# 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