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Incidence and Lethality of Immune Reconstitution Disease in HIV-Infected Patients Starting Antiretroviral Therapy: Systematic Review and Meta-Analysis

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Summary

This systematic review examines the incidence of Immune Reconstitution Disease (IRD) in HIV-1 infected patients starting antiretroviral combination therapy (ART). We analysed 13103 patients from 54 cohort studies; 1685 patients developed IRD. Pooled incidences with 95% credibility intervals (CrI) were calculated using Bayesian methods. In patients with previously diagnosed AIDS-defining conditions the incidence was 37.7% (95% CrI 26.6–49.4%) for CMV retinitis, 19.5% (6.7–44.8%) for cryptococcal meningitis, 15.7% (9.7–24.5%) for tuberculosis, 16.7% (2.3–50.7%) for progressive multifocal leukencephalopathy and 6.4% (1.2–24.7%) for Kaposi's sarcoma. The incidence of any type of IRD, based on studies of unselected patients starting ART, was 16.1% (11.1–22.9%). Lethality was 4.5% (2.1–8.6%) for any type of IRD, 3.2% (0.7–9.2%) for tuberculosis and 20.8% (5.0–52.7%) for cryptococcal meningitis. Meta-regression analyses showed that the incidence is largely determined by the CD4 cell count at the start of ART, with a high risk in patients starting below 50 cells/μl. Many of the IRD events might therefore be prevented with earlier initiation of ART.

Introduction

Combination antiretroviral therapy (ART) substantially reduces the incidence of opportunistic events and mortality.[1] The beneficial effects of ART result from gradual

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Conflict of interest
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restoration of pathogen-specific immune responses, mediated by the suppression of HIV-1 replication and increases in CD4 positive T-cells (CD4 cells).[23] The World Health Organisation (WHO) estimates that about 4 million people were receiving antiretroviral therapy (ART) in low- and middle-income countries by then end of 2008, a ten-fold increase during the past five years.[4] However, many patients in resource-poor settings start ART late, with advanced immunodeficiency.[56]

Complications related to ART-induced immune reconstitution include paradoxical worsening of treated opportunistic infections or the unmasking of previously sub-clinical, untreated infections.[7–10] This Immune Reconstitution Disease (IRD) is usually a consequence of exaggerated activation of the immune system against persisting antigen (paradoxical IRD) or viable pathogens (unmasking IRD), but may also manifest itself as progression of proliferative disease in patients with cancers.[11] IRD has been associated with a wide range of pathologies, including mycobacterial and cryptococcal infections, Kaposi's sarcoma, Non-Hodgkin lymphoma and progressive multifocal leukencephalopathy (PML).[8–1012–14] Non-AIDS defining conditions such as sarcoidosis[15] and rheumatic diseases[16] may also transiently deteriorate after starting ART.

The incidence of IRD in patients initiating ART is not well defined at present, with published estimates ranging from less than 10% to over 50%.[17–21] Several studies,[101422–24] but not all[182526] found an increased risk of IRD in patients starting ART with advanced immune deficiency. We performed a systematic review and meta-analysis of cohort studies to better define the incidence and lethality of IRD events in patients starting ART in low- and high-income countries.

Methods

Literature search and study selection

We searched the MEDLINE and EMBASE databases from January 1996 to October 2009 to identify relevant studies published in any language. We used the terms 'immune reconstitution syndrome', 'immune reconstitution disease', 'immune restitution syndrome', 'immune restitution disease', 'immune reconstitution inflammatory syndrome', and 'immune recovery uveitis'. Articles, brief reports and letters to the editors were included. Reference lists of relevant papers were screened. In addition we searched the abstracts of the International AIDS Society conferences (International AIDS conference and Conference on HIV Pathogenesis, Treatment and Prevention) and the Conference on Retroviruses and Opportunistic Infections (CROI) 2000 to 2009. We included longitudinal studies of patients starting ART. The cohort had to consist of at least ten adults starting ART and systematically record IRD events and/or the mortality of patients with IRD.

Data collection and definitions

Data on eligibility criteria, study and patient characteristics as well as IRD events (type of event, number of patients developing event, number of deaths from IRD) and duration of follow up were extracted in duplicate by two reviewers (MM and SA) using a standardized form. Disagreements were resolved by discussion with a third reviewer (ME). Common

definitions used in these studies for IRD are summarized in Table 1. We used the 2008 World Bank country classification to classify countries into high-income, higher and lower middle-income countries and low-income countries.[27]

Statistical Analysis

We used a fully probabilistic (Bayesian) approach for meta-analysis, which is particularly suitable when there is substantial heterogeneity between the results of individual studies, by providing a flexible framework for hierarchical modelling with random effects at the study level.[2829] For each study 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, i.e. 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 1,000), and a uniform distribution ranging from 0 to 2 for the standard deviation of the random-effects.[29] Results are based on 30,000 iterations after a burn-in period of 50,000 iterations. Between-trial heterogeneity was assessed using an approximate I-squared for Bayesian meta-analysis. Further details on the Bayesian model, the choice of prior distributions and the implementation in WinBugs are provided in Webappendix 1.

