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INCIDENCE, MORTALITY AND LETHALITY OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN HIV- INFECTED PATIENTS STARTING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY: Systematic Review and Meta-analysis

TESIS

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TABLA DE CONTENIDOS

9

ABSTRACT

Background

The Immune Reconstitution Inflammatory Syndrome (IRIS) is a relatively frequent complication in patients who start ART and it has, over all, not been consistently described before. We made a systematic review and meta-analysis to obtain its incidence and lethality.

Methods

We included retrospective and prospective cohorts that unspecifically evaluated IRIS in HIV-infected adults initiating HAART, with a minimum follow-up of 6 months. We searched LILACS, PUBMED, Cochrane Library, SCOPUS and Google Scholar databases, and assessed study quality with the Newcastle-Ottawa Scale (NOS). Rates were estimated with a 95% confidence interval using binomial distribution random-effects pooled model.

Results

We included 8,124 patients from 8 different countries. IRIS incidence ranged from 38‰ to 314‰ patients, with a 170‰ patients as pooled index. It was most common in patients with a baseline T CD4+ ≤100 cells/mm3 and from high-income countries. Pooled mortality and lethality were 10‰ and 4%, respectively. Mortality was more frequent in patients with ≤100 cells/mm3 T CD4+ baseline count and in middle-income countries. Lethality was slightly higher in patients with lower T CD4+ baseline count, regardless of where they came from.

Conclusions

We found a high overall IRIS incidence in HIV HAART-naïve patients, higher in ≤100 cells/mm3 T CD4+ baseline cell count group. Nonetheless, it varies according to studied population and clinical context. Moreover, lethality was homogenous in all studies. We consider further research on costs on diagnosis and management of IRIS should be done so that cost-effective interventions to avoid this phenomenon can take place.

MeSH terms: Immune Reconstitution Syndrome; HIV infections; HAART; Meta-Analysis; Humans.

TABLE INDEX

Table 1. Studies characteristics

Author, year	Country	CCBI	Number of patients	Sex (female)	Age (SD)	Baseline viral load[a] (SD)	Baseline CD4+ count[b] (SD)	Incidence	Lethality*	Criteria diagnosis	NOS
Musselwhite L (2016)[20]	South Africa and Mexico	Upper-middle	276	92	36.3 (9.7)	5.37 (0.52)	36.67 (30.55)	225‰	8.1%	NS	6
Thambuchetty N (2017)[21]	India	Lower-middle	627 599‡	256	36.6 (7.8)	5.93 (0.82)	210 (89)	313‰	4.3%	NS	7
Espinosa E (2010)[22]	Mexico	Upper-middle	99 76‡	NS	35.2(8.7)	5.528 (5.02–5.87)	50.5 (22.5–100.3)	303‰	13%	NS	7
Ratnam I (2006)[8]	UK	High	249 199‡	98	35.2(7.8)	4.6 (3.7-5.2)	174 (82-285)	221‰	NS	NS	6
Haddow LJ (2012)[23]	South Africa	Upper-middle	498 477‡	123	35.3 (8.1)	5.0 (4.4-5.6)	106 (53-165)	255‰	5.3%	Haddow *et al*	8
Kumarasamy N (2008)[24]	India	Lower-middle	1972	460	Male 35.5 (7.9) Female 32.8 (8.6)	Male 5 Female 4.8	Male 126.3 (25.8) Female 141.5 (24)	51‰	NS	NS	7
Klotz SA (2009)[25]	Ethiopia	Low	2610	568	34 (11.9)	89	102 (77)	74‰	5.4%	Shelburne *et al* Robertson *et al*	6
Zaidi I (2012)[26]	Gambia	Low	80 71‡	46	41	41	96.7 (98.4)	282%	NS	Haddow *et al*	6
Kumarasamy N (2008)[27]	India	Lower-middle	3184	1003	34.8 (13.4)	NS	109.33(89.74)	38‰	NS	NS	6
Janssen S (2017)[28]	Gabon	Upper-middle	101 60‡	67	38.6 (12)	4.86 (0.1)	167 (137.6)	83‰	0%	INSHI	7
Zheng Y (2014)[29]	China	Upper-middle	238	65	38.3	NS	NS	197‰	NS	INSHI	6

***Lethality was estimated between those who developed IRIS. ‡Number of patients who completed follow-up by the end of study, if mentioned in the article.**

[a]Measured in log10 [b]Measured in cells/mm^3

CCBI: country classification by income, NS: not specified, INSHI: International Network for the Study of HIV-associated IRIS, NOS: NewCastle-Ottawa Score

Table 2. Analysis of subgroups for incidence of IRIS

Variables	**No. of studies**	**Events**	**No. of patients**	**Incidence° (95%IC)**	**I^2 (%)**	***p* value**
CCBI						
High	1	44	199	221 (165-285)	-	-
Upper-middle	5	251	1097	215 (166-268)	72	0.00
Lower-middle	3	408	5755	110 (25-245)	-	-
Low	2	94	1073	82 (66-99)	-	-
Period						
2001-2010	5	361	6433	107 (64-159)	97	0.00
≥2011	6	436	1691	230 (179-285)	82	0.00
CD4+ baseline count[a]						
≤100	4	110	750	218 (139-309)	76	0.00
>100	6	640	7886	140 (66-236)	99	0.00
Global	11	797	8124	170 (104-248)	98	0.00

°Expressed in cases per 1000 patients. [a]Measured in cells/mm3

CCBI: country classification by income.

Table 3. Analysis of subgroups for mortality of IRIS.

Variables	No. of studies	Deaths	No. of patients	Mortality° (95%IC)	I^2 (%)	*p* value
CCBI						
High	0	-	-	-	-	-
Upper-middle	4	14	859	13 (5-25)	15	0.00
Lower-middle	1	8	599	13 (6-26)	-	-
Low	1	4	1073	4 (1-10)	-	-
Period						
<2010	2	7	1078	3 (0-8)	-	-
≥2011	4	19	1453	12 (6-19)	0	1
CD4+ baseline count[a]						
≤100	3	8	483	15 (2-39)	-	-
>100	3	18	2048	9 (3-18)	-	-
Global	6	26	2531	10 (3-19)	59	0.00

°Expressed in cases per 1000 patients. [a]Measured in cells/mm3

CCBI: country classification by income.

Table 4. Analysis of subgroups for lethality of IRIS.

Variables	No. of studies	Deaths	No. of IRIS cases	Lethality° (95%IC)	I^2 (%)	*p* value
CCBI						
High	0	-	-	-	-	-
Upper-middle	4	14	204	5 (2-9)	0	1
Lower-middle	1	8	188	4 (2-8)	-	-
Low	1	4	74	5 (1-13)	-	-
Period						
<2010	2	7	97	7 (2-13)	-	-
≥2011	4	19	369	3 (1-6)	0	1
CD4+ baseline count[a]						
≤100	3	8	90	7 (2-14)	-	-
>100	3	18	376	5 (3-7)	-	-
Global	6	26	466	4 (2-6)	0.00	1

°Expressed in deaths per 100 IRIS cases. [a]Measured in cells/mm3

CCBI: country classification by income.

