al (2006)[36] 4/16 25·0% (7·3–52·4)
Manosuthi et al (2006)[37] 21/167 12·6% (8·0–18·6)
Elliott et al (2007)[38] 6/27 22·2% (8·6–42·3)
Lawn et al (2007)[39] 19/160 11·9% (7·3–17·9)
Park et al (2007)[40] 9/482 1·9% (0·9–3·5)
Serra et al (2007)[41] 10/84 11·9% (5·9–20·8)
Eshun-Wilson et al (2009)[42] 56/337 16·6% (12·8–21·0)
Kumarasamy et al (2009)[43] 95/1731 5·5% (4·5–6·7)
Manosuthi et al (2009)[44] 21/126 16·7% (10·6–24·3)
Combined 15·7% (95% CrI 9·7–24·5) I²=93·1%
Cryptococcal meningitis
Jenny-Avital et al (2002)[45] 5/10 50·0% (18·7–81·3)
Lawn et al (2005)[23] 9/434 2·1% (1·0–3·9)
Shelbume et al (2005)[15] 18/59 30·5% (19·2–43·9)
Jenkin and Karstaedt (2006)[46] 23/59 39·0% (26·6–52·6)
Sungkanuparph et al (2007)[47] 10/52 19·2% (9·6–32·5)
Bicanic et al (2009)[48] 11/65 16·9% (8·8–28·3)
Combined 19·5% (95% CrI 6·7–44·8) I²=93·7%
Immune recovery uveitis
Nguyen et al (2000)[49] 6/33 18·2% (7·0–35·5)
Karavellas et al (2001)[13] 19/30 63·3% (43·9–80·1)
Banker and Patel (2002)[50] 5/12 41·7% (15·2–72·3)
Arevalo et al (2003)[51] 12/32 37·5% (21·1–56·3)
Colombero et al (2004)[52] 9/30 30·0% (14·7–49·4)
Ortega-Larrocea et al (2005)[24] 23/43 53·5% (37·7–68·8)
Sarkar et al (2006)[53] 8/20 40·0% (19·1–64·0)
Uemura et al (2006)[54] 3/10 30·0% (6·7–65·3)
Dujic and Jertovic et al (2007)[55] 9/21 42·9% (21·8–66·0)
Lin et al (2007)[56] 10/41 24·4% (12·4–40·3)
Combined 37·7% (95% CrI 26·6–49·4) I²=63·7%
Herpes zoster
Dunic et al (2005)[57] 14/115 12·2% (6·8–19·6)
Combined 12·2% (95% CrI 6·8–19·6) I²=NA
Kaposi's sarcoma
Bower et al (2005)[20] 10/150 6·7% (3·2–11·9)
De Schacht et al (2005)[58] 2/29 6·9% (0·9–22·8)
Combined 6·4% (95% CrI 1·2–24·7) I²=45·4%
Progressive multifocal leukoencephalopathy
Vidal et al (2008)[59] 1/12 8·3% (0·2–38·5)
Corral et al (2009)[60] 12/53 22·6% (12·3–36·2)
Combined 16·7% (95% CrI 2·3–50·7) I²=97·1%
Any IRIS
French et al (2000)[25] 33/132 25·0% (17·9–33·3)
Wnuk et al (2003)[61] 15/90 16·7% (9·6–26·0)
Thomas et al (2004)[62] 6/23 26·1% (10·2–48·4)
Jevtovic et al (2005)[26] 65/389 16·7% (13·1–20·8)
Shelbume et al (2005)[63] 57/180 31·7% (25·0–39·0)
Bhrushundi and Mishral (2006)[64] 68/720 9·4% (7·4–11·8)
Chengat et al (2006)[65] 42/1342 3·1% (2·3–4·2)
Ratnam et al (2006)[66] 44/199 22·1% (16·6–28·5)
Rjasekaran et al (2006)[67] 302/2330 13·0% (11·6–14·4)
Wijeyasangary et al (2006)[68] 7/200 3·5% (1·4–7·1)
Pulimood et al (2007)[29] 24/212 11·3% (7·4–16·4)
Murdoch et al (2008)[69] 43/423 10·2% (7·5–13·5)
Sharma et al (2008)[70] 20/90 22·2% (14·1–32·2)
Haddow et al (2009)[71] 116/498 23·3% (19·7–27·3)
Hoyo-Ulloa et al (2009)[72] 107/390 27·4% (23·1–32·2)
Khaykin et al (2009)[73] 181/1014 17·9% (15·5–20·4)
Poda et al (2009)[74] 40/102 39·2% (29·7–49·4)
Combined 16·1% (95% CrI 11·1–22·9) I²=97·1%
0 10 20 30 40 50 60 70 80 90 100

4% of patients with IRIS died, but the proportion was much higher if the syndrome was associated with cryptococcal meningitis.