We used random-effects meta-regression with inverse variance weights to examine the relationship between median CD4 cell count and incidence of IRD, and to investigate the importance of the study setting (2008 World Bank country classification[27]) and type of publication (full article, letter, abstract). In some instances we converted median age to mean age using the method proposed by Hozo et al.[30] Analyses were done in WinBUGS (version 1.4.3, Cambridge, UK) and Stata (version 10.0, College Station, TX, USA). Data are presented as percentage of patients developing IRD events, with 95% credibility intervals (CrI) for combined estimates from meta-analysis, and 95% confidence intervals (CI) for study-specific estimates, and as coefficients from meta-regression models, which can be interpreted as risk ratios.

Results

The search identified 856 reports and 118 abstracts. 54 eligible cohort studies were identified: 22 (41%) were published as full articles, 21 (39%) as abstracts and eleven (20%) as letters to the editor. Figure 1 illustrates the process of identifying eligible studies and gives reasons for exclusions.

Table 2 summarises study and patient characteristics. The 54 studies were from 23 different countries. Seventeen cohorts (31%) were in unselected patient groups that included patients with and without AIDS and studied any type of IRD.[22232631–38] The remaining studies were in patients with previously diagnosed conditions and examined their paradoxical worsening after starting ART: tuberculosis (16 studies, 30%),[1819242539–47] cryptococcal meningitis (6 studies, 11%),[122048–50] cytomegalovirus (CMV) retinitis (10 studies, 19%),[2151–58] herpes zoster (1 study, 2%),[59] Kaposi's sarcoma (2 studies, 4%)[1760] and progressive multifocal leucencephalopathy (2 studies, 4%). Twenty studies (37%) used one of the definitions listed

in Table 1, fourteen (26%) used another definition and in twenty studies (37%) the definition was unclear.

The cohorts included a median of 75 patients (range 10 to 2330 patients), the total number was 13103 patients. Length of follow up was reported in 17 studies: the median was 12 months (range 5 to 37 months). Nineteen studies (35%) were from high-income countries (Australia, France, Ireland, Japan, South Korea, Spain, United Kingdom, Germany, Taiwan and USA), 17 (31%) from higher middle-income countries (Argentina, Brazil, Mexico, Poland, Serbia, South Africa and Venezuela), another 15 (28%) from lower middle-income countries (India and Thailand) and three (6%) from low-income countries (Cambodia, Mozambique and Senegal). 19 cohorts (35%) were from the Asia-Pacific region, thirteen (24%) from Europe, seven (13%) from North America, six (11%) from South America and nine (17%) from Africa. Mean age was available for 21 studies (39%): the median across studies was 36.3 years (range 34 to 41 years). The CD4 count at the start of ART was reported in 22 studies (41%): the median across studies was 57 cells/μl (range 17 to 174 cells/μl).

A total of 1685 patients developed IRD. Figure 2 shows the meta-analysis of the incidence of IRD events in patients with previously diagnosed opportunistic illnesses and of any type of IRD, based on studies of unselected patients starting ART. The incidence of IRD ranged from 6.4% (95% CrI 1.2–24.7%) among patients with Kaposi sarcoma, based on two studies, to 37.7% (26.6–49.4%) among patients with CMV retinitis (10 studies); with the incidence of IRD associated with tuberculosis (16 studies), cryptococcal meningitis (6 studies), herpes zoster (one study) and progressive multifocal leucencephalopathy (2 studies) in intermediate positions. The incidence of any type of IRD, based on 17 studies of unselected patients starting ART, was 16.1% (11.1–22.9%). The degree of between-study heterogeneity ranged from moderate to high: approximate I-squared values were 45% for Kaposi sarcoma, 63.7% for immune recovery uveitis, 93.1% for tuberculosis, 93.7% for cryptococcal meningitis, 97.1% for progressive multifocal leucencephalopathy and 97.1% for any IRD (Figure 2).

The meta-regression analysis of the relationship between median CD4 counts at the start of ART and the incidence of IRD, based on 22 studies with available CD4 count data, is shown in Figure 3: there was an exponential increase in the incidence as the median CD4 count declined, independently of the pathology studied. As expected, in meta-regression models including both baseline CD4 counts and pathology, the coefficients associated with the different pathologies were attenuated whereas little change was seen in the coefficient for baseline CD4 count.

In stratified analyses, the incidence of tuberculosis-associated IRD was 20.7% (95% CrI 9.0–45.7%), based on four studies[244244] in patients starting ART with fewer than 50 cells/μl, compared to 17.7% (5.4–54.2%) in patients starting above this threshold (based on four studies[18253941]). The difference was more extreme for cryptococcal meningitis: incidences were 28.3% (6.1–68.2%) and 2.0% (0.2–15.5%), based on two[4850] and one study,[20] respectively. All four studies[215253] of CMV retinitis with information on CD4 cell counts at baseline reported median counts below 50 cells/μl; the combined incidence was 37.7%

(16.8–61.7%). Six studies reported a CD4 cell count for any type of IRD. All of them started with median counts above 50 cells/μl: the combined incidence was 17.7% (10.5–27.7%).