FIGURE INDEX

Figure 1. Identification of eligible cohort studies of HIV-infected patients starting antiretroviral therapy.

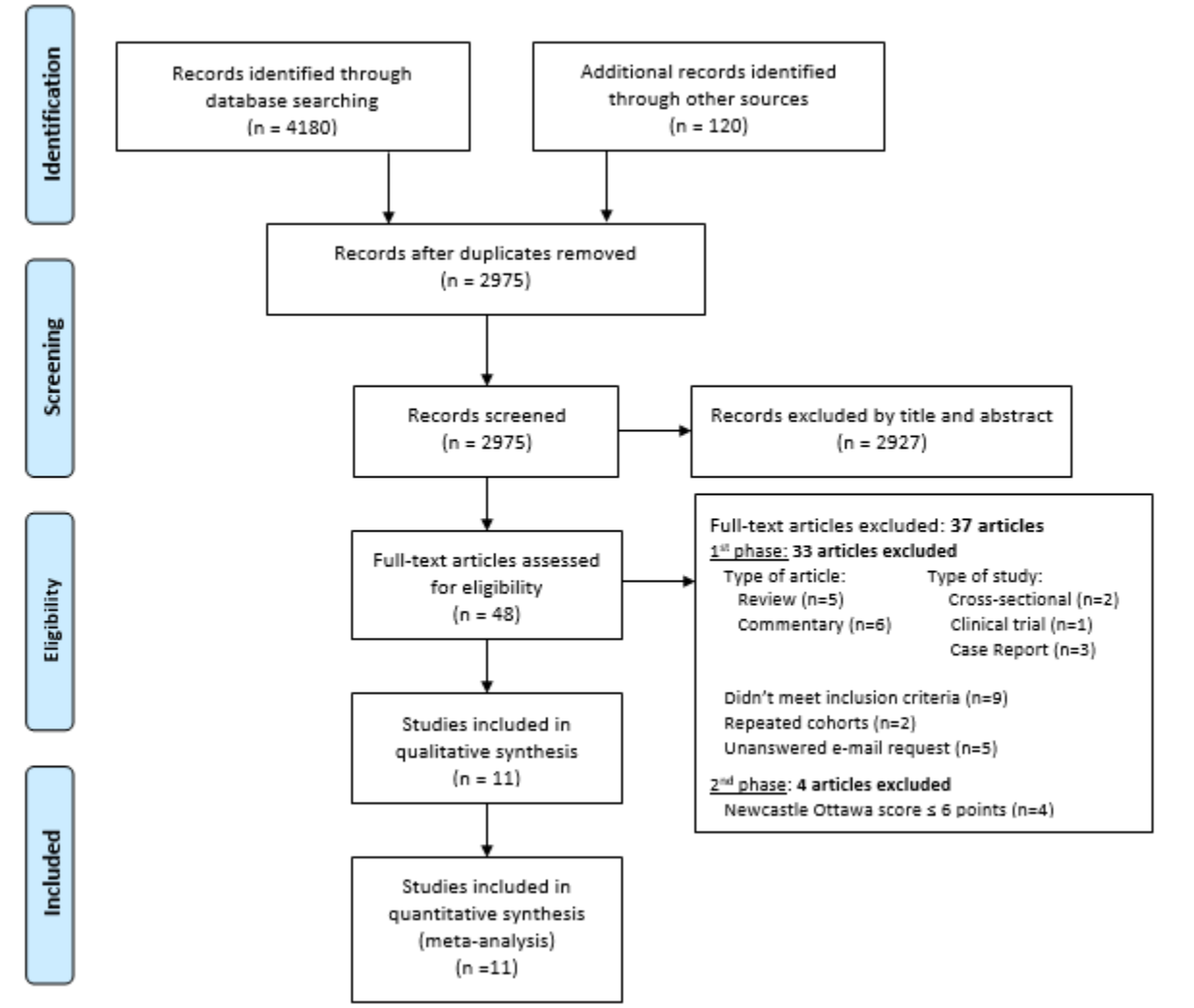


Figure 2. Forest plot for incidence of IRIS.