Our study was based on a comprehensive search of published reports, abstracts, and data that had been presented at conferences but were not published, thus reducing possible publication bias. We identified 54 cohort studies in more than 13 000 patients from 22 countries of high, middle, and low income. The studies included those patients with diagnosed opportunistic infections or cancers that specifically focused on paradoxical reactions to ART, and those in unselected groups of patients that assessed any type of IRIS, including the unmasking of subclinical infections.[11] Our meta-analysis provides the best available data for the incidence of IRIS in patients starting ART, but we acknowledge that the study design is prone to biases inherent in the original observational studies.[75] Our review was exclusively based on aggregated data, and important information, such as baseline CD4 cell count or duration of follow-up, was missing in many studies, especially those available as conference abstracts only. Consequently, in-depth assessments of study quality were not possible.

Substantial heterogeneity was recorded between results from different studies, particularly between studies of unselected groups of patients, but also between some studies in patients with AIDS-defining illnesses. Several factors could have contributed to such heterogeneity. First, diagnostic criteria for IRIS have not been standardised, although criteria for diagnosis in patients with tuberculosis have now been developed by the International Network for the Study of HIV-associated IRIS.[11] Differentiation between an opportunistic infection with normal presentation and a disorder with a presentation compatible with unmasking IRIS is particularly difficult.[76] In paradoxical IRIS, clinicians need to exclude alternative explanations for deterioration, such as the failure to treat opportunistic infection or the failure of ART because of poor adherence or drug resistance. Therefore, differences in the diagnostic criteria between the studies might well have introduced heterogeneity. The difference between intended ART-associated immune reconstitution and undesired manifestations of IRIS is probably a continuum, so even with clearly defined criteria, there will be some room for subjective interpretation.

Second, studies that planned data collection in advance would probably have achieved more complete ascertainment of cases and more consistent diagnoses than would those based on retrospective chart review. Although this information was often unclear from published reports, the nature of study and data collection will have been another source of heterogeneity. Moreover, diagnostic capacity in resource-limited settings might have restricted complete case ascertainment: the incidence of IRIS associated with tuberculosis and cryptococcal meningitis was lower in cohorts from countries of low and middle income than in cohorts from high-income countries. Conversely, the incidence of IRIS associated with immune recovery uveitis was high in all settings: inflammatory reactions, even if moderate, are more likely to be recognised in the eye than in other organs.

Third, the CD4 cell count at the start of ART is another source of heterogeneity. Results from the metaregression model showed that low CD4 cell counts were associated with increased incidence of IRIS, independently of the type of opportunistic infection or cancer. IRIS was common in patients starting ART with fewer than 50 cells per µL and previously diagnosed tuberculosis, cytomegalovirus-associated immune recovery uveitis, or cryptococcal meningitis. Diagnosis of cytomegalovirus retinitis and cryptococcal meningitis are expected at low CD4 cell counts,[77,78] whereas Kaposi's sarcoma and tuberculosis also occur at high counts.[78]

Our review did not cover all AIDS-defining illnesses. For example, we found no eligible study of IRIS in patients with *Pneumocystis jirovecii* pneumonia. A randomised clinical trial published in 2009 compared immediate ART with ART given after treatment for acute opportunistic infection, and the results showed that 13 (7%) of 177 patients with *P jirovecii* pneumonia developed IRIS.[79] This number was low given the median CD4 cell count of 29 cells per µL, and could have been related to inclusion criteria or the use of

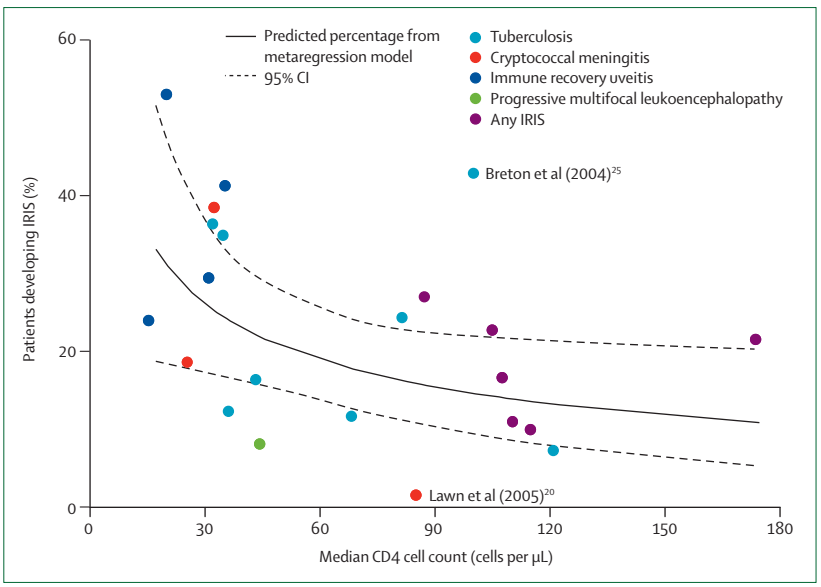


***Figure 3*: Incidence of immune reconstitution inflammatory syndrome (IRIS) according to CD4 cell count at the start of antiretroviral therapy**
Data are provided for 22 studies. Circle size is proportional to weighting in the random-effect model.