Finally, in a model including pathology and 2008 World Bank country classification, the risk of IRD decreased when moving from high-income to higher middle-income, lower middle-income and low-income country. The risk ratio per change in category was 0.76 (95% CI 0.59 to 0.97, p = 0.03). In stratified analyses the incidence of tuberculosis was 21.3% (95% CrI 8.9–43.0), based on eight studies in high-income countries, 13.9% (6.0–26.4%) based on three studies from higher middle-income countries, 9.4% (3.8–22.0%) based on four studies in lower middle-income countries and 22.2% (8.6–42.3%) based on one study from a low-income country. The corresponding incidences for cryptococcal meningitis were 36.0% (10.2–77.1%), based on two studies from high-income countries, 12.1% (2.2–45.2%) based on three studies from higher middle-income countries and 19.2% (9.6–32.5%) based on one study from a lower middle-income country. There were no studies of cryptococcal meningitis or CMV retinitis from low-income countries. There was little evidence of a trend in the incidence of immune recovery uveitis: 35.9% (9.6–72.9%) in four studies from high-income countries, 41.4% (23.1–60.0%) in four studies from higher middle-income countries and 32.4% (13.4–62.6%) in two studies from lower middle-income countries. In the same model there was little evidence for an association of publication type and incidence of IRD (p=0.40).

Information on deaths in patients developing IRD was available from 23 cohorts (Table 2). A total of 52 deaths were explicitly attributed to IRD. Lethality was 4.5% (95% CrI 2.1–8.6%) for any type of IRD, 3.2% (0.7–9.2%) for tuberculosis-associated IRD and 20.8% (5.0–52.7%) for IRD related to cryptococcal meningitis. Eleven cohorts reported both the total number of deaths and the number of deaths due to IRD: 33 (20.9%) of 158 deaths were attributed to IRD, including three studies reporting zero deaths. The proportion of deaths attributed to IRD was similar when restricting the latter analysis to the four studies of any type of IRD: 17 (21.8%) of 78 deaths were attributed to IRD.

Discussion

This systematic review and meta-analysis of cohort studies in patients starting ART showed that the incidence of IRD varies across groups of patients with different AIDS-defining events. The incidence was highest in patients with CMV retinitis and also high in patients with cryptococcal meningitis and tuberculosis, but less common in Kaposi’s sarcoma or herpes zoster. Interestingly, differences in the incidence of IRD between pathologies appeared to be explained by different CD4 cell counts at baseline. Based on the studies in unselected patients with and without a history of AIDS, which examined any type of IRD event, about every sixth patient developed the syndrome, but the results from these studies were highly heterogeneous. The lethality of patients developing IRD overall was about 4%, but much higher for IRD associated with cryptococcal meningitis.

Our study was based on a comprehensive literature search and included data that were presented at conferences but not published, thus reducing possible publication bias. We identified 54 cohort studies in over 13000 patients from 23 different countries, including

high-, middle- and low-income countries. We included both studies in patients with diagnosed pathologies, which focussed on paradoxical reactions to ART, and studies of unselected patient groups, which assessed any type of IRD, including the unmasking of sub-clinical infections.[61] The synthesis of these studies represents the best available evidence on the incidence of IRD following the initiation of ART, but we acknowledge that meta-analyses of observational studies are prone to the biases inherent in the original studies.[62] Our review was exclusively based on aggregated data, and important information, including, for example, on the CD4 count at the start of ART or the duration of follow up, was often missing. This was not surprising considering that many of the studies were available as conference abstracts only. It also meant that in-depth assessments of study quality were not possible.

There was substantial heterogeneity in the results from the different studies, particularly between studies of unselected patients groups, but also for some of the studies of patients with AIDS. Several factors may have contributed to between-study heterogeneity. Firstly, there is little agreement on the diagnostic criteria for IRD, although criteria for the diagnosis of tuberculosis-associated IRD have recently been developed by the International Network for the Study of HIV-associated IRD.[61] Particularly the unmasking type of IRD is difficult to diagnose: differentiating between an opportunistic infection with normal presentation and an infection with a presentation compatible with unmasking IRD is not straightforward.[63] In paradoxical IRD alternative explanations for the deterioration, including, for example, the failure of the treatment of the opportunistic infection or the failure of ART due to lack of adherence or drug resistance must be excluded. Differences in the diagnostic criteria used in the different studies may thus well have introduced heterogeneity. There is likely to be a continuum from intended ART-associated immune reconstitution to the undesired manifestations of IRD, and even with clearly defined criteria there will be some room for subjective interpretation.

Studies that planned data collection in advance will probably achieve more complete ascertainment of cases and more consistent diagnoses compared to studies based on retrospective chart review. While this was often unclear from the published reports, the nature of the study and data collection will have been another source of heterogeneity. The more limited diagnostic capacity might have rendered case ascertainment less complete in resource-constrained settings. Indeed, we found that the incidence of IRD tended to be lower in cohorts from middle- and low-income countries, compared to high-income countries. This result was mainly driven by IRD associated with tuberculosis and cryptococcal meningitis, whereas no such trend was observed for immune recovery uveitis. This is not surprising: inflammatory reactions, even if moderate, are more likely to be recognised in the eye than in other organs.