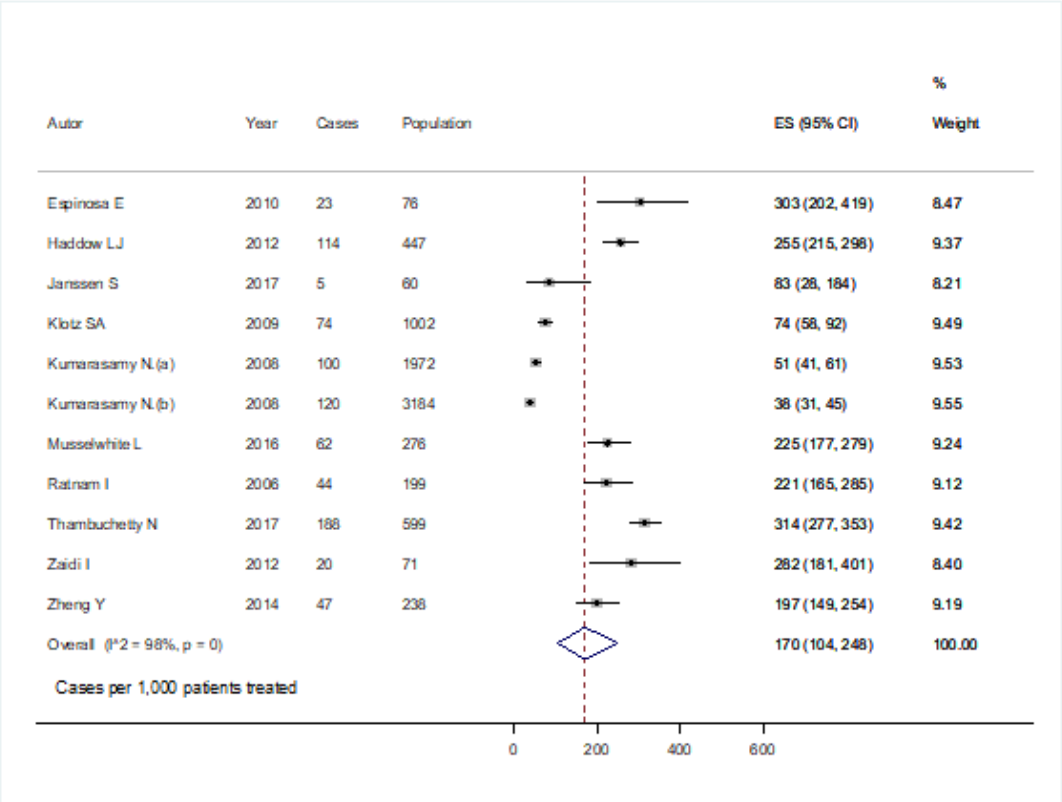


Figure 3. Forest plot for mortality of IRIS

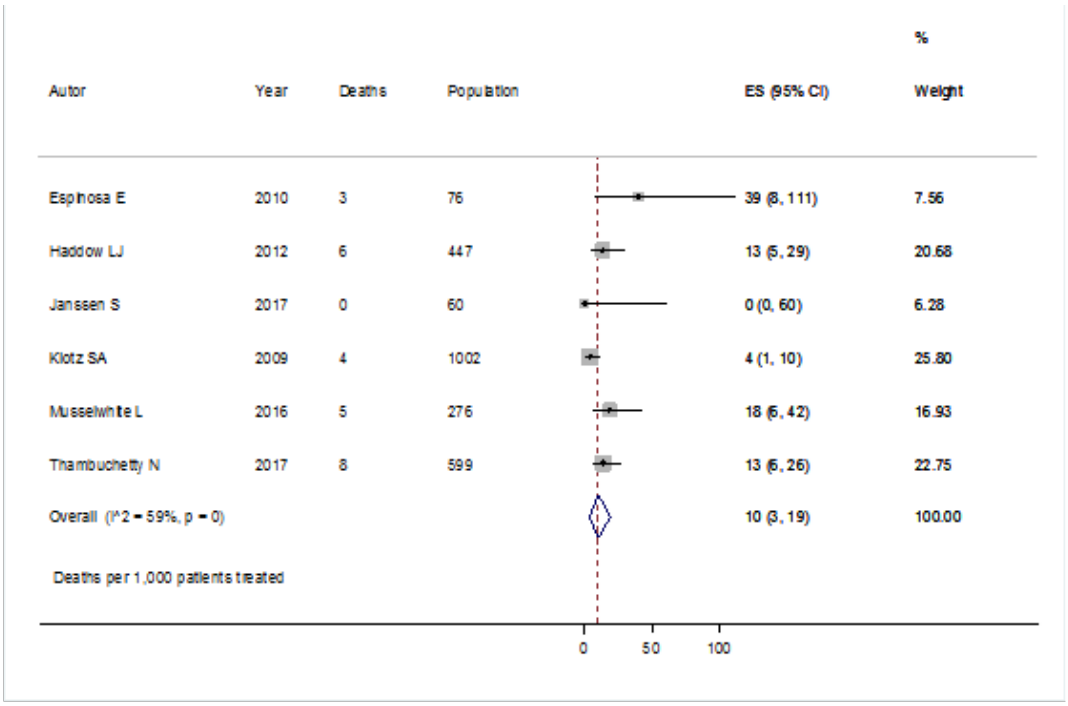
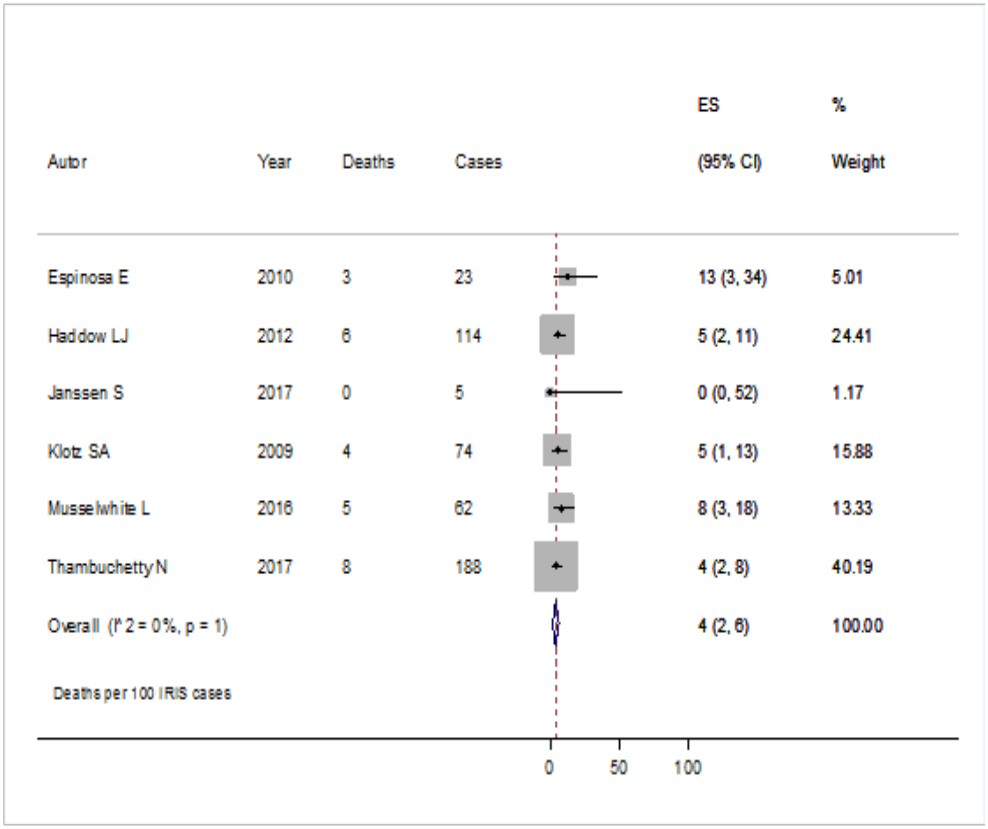


Figure 4. Forest plot for lethality of IRIS



INTRODUCTION

The human immunodeficiency virus (HIV) and the acquired immune deficiency syndrome (AIDS) continue to be a global public health issue. By the end of 2016, 36.7 million adults and children were living with HIV/AIDS, and only in that year, it was transmitted to 1.8 million people (1). The introduction of highly active antiretroviral therapy (HAART) to the United States of America in 1996 and its following popularization in middle and low-income countries from 2003-2005 (2), nevertheless, managed to lower the mortality rates and increase the survival ones in such patients.

The criteria for HAART initiation has changed over the years. In 2006, the World Health Organization (WHO) proposed that it should be initiated in every adolescent and adult with a <200 cells/mm^3 T CD4+ lymphocyte count, independent of WHO clinical stage; considered in patients with a 200-350 cells/mm^3 CD4+ count; and that it should not be initiated if CD4+ count was >350 cells/mm3(3). In 2010, it was recommended to treat all patients with CD4+ counts of ≤350 cells/mm3 irrespective of the WHO clinical stage and in patients with 3-4 WHO clinical stage (4). In 2013, the WHO recommended HAART to be initiated if CD4+ cell count was ≤500 cells/mm3 (5). Finally, in 2015, the WHO stated that it should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count (6).

Nonetheless, many related adverse events have been reported (4). One of them is the Immune Reconstitution Inflammatory Syndrome (IRIS), which is characterized by an inflammatory overreaction towards both infectious (e.g. M. tuberculosis, C. neoformans and Herpes Zoster) and non-infectious antigens (4). It presents in two forms: unmasked and paradoxical. The former is caused by an immune response to a subclinical or latent pre-HAART opportunistic infection (OI), while the latter presents as clinical worsening of an OI for which the patient was being treated before initiation of HAART. This syndrome is associated to a CD4+ count increase and an inflammatory mediator release as a response to HAART. Therefore, such patients present a greater risk of developing complications, followed by an increase in risk of admission, prolonged hospital length of stay and mortality (7).