***Figure 2*: Incidence of immune reconstitution inflammatory syndrome (IRIS) in patients starting antiretroviral therapy for HIV infection, by type of study population**
CrI=credibility interval. NA=not applicable.

	High income	High-middle income	Low-middle income	Low income
Tuberculosis	21·3% (8·9–43·0); eight studies	13·9% (6·0–26·4); three studies	9·4% (3·8–22·0); four studies	22·2% (8·6–42·3); one study
Cryptococcal meningitis	36·0% (10·2–77·1); two studies	12·1% (2·2–45·2); three studies	19·2% (9·6–32·5); one study	..
Immune recovery uvetitis	35·9% (9·6–72·9); four studies	41·4% (23·1–60·0); four studies	32·4% (13·4–62·6); two studies	..

Data are percentage of patients (95% credibility interval). ..=no studies available.

Table 2: **Incidence of immune reconstitution disease stratified by previously diagnosed opportunistic illness and study setting**

corticosteroids, or might have been because of chance (the 95% CI was wide at 4·0–12·2%). We cannot, however, exclude the possibility that the risk of IRIS is lower for some opportunistic infections, independently of the CD4 cell count.

21% of deaths were attributable to IRIS, with lethality ranging from about 3% in patients with tuberculosis to more than 20% in those with cryptococcal meningitis. By contrast, in a study from Uganda, only four (6%) of 69 HIV-related deaths in the first year of ART were caused by IRIS.[80] Our review could therefore have overestimated the contribution of IRIS to early death. Although we included deaths that were explicitly attributed to IRIS only, attribution could have been inaccurate: other AIDS-defining illnesses and toxic effects of drugs could have had a role in some of these deaths. Moreover, we included the studies that reported no deaths from IRIS, but studies with such deaths might nevertheless have been preferentially reported. Alternatively, the Ugandan study, which did not systematically assess all IRIS events and recorded causes of death on the basis of retrospective chart review and verbal autopsy, could have underestimated IRIS-related deaths. As Davies and Meintjes[76] have pointed out, the occurrence of IRIS events and their contribution to mortality in a given setting will be affected by the relative importance of different opportunistic infections, the degree of access to facilities for diagnosis of such illnesses, and the extent of screening for and treatment of opportunistic infections before the start of ART.

The immunopathological process underlying IRIS is not fully understood, but data from clinicopathological and immunological studies suggest that IRIS results from exaggerated and dysregulated cellular immune responses that depend on the associated pathogen.[14,81] If the pathogen is viral (eg, cytomegalovirus), CD8 T-lymphocytes predominate in inflammatory cell infiltrates, whereas granulomatous CD4 T-helper cell type 1 inflammation predominates if the pathogen is mycobacterial (eg, *Mycobacterium tuberculosis*), or a fungus (eg, *Cryptococcus neoformans*).[14,81] Expansion of *M tuberculosis* antigen-specific T cells also occurs in most patients who do not develop IRIS, suggesting that other factors contribute.[82] Regulatory T cells might not expand at the same rate as antigen-specific effector cells, resulting in dysregulated immune activation and a cytokine storm.[83,84] Findings from a comparative study in patients with HIV and tuberculosis showed similar expansion of regulatory T cells, but reduced functional capacity in patients with IRIS.[85] Little is known about how best to treat IRISD, although corticosteroid therapy seems effective in severe cases.[14,76]

IRIS is a common complication in patients starting ART, particularly in those with a history of cytomegalovirus retinitis, cryptococcal meningitis, and tuberculosis, and in those with low CD4 cell counts. Probable underdiagnosis in resource-limited settings could contribute to the high early mortality in these settings.[23,42] As for IRIS associated with tuberculosis,[11] international consensus case definitions need to be developed for other AIDS-defining illnesses. Studies in IRIS should always state which definitions were used, and whether data collection was prospectively planned or based on retrospective chart reviews. Further research is needed to better understand the immunopathogenesis of the various types of IRIS, so that diagnostic tests and effective therapies can be developed. Although our study has not established the best CD4 cell count for starting of ART, our results suggest that many IRIS events and the high mortality in the first few months of ART in resource-limited settings could be preventable with timely starting of ART, before patients are at risk of opportunistic infections.

Search strategy and selection criteria

These are described in detail in the Methods section.

Contributors

MM contributed to the systematic review, selection of studies, data extraction, data analysis, and writing of the report. SW did the statistical analyses and contributed to writing of the report. RC contributed to the data interpretation, and writing and revision of the report. SA contributed to the study selection and data extraction. HF contributed to the data interpretation and writing of the report. ME conceived and supervised the study, and contributed to the data extraction, and writing and revision of the report. All authors have seen and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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