The CD4 cell count at the start of ART is another source of heterogeneity. We could examine the relationship between the incidence of IRD and the median CD4 cell count at the start of ART in 22 studies. The results from the meta-regression model showed that low CD4 counts at the start of ART drive the incidence of IRD, independently of the pathology involved. Indeed, we found a high incidence of IRD events in patients starting ART below 50 cells//μl, including events associated with tuberculosis, CMV-associated immune

recovery uveitis and cryptococcal meningitis. The high incidence of IRD in patients with CMV retinitis is not surprising: this diagnosis is typically made when the CD4 count has dropped below 50 cells//μl.[6465] Cryptococcal meningitis also tends to occur at low CD4 counts, whereas Kaposi's sarcoma and tuberculosis also occur at higher counts.[65]

Our review did not cover all AIDS-defining events. For example, we failed to identify an eligible study of IRD in patients with *Pneumocystis jirovecii* pneumonia. A recent randomised clinical trial in patients with acute opportunistic infections, which compared immediate ART with ART given after treatment of the acute infection, found that 7.3% of 177 patients with *Pneumocystis jirovecii* pneumonia developed IRD.[66] This incidence was low considering the median CD4 cell count of 29 cells/μL. The low incidence of IRD in this trial might be related to the patient inclusion criteria, the use of corticosteroids, or to chance: the 95% confidence interval was wide (4.0%–12.2%). We cannot, however, exclude that the risk of IRIS may be lower for some opportunistic infections, independently of the CD4 count.

We found that 21% of all deaths had been attributed to IRD, with lethality ranging from about 3% in patients with tuberculosis-associated IRD to over 20% in patients with cryptococcal meningitis. In contrast, a recent study from Uganda reported that only four (5.8%) out of 69 HIV-related deaths in the first year of ART were due to IRD.[67] Our review may thus have overestimated the contribution of IRD to early mortality. Although we included deaths that were explicitly attributed to IRD only, attribution may have been inaccurate: other AIDS-defining conditions and drug toxicity may have played a role in some of these deaths. We included the studies that reported zero deaths in patients with IRD, but selective reporting of data on mortality in studies where such deaths occurred may also have played a role. Alternatively, the Ugandan study, which did not systematically assess all IRD events and determined causes of death based on retrospective chart review and verbal autopsy, may have under ascertained IRD-related deaths. As Davies and Meintjes pointed out in their commentary, the relative importance of different opportunistic infections, the degree of access to facilities for their diagnosis and the extent of screening for and treatment of opportunistic infections before ART initiation will influence the incidence of IRD events and their contribution to mortality in a given setting.[63]

The immunopathological process underlying IRD is not fully understood at present, but data from clinico-pathological and immunological studies indicate that IRD results from exaggerated and dysregulated cellular immune responses that depend on the pathogen involved.[1168] If the provoking pathogen is viral, for example *Cytomegalovirus*, CD8 positive T-lymphocytes predominate in inflammatory cell infiltrates whereas granulomatous CD4 T helper cell type 1 (Th1) inflammation predominates if the pathogen is mycobacterial, for example *M. tuberculosis*, or a fungus, for example *Cryptococcus neoformans*.[1168] A recent study showed that expansion of *M. tuberculosis* antigen-specific T-cells also occurred in the majority of patients not developing IRD, suggesting that other factors are involved.[69] Regulatory T cells may not expand at the same rate as the antigen-specific effector cells, resulting in dysregulated immune activation and a "cytokine storm".[7071] A comparative study in patients with HIV and tuberculosis recently showed similar expansion of regulatory T cells but reduced functional capacity in patients with IRD.[72] Finally, little is known about

how best to treat IRD although corticosteroid therapy appears to be efficacious in severe cases.[1163]

In conclusion, IRD is a common complication in patients starting ART. It is particularly common in patients with a history of CMV retinitis, cryptococcal meningitis and tuberculosis, and in patients who start ART at low CD4 cell counts. It is probably under diagnosed in resource-limited settings, and may contribute to the high early mortality in these settings.[2073] As was done for IRD associated with tuberculosis[61] it is important that international consensus case definitions for IRD are developed for other AIDS-defining events. Authors reporting on IRD 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 IRD, so that diagnostic tests and effective therapies can be developed. Finally, although our study cannot determine the CD4 cell count when ART should best be started, our results indicate that many IRD events and much of the excess mortality that is observed in the first few months ART in resource-limited settings might be preventable with timely initiation of ART, before patients are at risk for developing opportunistic infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Search strategy and selection criteria

These are described in detail in the Methods section on page xxx.