The incidence and mortality of IRIS have not been defined well, several studies have reported values with great variation between them. Incidence can variate from 10 to 25% for unmasked

IRIS and from 10 to 45% for paradoxical IRIS (8), and mortality, from 3 to 20% for both (9). Even though IRIS cases have been described in such studies, it has not been adequately done as a whole, complex syndrome. Regarding Peru, few studies about incidence of cases have been reported. The two that were found had pediatric patients as study subjects only, none of them were included in this systematic review and meta-analysis (10,11). On the other hand, possibly associated factors (e.g. baseline T CD4+ lymphocyte >100 cells/mm^3) have been found to variate, similarly to incidence and mortality, depending on the settings of the population in study, for instance, socioeconomic context (12).

In spite of its limited efficacy evidence, therapy management with corticosteroids has been associated with clinical improvement and resolution of IRIS. Its use is currently recommended in severe presentations, such as secondary mass effect due to JC virus, Cytomegalovirus vitritis and Kaposi's sarcoma; and infections caused by Mycobacterium avium complex (MAC), Mycobacterium tuberculosis (MTB) and Cryptococcus neoformans (12-16). Moreover, its use is not recommended some infections, such as Hepatitis B or C infections (14).

A previous IRIS systematic review (17) reported a 16.1% (CI 11.1-22.9) incidence and a 4.5% (CI 2.1-8.6) lethality. However, paradoxical IRIS was not distinguished from unmasked for the mentioned etiologies. The importance of this study lies in the fact that, as mentioned before, the findings may vary depending on clinical and population context (12,17), and that new articles about IRIS and evidence concerning HAART initiation have been published in these 7 years since the last systematic review. Thus, this new information was included in a new analysis for an update on IRIS.

The following systematic review and meta-analysis determined the incidence, mortality and lethality of IRIS in HIV-infected patients starting ART, in countries of low, middle, and high income according to country classification by income (CCBI) of the World Bank (18), baseline T CD4+ lymphocyte count, and the year the study was made.

METHODS

Study selection

We included all retrospective and prospective cohort studies (with a minimum of 10 subjects) that unspecifically evaluated IRIS in HIV-infected adults (≥18 years) initiating HAART, with a minimum follow-up of 6 months. Such studies were obtained from original articles, letters to the editor, conferenced abstracts and grey literature. Whenever two or more studies described the same HIV patients on a HAART cohort but at different periods of time, the one with the greater sample size was selected.

Studies that restricted their population to only subjects with previously diagnosed concomitant infections (other than HIV), for which they were already on treatment before starting ART, were excluded as the rate of the inflammatory syndrome would be larger and not representative of the general HIV HAART-naive patients. Similarly, those studies that only reported the rate of IRIS of one organ or system (i.e. ocular, brain, respiratory) or by type of infectious etiology (i.e. cytomegalovirus, mycobacterium tuberculosis) were excluded.

Literature search and selection LILACS, PUBMED, Cochrane Library, SCOPUS and Google Scholar databases were searched using the terms listed in Appendix 1. We used EndNote X7 to create a database of our own with the results and began by eliminating duplicates. Then, we continued to select and filter articles by title and abstract. Those that were selected were read on their full-text version. We discarded each that didn't meet our inclusion criteria (i.e. not HAART-naïve patients, not a cohort, etc.), studied a cohort another article did with a greater sample size and whose authors didn't respond to our e-mails asking on information about their article when it wasn't unavailable online. Second and last, we proceeded to eliminate the remaining ones that were <6 points on the Newcastle-Ottawa scale, as will be explained further below. All tasks were done independently by two of the authors (FAC, DFB), having the third author (CCA) to guide the former two towards a consensus in case of disagreement.

Data extraction

We extracted information from each article to create a table in Microsoft Office Excel 2016, including information about the article [author, year of publication, language, country, CCBI according to World Bank at the moment of publication and IRIS diagnosis criteria (APPENDIX 2)], about the study (start and end of follow-up date, number or participants, ethnic groups, loss of follow-up), about the patients [average age, HAART regimen, baseline T CD4+ lymphocyte count average, viral load average, percentage of patients in AIDS stage, IRIS classification (unmasked and paradoxical)], proportion and lethality of the patients who developed IRIS (incidence of reported IRIS cases until the end of follow-up and how many of them died), information about interventions (corticoid therapy (yes/no), the number of patients who received it, its regimen and number of deaths after it if the article provided with that information). In case of absence of needed data, we proceeded to send an e-mail to the corresponding authors of such articles.

Quality assessment

The evaluation of quality for each study was performed with the Newcastle-Ottawa scale (NOS) for cohort studies (see Appendix 3), which is a 9-point scale with 3 different categories: selection, comparability and outcome. Each category has items of their own: the first has 4 (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study), the second has 1 (comparability of cohorts on the basis of the design or analysis) and the third has 3 (assessment of outcome, length of follow-up enough or not for outcome to occur, adequacy of follow-up of cohorts [defined as <10% loss of follow-up]). We defined "good quality" as a score of ≥6 points over 8, since we excluded the "selection of a non-exposed cohort" item as all studies included HAART-naïve patients.

Statistical analysis

We performed a pooled analysis for proportions based in a binomial distribution and under the random effects model (19). First, we reported the overall analysis for incidence, mortality and lethality and then proceeded with the subgroup assessment by: CCBI, CD4+ baseline count and year of study. We used forest plot graphics and I^2 statistical formula for heterogeneity.

Ethical and other aspects

The protocol of this study was approved by the Ethics Committee of Universidad Peruana de Ciencias Aplicadas on April 25th, 2016 (PI008-16). The protocol was uploaded to Prospero under the code CRD42018084446, available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018084446

RESULTS

The search was made on March 1st, 2016 in databases of LILACS, PUBMED, Cochrane Library, SCOPUS and Google Scholar, followed by an update on PUBMED search up to January 15th, 2018. We identified 48 original articles, of which 11 were eligible for this paper (figure 1).

A total of 8,124 patients were included in the analysis, 2778 were female (34.2%), the mean age was 36 years, and they came from 8 different countries: one study from one high-income country (UK), five studies from 4 upper-middle-income countries (Mexico, South Africa, China and Gabon), three from one lower-middle-income country in common (India) and 2 from low-income countries (Gambia and Ethiopia). Mean baseline count of T CD4+ was 132 cells/mm^3 and mean viral load was 17log10.

Incidence of IRIS was heterogenous and ranged from 38 per 1000 patients (95% CI 31-45) (20) to 314 per 1000 patients (95% CI 277-353) (21), with a pooled rate of 170 per 1000 patients (95% CI; 104-248) (figure 2). It was most common in patients with a T CD4+ baseline count of ≤100 cells/mm3 (21,31,32,34) with 218 per 1000 patients (95% CI 139-309; I^2=76%) and in those who came from high-income countries with an incidence of 221 per 1000 patients (95% CI 165-285), followed by the upper-middle-income group with 218 per 1000 patients (95% CI 156-288%) (table 2). Moreover, it was found that it was more incident in more recent studies with 230‰ (95% CI 179-285).

In the analysis for mortality (figure 3) out of 6 studies that informed their number of deaths due to IRIS, a lower heterogeneity is seen with a global mortality of 10 deaths per 1000 treated patients (95% CI 3-19; I^2=59%). The highest was reported by Espinosa E with 39 deaths per 1000 treated patients, while the lowest was found in Janssen's study with 0 reports of deaths due to IRIS. It was more frequent in patients with a ≤100 cells/mm3 T CD4+ baseline count (15 per 1000 patients, CI 2-39) and who came from middle-income countries (13 per 1000 patients, 95% CI 5-25 and 6-26 for upper-middle and lower-middle-income scenarios, respectively).

Concerning the lethality of IRIS (figure 4), all the studies were homogenous for this outcome and the pooled rate was 4 deaths per 100 IRIS cases (95% CI 2-6; I^2=0%), being the highest 13% (CI

18-29) in Espinosa's study and the lowest, Janssen's with 0% (CI 0-52). Lethality was the same on all CCBI subgroups (4-5%) and it was slightly more common in patients with lower T CD4+ baseline count with 7% (95% CI 2-14) and before 2011 with also 7% (95% CI 2-13).

The subgroup incidence analysis by CCBI shows a majority of upper-middle-income country studies (4/10), in which variable incidences were obtained, being Janssen S the study with the lowest (83 IRIS cases per 1000 treated patients) and Espinosa E (303 cases per 1000 treated patients) the study with the highest, and a global incidence of 215 cases per 1000 treated patients (CI 166-268) for such subgroup. Because of the limited number of studies in both high-income and low-income countries (1 and 2 studies, respectively), whether CCBI can statistically modify IRIS incidence cannot be accurately determined.

Concerning IRIS diagnostic criteria (Appendix 2), out of the 11 selected studies, only 5 of them used established and validated criteria while the lasting 6 used a compendium of different ones. Two of the 4 used Haddow *et al* (30), other two used International Network for the Study of HIV-associated IRIS criteria (INSHI) (17,29) and one used both Shelburne e*t al* (31) and Robertson *et al* (32). About IRIS classification, also four studies classified their events as unmasked or paradoxical, out of 369 events, 92 were unmasked (24.9%) and 118 were paradoxical (40%), the remaining ones weren't categorized.

Eight studies (8,20-25,27) reported starting ART with standard regimen in HIV-patients, receiving nucleoside reverse transcriptase inhibitors (NRTIs) plus non-nucleoside reverse transcriptase inhibitors (NNRTIs). Of these studies, Musselwhite et al (20) selected subjects from CADIRIS Trial (33), receiving 50.6% of total patients (135/267) CCR5 antagonist maraviroc as an adjuvant to standard ART regimen with no significant effect on occurrence of IRIS. Likewise, Espinosa E et al (22) reported 7 patients (9.2%) who received protease inhibitor without ART regimen response analysis.

The studies that took place between 2001 and 2010 (8,22,24-25,27) showed both lower incidence and mortality with 107 IRIS cases and 3 deaths per 1000 treated patients, respectively. Meanwhile, those that took place on 2011 and forward, reported higher rates with 237 IRIS cases and 12 deaths per 1000 treated patients. However, this was different for lethality, since it was higher in the former subgroup (7 deaths per 100 IRIS cases vs. 3 deaths per 100 cases), as mentioned before.

The Newcastle-Ottawa (NCO) scale was used for quality assessment of each study (Appendix 3) with 6 points over 8 as cut-off point, excluding the "selection of a non-exposed cohort" item, since all studies included HAART-naïve patients. Five studies had a score of 6, five had a score of 7 and one study had a score of 8. The main reason for subtracting points was adequacy of follow-up of cohorts (outcome category, item 3). In addition, almost half of studies (20,22,23,26) followed patients for 6 months only, while others did it for longer (≥ 1 year).

DISCUSSION

This systematic review found a high incidence of IRIS (170‰) but shows a significant variability depending on CCBI, year of study and baseline T CD4+ cell count. According to the selected cohorts, incidence can range from 38 per 1000 patients (CI 31-45) (20) to 314 per 1000 patients (CI 277-353) (21). Lethality, on the other hand, was homogenous with a pooled overall rate of 4 deaths per 100 patients (95% CI 2-6; I^2=0%), regardless of subgroups, where the rates were almost the same (table 4).

Concerning baseline T CD4+ cell count, this study coincides with most of the previous IRIS reviews (16,34-35), which report that a low pre-HAART baseline cell count (≤100 cells/mm3) is associated with higher IRIS incidence and mortality, as seen in table 2 and 3. This fact is reflected on the 218‰ (95% CI 139-309; I^2=76%) incidence and 15‰ (95% CI 2-39) mortality in such subgroup vs. the 140‰ (95% CI 66-236; I^2=99%) incidence and 9‰ (95% CI 3-18) mortality on those with >100 cell/mm3 baseline cell count. However, not every study on this systematic review could be included in the meta-analysis for this subgroup owing to the absence of mortality data in 5 studies (8,20,24,26,29).

Regarding the incidence of IRIS by CCBI (country classification by income), although the highest incidence seems to occur in high-income (8) and upper-middle-income scenarios (20,22,23,28) with 221‰ (95%CI 165-285) and 215‰ (95% CI 166-268; I^2=77%), respectively, there is no clear tendency for IRIS to be more incident as the country income improves. This is due to the fact that the study that took place in a high-income country (UK) featured a majority of recent migrants from a lower income setting (eastern/southeastern Africa) as study subjects. Thus, the tendency could be biased. Nonetheless, it is known that higher income countries tend to have better resources for diagnosis and management of diseases compared to their resource-constrained counterparts, where subrreporting and subdiagnosis happen more often.

Furthermore, mortality was higher in middle-income countries with 13‰ (95% CI 5-25 and 6-26). Nevertheless, we must remark that no high-income country studies mentioned their death rates and that the only study coming from a low-income country that did (Klotz), might have had a greater lethality since, according to the authors, a majority of the patients who required

hospitalization for an IRIS event were lost to follow-up. Pooled lethality, on the contrary, was constant in subgroup analysis regardless of loss of follow-up and since it was 4%, it may imply that most of IRIS episodes are either well managed or self-limited regardless of the setting where it occurs.