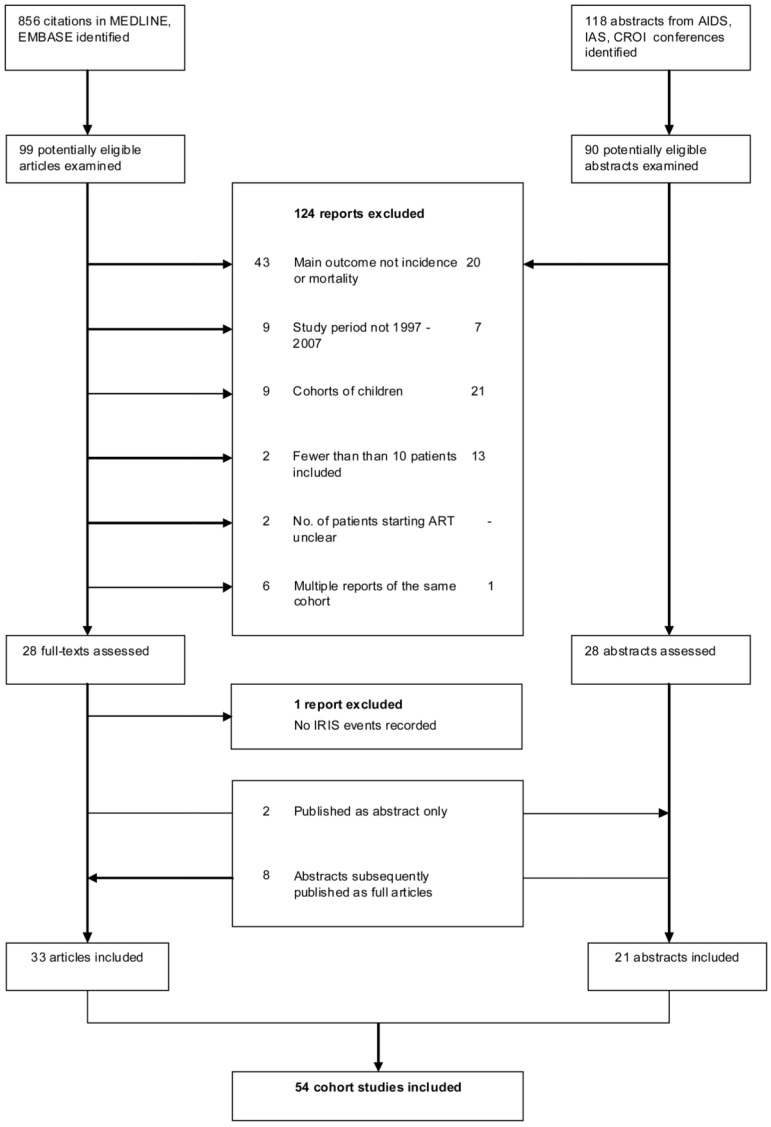

Figure 1.

Identification of eligible cohort studies of HIV-infected patients starting antiretroviral therapy.