The multiple IRIS diagnostic criteria (appendix 2) used in some studies (23,25,26,28), and lack of referencing in others represent a significant information bias as some events might have been incorrectly categorized as IRIS, since there is no standardization for this syndrome's diagnosis, which means it depends on clinical consensus criteria of the committee of each study most of the time (17,30-33). Consequently, a possibility to either overestimate or underestimate the proportion of patients who develop IRIS remains, which may have also reflected on the studies heterogeneity for incidence. As mentioned before, only 5/11 studies mentioned the diagnostic criteria they used for IRIS and two pairs used the same: Haddow *et al* (23) and Zaidi *et al* (26) used Haddow e*t al* criteria, and Zaidi I *et al* (28) and Janssen *et al* (29) used INSHI criteria.

The last systematic review and meta-analysis by Muller *et al* in 2010 reported a high incidence of IRIS cases in HAART-naïve patients and a relatively low lethality depending on the severity and self-limitation on the reported cases, the medical management and whether there was or not an adequate follow-up process, etc. This lethality, which was similar to the one in our study, implies that the better representativeness of these patients is found in the incident ones requiring medical attention. Therefore, new studies on determining a consensus for this syndrome's diagnostic criteria and management should be carried out. No other systematic reviews and meta-analyses searching for such outcomes were found.

We acknowledge the fact that as this is a systematic review and meta-analysis, we are prone to the information bias immanent to each study that may have led to an underreport or overreport of IRIS cases. Another factor contributing to this is the lack of consensus for this syndrome's diagnostic criteria, which may have influenced on the heterogeneity for IRIS incidence, as we already mentioned. Thus, the reason why an absolute value for IRIS incidence would not be significative of all HIV-patients. Moreover, since a limited number of studies from both high-income and low-income countries was retrieved, whether CCBI can statistically modify IRIS incidence cannot be accurately determined. This is important over all in the latter setting, where a high incidence of HIV is reported. Therefore, there is a need of more studies in such settings to better define these subgroups' rates.

The main assets of our study rely on the update on previous information, since the last systematic review was published 7 years ago. In addition to this, we estimated the incidence ranges of IRIS in a more precise way since the outcome was evaluated in unselected patients of every setting, rather than only or predominantly in subgroups that may have had a higher probability of developing this syndrome (patients in AIDS stage, patients with opportunistic infections, and other associated pathologies); and also, where IRIS was studied as a whole syndrome with each of its many etiologies instead of studies where a particular one was the outcome of interest. All in all, new, unreported information on IRIS was provided and presented systematically in this article.

In terms of management, we know it is still in ongoing research. Corticoids have been used mostly in severe presentations of IRIS (11-12,14-15). No statistically significant information was obtained in this study seeing that only Musselwhite LW et al (20) specified use of corticoids in a total of 9 patients. Even so, whether this measure had a positive impact on IRIS lethality couldn't be assessed as evaluation of response to such therapy, administered dosage and other data of interest were not specified. Four out of 10 cohorts report a total of 92 admissions to healthcare facilities due to IRIS (23,25-26), being Klotz SA *et al* the ones who held the highest rate as 43% of the admissions in their study were because of this syndrome (74 out of 172) (25). The authors mention that in their experience, specifically in Ethiopia, IRIS was a common cause of admission. In fact, it was the most common cause of hospitalization after initiation of HAART, while treatment of an opportunistic disease was the most common cause prior to it. The high proportion of hospitalizations may be due to the urgency of early treatment of their most common IRIS etiologies: tuberculosis and cryptococcal meningitis. It must be noted, though, that developing IRIS is associated with an increase of risk of hospitalization, sometimes as much as three-fold (36)

According to the Joint United Nations Programme on HIV and AIDS (UNAIDS), it is estimated that US$ 26.2 billion will be required for HIV/AIDS patient care by 2020 (37). However, broad research on costs for IRIS inpatient management hasn't been carried out yet. Despite this fact, it should be noted that the broad diversity of this syndrome's clinical presentations and complications needs a multidisciplinary medical management, for which measures that allow both standardized diagnosis and early management of IRIS should be implemented to decrease IRIS lethality. According to Liu et al, the hospital burden that IRIS implies may decrease over time as early diagnosis and rapid ART onset increases, joined to follow-up and control of HIV-patients, preventing subsequent intercurrences during permanent treatment with ART, reducing morbidity, hospitalizations and costs in HIV-patient care with IRIS (38-39).

Lastly, for this reason as well, we suggest that studies on costs for diagnosis and treatment of IRIS should be made, seeing that HIV patient admissions count for a great part of the expenses on the management and care of these patients as previously mentioned (40). Moreover, it should be considered that the majority of these are due to HAART adverse effects and IRIS (41). It is important that healthcare centers are not only prepared to afford these costs and be correctly implemented for the management of these patients, but to also look for cost-effective measurements to lessen the former.

CONCLUSIONS

We found a high overall IRIS incidence in HIV HAART-naïve patients, higher in those who have a ≤100 cells/mm^3 T CD4+ baseline cell count. Nonetheless, it varies according to studied population and clinical context, which is why one absolute value would not be representative of all HIV patients around the world. Lethality, on the other hand, was homogenous in all studies, which means most of IRIS episodes are either well managed or self-limited regardless of the setting where it occurs.

We emphasize the necessity of standardization for IRIS diagnostic criteria and its use on research and daily practice for efficient and early diagnosis of IRIS. Moreover, we consider further research on costs of diagnosis and management of IRIS should be done so that cost-effective interventions to avoid this phenomenon can take place.

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CONFLICT OF INTEREST

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BIBLIOGRAPHY AND APPENDIX

REFERENCES

1. The Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet – World AIDS day 2017. Geneva: UNAIDS; 2017. Available at: http://www.unaids.org/en/resources/fact-sheet
2. World Health Organization (WHO). Progress on Global Access to HIV Antiretroviral Therapy. A Report on 3 by 5 and Beyond. Geneva: WHO; 2006. Available at: http://www.who.int/hiv/fullreport_en_highres.pdf
3. World Health Organization (WHO). Antiretroviral therapy for HIV infection in adults and adolescents: WHO; 2006. Available at: http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf?ua=1
4. World Health Organization (WHO). Antiretroviral therapy for HIV infection in adults and adolescents Recommendations for a public health approach: WHO; 2010. Available at: http://apps.who.int/iris/bitstream/10665/44379/1/9789241599764_eng.pdf
5. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: WHO; 2013. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1
6. World Health Organization (WHO). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV: WHO; 2015. Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf
7. Kumarasamy N, Chaguturu S, Mayer KH, Solomon S, Yepthomi HT, Balakrishnan P, Flanigan TP. Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. J Acquir Immune Defic Syndr. 2004 Dec 15;37(5):1574-6.
8. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort.Clin Infect Dis. 2006;42:418–27.
9. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clin Infect Dis. 2006 Jun 1;42(11):1639-46.

10. Wang ME, Castillo ME, Montano SM, Zunt JR. Immune Reconstitution Inflammatory Syndrome in Human Immunodeficiency Virus-Infected Children in Peru. The Pediatric infectious disease journal. 2009;28(10):900-903.
11. Miranda-Choque E, Candela-Herrera J, R Segura E, Farfán-Ramos S, Barriga A.[Immune reconstitution syndrome due to BCG in HIV-treated children]. Rev Peru Med Exp Salud Publica. 2012 Oct-Dec;29(4):498- 502.
12. Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). *The Indian Journal of Medical Research*. 2011;134(6):866-877.
13. Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. *AIDS Research and Therapy*. 2007;4:9.
14. Lesho E. Evidence base for using corticosteroids to treat HIV-associated immune reconstitution syndrome. Expert Rev Anti Infect Ther. 2006 Jun;4(3):469-78.
15. Meintjes G, Scriven J, Marais S. Management of the immune reconstitution inflammatory syndrome. Curr HIV/AIDS Rep. 2012 Sep;9(3):238-50.
16. Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV/AIDS (Auckland, NZ)*. 2015;7: 49-64.
17. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M; IeDEA Southern and Central Africa. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010 Apr;10(4):251-61.
18. The World Bank | Country and Lending groups [Internet]. World Bank. [citado el 15 de septiembre de 2015].
19. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014 Nov 10;72(1):39.
20. Musselwhite LW, Andrade BB, Ellenberg SS, Tierney A, Belaunzaran-Zamudio PF, Rupert A, Lederman MM, Sanne I, Sierra Madero JG, Sereti I. Vitamin D, D-dimer, Interferon γ, and sCD14 Levels are Independently Associated with Immune Reconstitution Inflammatory Syndrome: A Prospective, International Study. EBioMedicine. 2016 Jan 14;4:115-23.
21. Thambuchetty N, Mehta K, Arumugam K, Shekarappa UG, Idiculla J, Shet A. The Epidemiology of IRIS in Southern India: An Observational Cohort Study. J Int Assoc Provid AIDS Care. 2017 Sep/Oct;16(5):475-480.

22. Espinosa E, Ormsby CE, Vega-Barrientos RS, Ruiz-Cruz M, Moreno-Coutiño G, Peña-Jiménez A, Peralta-Prado AB, Cantoral-Díaz M, Romero-Rodríguez DP, Reyes-Terán G. Risk factors for immune reconstitution inflammatory syndrome under combination antiretroviral therapy can be aetiology-specific. Int J STD AIDS. 2010 Aug;21(8):573-9.
23. Haddow LJ, Moosa M-YS, Mosam A, Moodley P, Parboosing R, Easterbrook PJ. Incidence, Clinical Spectrum, Risk Factors and Impact of HIV-Associated Immune Reconstitution Inflammatory Syndrome in South Africa. Ahuja SK, ed. PLoS ONE. 2012;7(11):e40623.
24. Kumarasamy N, Venkatesh KK, Cecelia AJ, et al. Gender-Based Differences in Treatment and Outcome among HIV Patients in South India. Journal of Women's Health. 2008;17(9):1471-1475.
25. Klotz SA, Aziz Mohammed A, Girmai Woldemichael M, Worku Mitku M, Handrich M. Immune reconstitution inflammatory syndrome in a resource-poor setting. J Int Assoc Physicians AIDS Care (Chic). 2009 Mar-Apr;8(2):122-7.
26. Zaidi I, Peterson K, Jeffries D, Whittle H, de Silva T, Rowland-Jones S, Jaye A, de Jong BC. Immune reconstitution inflammatory syndrome and the influence of T regulatory cells: a cohort study in The Gambia. PLoS One. 2012;7(6):e39213.
27. Kumarasamy N, Venkatesh KK, Cecelia AJ, Devaleenal B, Lai AR, Saghayam S, Balakrishnan P, Yepthomi T, Poongulali S, Flanigan TP, Solomon S, Mayer KH. Spectrum of adverse events after generic HAART in southern Indian HIV-infected patients. AIDS Patient Care STDS. 2008 Apr;22(4):337-44.
28. Janssen S, Osbak K, Holman R, Hermans S, Moekotte A, Knap M, Rossatanga E, Massinga-Loembe M, Alabi A, Adegnika A, Meenken C, van Vugt M, Kremsner PG, Meintjes G, van der Poll T, Grobusch MP. Low incidence of the immune reconstitution inflammatory syndrome among HIV-infected patients starting antiretroviral therapy in Gabon: a prospective cohort study. Infection. 2017 Oct;45(5):669-676.
29. Zheng Y, Zhou H, He Y, Chen Z, He B, He M. The Immune Pathogenesis of Immune Reconstitution Inflammatory Syndrome Associated with Highly Active Antiretroviral Therapy in AIDS. *AIDS Research and Human Retroviruses*. 2014;30(12):1197-1202.
30. Haddow LJ, Easterbrook PJ, Mosam A, Khanyile NG, Parboosing R, Moodley P, Moosa MY. Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion versus 2 case definitions in a South African cohort. Clin Infect Dis. 2009 Nov 1;49 (9):1424-32.

31. Shelburne S, Montes M, Hamill R. Immune reconstitution inflammatory syndrome: more answers more questions. J Antimicrob Chemother. 2006;57:167-170.
32. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clin Inf Dis. 2006;42:1639-1646.
33. Sierra-Madero JG, Ellenberg SS, Rassool MS, Tierney A, Belaunzarán-Zamudio PF, López-Martínez A, Piñeirúa-Menéndez A, Montaner LJ, Azzoni L, Benítez CR, Sereti I, Andrade-Villanueva J, Mosqueda-Gómez JL, Rodriguez B, Sanne I, Lederman MM; CADIRIS study team. Effect of the CCR5 antagonist maraviroc on the occurrence of immune reconstitution inflammatory syndrome in HIV (CADIRIS): a double-blind, randomised, placebo-controlled trial. Lancet HIV. 2014 Nov;1(2):e60-7.
34. Grant PM, Komarow L, Andersen J, et al. Risk Factor Analyses for Immune Reconstitution Inflammatory Syndrome in a Randomized Study of Early vs. Deferred ART during an Opportunistic Infection. Grinsztejn B, ed. *PLoS ONE*. 2010;5(7).
35. Breton G, Duval X, Estellat C, Poaletti X, Bonnet D, Mvondo Mvondo D, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 2004; 39:1709–1712.
36. Hoyo-Ulloa I, Belaunzarán-Zamudio PF, Crabtree-Ramirez B, Galindo-Fraga A, Pérez-Aguinaga ME, Sierra-Madero JG. Impact of the immune reconstitution inflammatory syndrome (IRIS) on mortality and morbidity in HIV-infected patients in Mexico. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases*. 2011;15(6):e408-e414.
37. Joint United Nations Programme on HIV and AIDS (UNAIDS). HIV/AIDS [fact sheet 2015]. UNAIDS; 2015. Available at: http://www.unaids.org/sites/default/files/media_asset/20150901_FactSheet_2015_en.pd
38. Liu P, Dillingham R, McManus K. Hospital days attributable to immune reconstitution inflammatory syndrome in persons living with HIV before and after the 2012 DHHS HIV guidelines. *AIDS Research and Therapy*. 2017;14:25.
39. Meyer-Rath G, Brennan AT, Fox MP, Modisenyane T, Tshabangu N, Mohapi L, Rosen S, Martinson N. Rates and cost of hospitalization before and after initiation of antiretroviral therapy in urban and rural settings in South Africa. J Acquir Immune Defic Syndr. 2013 Mar 1;62(3):322-328.