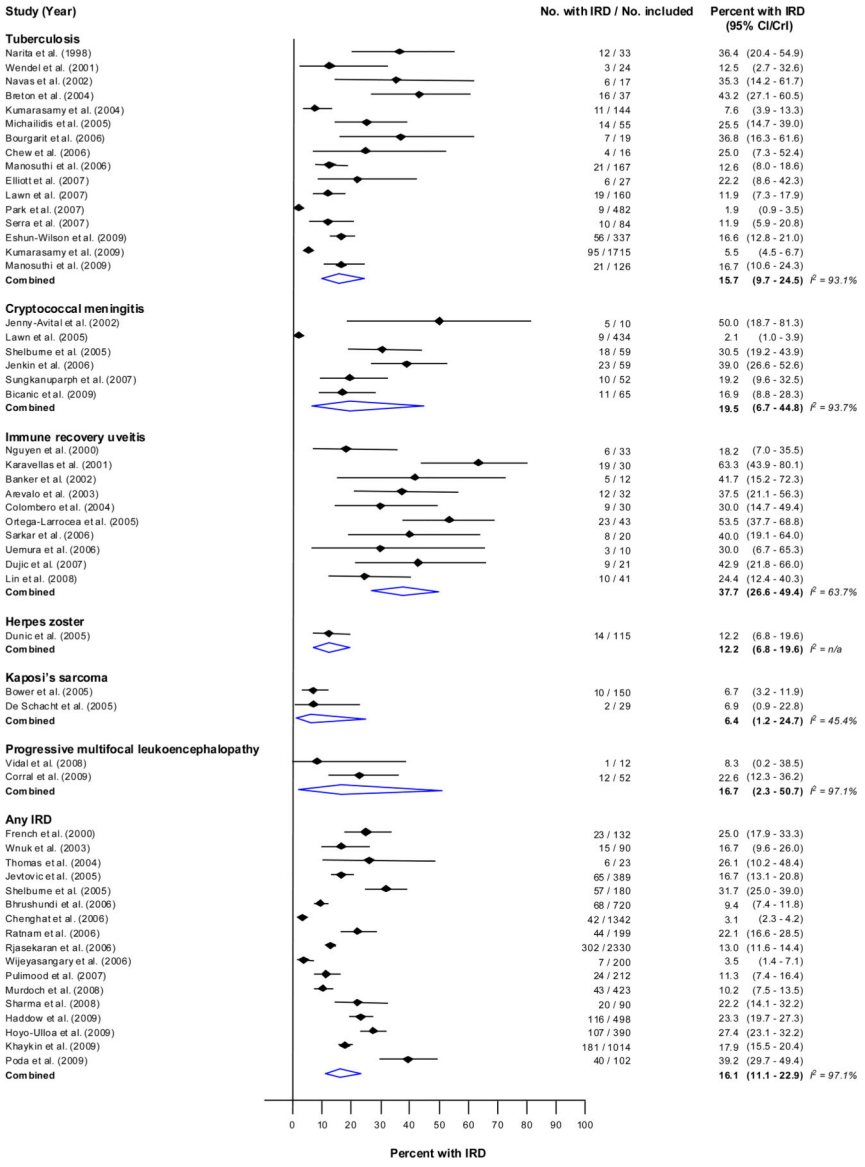

Figure 2. Meta-analysis of 54 cohort studies of the incidence of immune reconstitution disease (IRD) in HIV-infected patients starting antiretroviral therapy

Estimates of incidences in percent from individual studies with 95% confidence intervals (95% CI) and combined estimates with 95% credibility intervals (95% CrI) are shown.

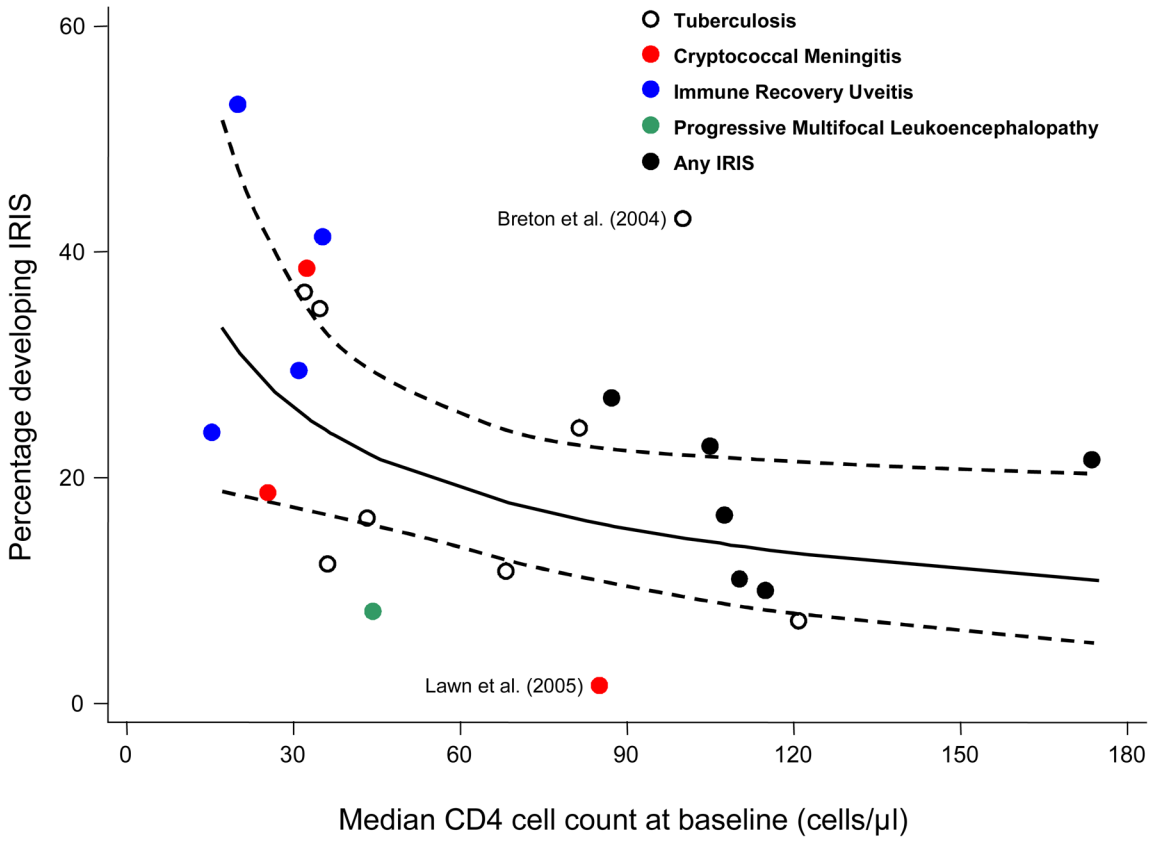

Figure 3. Incidence of immune reconstitution disease (IRD) in 22 cohort studies according to median CD4 count at the start of antiretroviral therapy

The solid line shows the predicted percentage from the meta-regression model, the dotted lines indicate the 95% confidence intervals. The size of circles is proportional to the weight in the random-effect model.