40. Levy A, James D, Johnston K, Hogg R, Harrigan P, Harrigan B, Sobolev B, Montaner J. Direct costs of HIV/AIDS Care. Lancet Infect Dis. 2006;6:171–177.
41. de Cherif TK, Schoeman JH, Cleary S, Meintjes GA, Rebe K, Maartens G. Early severe morbidity and resource utilization in South African adults on antiretroviral therapy. BMC Infect Dis. 2009 Dec 15;9:205.

APPENDIX 1: Supplementary files

Search method according to biomedical database.

DATABASE	SEARCH TERMS
PUBMED/ Cochrane Library	((((((((((((antiretroviral agents[MeSH Terms]) OR highly active antiretroviral therapy[MeSH Terms]) OR zidovudine[MeSH Terms]) OR inhibitors, reverse transcriptase[MeSH Terms]) OR nevirapine[MeSH Terms]) OR efavirenz[MeSH Terms]) OR haart[Title/Abstract]) OR ((antiretroviral[Title/Abstract]) AND therapy[Title/Abstract]))) OR (((((((hiv[MeSH Terms]) OR AIDS[MeSH Terms]) OR acquired immune deficiency syndrome[MeSH Terms]) OR acquired immune deficiency syndrome virus[MeSH Terms]) OR HIV[Title/Abstract]) OR AIDS[Title/Abstract]) OR (((acquired[Title/Abstract]) AND immune[Title/Abstract]) AND deficiency[Title/Abstract])))) AND (((immune reconstitution inflammatory syndrome[MeSH Terms]) OR IRIS[Title/Abstract]) OR (((immune[Title/Abstract]) AND ((reconstitution[Title/Abstract]) OR restoration[Title/Abstract])) AND ((disease[Title/Abstract]) OR syndrome[Title/Abstract])))) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms])
SCOPUS	(TITLE-ABS-KEY (iris) OR TITLE-ABS-KEY ("reconstitution syndrome") OR TITLE-ABS-KEY ("restoration syndrome")) AND ((TITLE-ABS-KEY (hiv) OR TITLE-ABS-KEY (aids) OR TITLE-ABS-KEY ("acquired immune deficiency")) OR (TITLE-ABS-KEY (haart) OR TITLE-ABS-KEY ("antiretroviral therapy") OR TITLE-ABS-KEY ("antiretroviral agents") OR TITLE-ABS-KEY (nevirapine) OR TITLE-ABS-KEY (zidovudine) OR TITLE-ABS-KEY ("reverse transcriptasa")))
LILACS	“Reconstitucion inmune” and (TARGA or VIH)
Scholar	"Immune reconstitution inflammatory syndrome" AND "incidence" AND "cohort" AND "haart" AND "hiv" AND "ART" OR "antiretroviral therapy" OR "antiretroviral agents" AND "reverse transcriptase" AND naive -animals

APPENDIX 2: IRIS DIAGNOSTIC CRITERIA

1) International Network for the Study of HIV-associated IRIS (INSHI) (17)

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

Antecedents

- TB-diagnosis according to WHO guidelines before starting ART
- TB should have stabilized or improved before starting ART

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

Exclusion of alternative cause

- Failure of TB treatment (non-compliance or resistance)
- Other opportunistic infection or neoplasm
- Drug toxicity reaction

2) Haddow et al (30)

Case definition 1

Major criteria

A) Atypical presentation of opportunistic infections of tumors in patients responding to ART, including

- Localized disease (eg. Lymph nodes, liver, or spleen)
- Exaggerated inflammatory reaction (eg. Severe fever or painful lesions)

- Atypical inflammatory response (eg. Granulomas, suppuration, necrosis, or perivascular lymphocytic inflammatory cell infiltrate)

- Progression of organ dysfunction or enlargement of preexisting lesions after definite clinical improvement with pathogen-specific therapy prior to ART and exclusion of treatment toxicity and new diagnoses

B) Decrease in viral load (VL) >1 log $_{10}$ copies/mL

Minor criteria

A) Increased CD4+ cell count

B) Increase in an immune response specific to the relevant pathogen (eg. Delayed-type hypersensibility [DTH] response to mycobacterial antigens)

C) Spontaneous resolution of disase without speecific antimicrobial thrapy or tumor chemotherapy with continuation of ART

Case definition 2

A) New onset of worsening symptoms of an infection or inflammatory condition after start of ART

B) Symptoms not explained by

- Newly acquired infection

- Predicted course of previously diagnosed infection

- Adverse effects of drug therapy

C) Decrease in VL >1 $\log_{10}$ copies/mL

Note: Must have both major A and B, or both major criterion A and any 2 minor criteria. Must meet all of the criteria.

3) Shelburne et al (31)

Criteria for IRIS diagnosis include:

1. HIV-infected patient

2. Receiving effective ART as evidenced by a decrease in HIV-1 RNA concentration from baseline or an increase in CD4+ T cells from baseline (may lag behind HIV-1 RNA decrease)

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 infection, or drug toxicity

4) Robertson et al (32)

Required criterion

a) Worsening symtoms of inflammation/infection

b) Temporal relationship with starting antiretroviral treatment

c) Symptoms not explained by newly acquired infection of disease or the usual course of a previously acquired disease

d) $\geq 1 \log_{10}$ disease in plasma HIV load

Supportive criterion

a) Increase in CD4+ cell count of ≥ 25 cells/mm^3

b) Biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory disease.

APPENDIX 3 : COHORT QUALITY ASSESSMENT WITH NEWCASTLE-OTTAWA SCALE

Cohorts Criteria	Ratnam I, 2006	Zaidi I, 2012	Haddow LJ, 2012	Klotz SA, 2009	Janssen S, 2017	Espinosa E, 2010	Kumarasamy N, 2008 (a)	Musselwhite L, 2016	Kumarasamy N, 2008 (b)	Zheng Y (2014)	Thambuchetty N, 2017
Representativeness of the exposed cohort	★	-	★	★	★	★	★	★	★	★	★
Ascertainment of Exposure	★	-	★	★	★	★	★	★	★	★	★
Demonstration that outcome of interest was not present at start of study	★	★	★	★	★	★	★	★	★	★	★
The study controls for age and sex	★	★	★	-	★	★	★	★	★	-	★
The study controls for at least 3 other factors	★	★	★	-	★	★	★	★	-	-	★
Assessment of Outcome	-	★	★	★	★	★	-	★	★	★	★
Was follow-up long enough for outcomes to occur?	★	★	★	★	★	★	★	★	★	★	★
Adequacy of follow-up of cohorts	-	★	★	★	-	-	★	-	-	★	-
OVERALL SCORE	6/8	6/8	8/8	6/8	7/8	7/8	7/8	7/8	6/8	6/8	7/8