Table 1

Commonly used definitions of the Immune Reconstitution Inflammatory Syndrome

1) French[10]

Diagnosis requires both major criteria or one major criterion plus two minor criteria:

Major criteria

1. 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 the initiation of ART
   - Exclusion of alternative causes (drug toxicity, newly acquired infection or tumor, treatment failure)
2. Decrease in plasma HIV RNA level by >1log copies/ml

Minor criteria

1. Increased blood CD4-count after ART
2. Increase in an immune response specific to the relevant pathogen, e.g. DTH response to mycobacterial antigens
3. spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of ART

2) Shelburne[9]

Criteria for diagnosis of any IRIS case include the following four criteria:

1. HIV-infected patient
2. Receiving effective ART as evidenced by a decrease in HIV RNA concentration from baseline or increase in CD4 cells from baseline
3. Clinical symptoms consistent with inflammatory process
4. Clinical course not consistent with
   - expected course of previously diagnosed opportunistic infection
   - expected course of newly diagnosed opportunistic
   - drug toxicity

Additional criteria for cryptococcal meningitis:

1. Decrease of CSF antigen
2. Negative CSF fungal cultures
3. Inflammatory reaction in CSF (increased WBC count)

3) International Network for the Study of HIV-associated IRIS (INSHI)[61]

Case definition for TB-associated IRIS in resource-limited settings

A. Antecedents

TB-diagnosis according to WHO guidelines before starting ART

TB should have stabilized or improved before starting ART

B. Clinical criteria

New enlaging lymph nodes, cold abscesses or other focal tissue involvement

New or worsening radiological features of TB

New or worsening CNS tuberculosis

New or worsening serositis

C. Exclusion of alternative causes

Failure of TB treatment (non-compliance or resistance)

Other opportunistic infection or neoplasm

Drug toxicity reaction

4) Wendel[47]

Paradoxical worsening of Tuberculosis is defined as:

1 Documented worsening of signs or symptoms of TB (fever, cough, adenopathy) or exacerbation of disease at other extrapulmonary sites during appropriate treatment

2 Worsening of pulmonary infiltrates on chest radiograph or CT without other etiology

5) Karavellas[55]

Immune reconstitution uveitis is defined as:

1 Patients with symptomatic onset of vitreous inflammation in the setting of inactive CMV retinitis, i.e.:

- vitritis of 1+ or greater severity
- significant floaters and/or decrease in vision of one or more lines

2 With or without papillitis or macula changes

Table 2

Characteristics of 54 cohort studies of Immune Reconstitution Disease in HIV-infected patients starting antiretroviral therapy.

Author (Year)	Percent with AIDS at enrolment	Definition of IRIS *	Type of publication	Country	Study period	Mean age (years)	Median CD4 cell count (cells/µl)	No. of patients	No. developing IRIS	No. of deaths from IRIS
Tuberculosis (pulmonary and extrapulmonary										
Narita (1998)[19]	100%	4	Article	USA	1996–1997	n.r.	n.r.	33	12	n.r.
Wendel (2001)[47]	100%	4	Article	USA	1996–2000	n.r.	n.r.	24	3	n.r.
Navas (2002)[44]	100%	Other	Letter	Spain	1995–1998	36.3	35	17	6	0
Breton (2004)[25]	100%	2	Letter	France	1996–2001	35.0	100	37	16	n.r.
Kumarasamy (2004)[18]	100%	Other	Letter	India	2000–2003	34.0	122	144	11	n.r.
Michailidis (2005)[43]	100%	Other	Article	United Kingdom	2001–2003	37.4	n.r.	55	14	n.r.
Bourgarit (2006)[24]	100%	1	Article	France	n.r.	39.1	32	19	7	n.r.
Chew (2006)[39]	100%	n.r.	Abstract	Ireland	2004–2006	n.r.	82	16	4	0
Manosuthi (2006) [42]	100%	1	Article	Thailand	2003–2004	34.5	36	167	21	2
Elliott (2007)[40]	100%	n.r.	Abstract	Cambodia	n.r.	n.r.	n.r.	27	6	1
Lawn (2007)[41]	100%	Other	Article	South Africa	2002–2005	n.r.	68	160	19	2
Park (2007)[45]	n.r.	2	Letter	South Korea	1998–2005	38.0	n.r.	482	9	n.r.
Serra (2007)[46]	100%	4	Article	Brasil	2000–2003	n.r.	n.r.	84	10	0
Eshun-Wilson (2009)[73]	100%	3	Abstract	South Africa	2003–2008	n.r.	n.r.	337	56	6
Kumarasamy (2009)[74]	100%	1	Abstract	India	1996–2008	n.r.	n.r.	1731	95	0
Manosuthi (2009)[75]	100%	3	Abstract	Thailand	2006–2007	35	43	126	21	0
Cryptococcal meningitis										
Jenny-Avital (2002)[49]	100%	n.r.	Article	USA	1998–2001	n.r.	n.r.	10	5	n.r.
Lawn (2005)[20]	95%	n.r.	Letter	South Africa	2002–2005	34.0	86	434	9	6
Shelburne (2005)[12]	n.r.	2	Letter	USA	n.r.	n.r.	n.r.	59	18	1
Jenkin (2006)[48]	100%	2	Abstract	South Africa	2004–2005	n.r.	32.5	59	23	9

Author (Year)	Percent with AIDS at enrolment	Definition of IRIS *	Type of publication	Country	Study period	Mean age (years)	Median CD4 cell count (cells/µl)	No. of patients	No. developing IRIS	No. of deaths from IRIS
Sungkanuparph (2007)[50]	100%	1	Letter	Thailand	n.r.	34.4	26	52	10	0
Bicanic (2009)[76]	100%	Other	Article	South Africa	2005–2006	n.r.	n.r.	65	11	3
Immune recovery uveitis										
Nguyen (2000)[56]	100%	Other	Article	USA	1995–1998	n.r.	n.r.	33	6	n.r.
Karavellas (2001)[55]	100%	5	Article	USA	1996–1998	n.r.	n.r.	30	19	n.r.
Banker (2002)[52]	100%	5	Article	India	1998–2000	37.3	36.5	12	5	n.r.
Arevalo (2003)[51]	100%	5	Article	Venezuela	1998–2000	n.r.	n.r.	32	12	n.r.
Colombero (2004)[53]	100%	1	Abstract	Argentina	n.r.	n.r.	32	30	9	n.r.
Ortega-Larrocea (2005)[21]	100%	Other	Letter	Mexico	1996–2003	n.r.	19.7	43	23	n.r.
Sarkar (2006)[57]	100%	n.r.	Abstract	India	2002–2004	n.r.	n.r.	20	8	n.r.
Uemura (2006)[58]	100%	n.r.	Abstract	Japan	2002–2003	n.r.	n.r.	10	3	n.r.
Dujic (2007)[54]	100%	5	Abstract	Serbia	n.r.	n.r.	n.r.	21	9	n.r.
Lin (2008)[77]	100%	5	Article	Taiwan	1995–2006	40.3	16.6	41	10	n.r.
Herpes zoster										
Dunic (2005)[59]	100%	n.r.	Article	Serbia	2000–2001	38.1	n.r.	115	14	n.r.
Kaposi's sarcoma										
Bower (2005)[17]	100%	n.r.	Article	United Kingdom	1996–2004	37.9	n.r.	150	10	n.r.
De Schacht (2005)[60]	100%	n.r.	Abstract	Mozambique	2004	n.r.	n.r.	29	2	0
Progressive multifocal leucencephalopathy										
Vidal (2008)[78]	100%	Other	Article	Brazil	2003–2004	37.3	45	12	1	0
Corral (2009)[79]	100%	Other	Abstract	Spain	1996–2008	n.r.	n.r.	53	12	n.r.
Any IRIS										
French (2000)[22]	5.3%	n.r.	Article	Australia	1996–1997	n.r.	n.r.	132	33	n.r.
Wnuk (2003)[38]	n.r.	n.r.	Abstract	Poland	n.r.	n.r.	n.r.	90	15	n.r.
Thomas (2004)[36]	43.5%	n.r.	Abstract	India	n.r.	n.r.	n.r.	23	6	n.r.

Author (Year)	Percent with AIDS at enrolment	Definition of IRIS *	Type of publication	Country	Study period	Mean age (years)	Median CD4 cell count (cells/µl)	No. of patients	No. developing IRIS	No. of deaths from IRIS
Jevtovic (2005)[23]	3.2%	n.r.	Article	Serbia	1998–2004	41.0	108	389	65	1
Shelburne (2005)[35]	25.6%	2	Article	USA	1997–2003	38.8	n.r.	180	57	2
Bhrushundi (2006)[31]	n.r.	n.r.	Abstract	India	n.r.	n.r.	n.r.	720	68	2
Chenghat (2006)[32]	n.r.	n.r.	Abstract	India	2004–2006	n.r.	n.r.	1342	42	n.r.
Ratnam (2006)[80]	2.5%	Other	Article	United Kingdom	2000–2002	35.0	174	199	44	n.r.
Rajasekaran (2006)[33]	n.r.	n.r.	Letter	India	2004–2005	n.r.	n.r.	2330	302	n.r.
Wijeyasangary (2006)[37]	n.r.	n.r.	Abstract	India	n.r.	n.r.	n.r.	200	7	2
Pulimood (2007)[26]	n.r.	Other	Abstract	India	2004–2006	n.r.	110.5	212	24	n.r.
Murdoch (2008)[81]	n.r.	Other	Article	South Africa	2006	34	115	423	43	2
Sharma (2008)[82]	n.r.	Other	Letter	India	2004–2006	n.r.	n.r.	90	20	n.r.
Haddow (2009)[83]	68.9%	Other	Abstract	South Africa	2006–2007	35	106	498	116	5
Hoyo-Ulloa (2009)[84]	n.r.	n.r.	Abstract	Mexico	2001–2007	35	87	390	107	8
Khaykin (2009)[85]	43.6%	n.r.	Abstract	Germany	2001–2007	n.r.	n.r.	1014	181	n.r.
Poda (2009)[86]	n.r.	n.r.	Letter	Senegal	2003–2006	n.r.	n.r.	102	40	n.r.

n.r.; not reported

* See table 1 for definitions