Incidence and impact of immune reconstitution inflammatory response syndrome associated with tuberculosis regarding the initiation of antiretroviral treatment during antituberculosis therapy in adult patients co-infected with tuberculosis and HIV: A systematic review

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ABSTRACT

Antiretroviral therapy (ART) is a fundamental key in the fight against HIV, it allows the patient to have a prolonged and high quality life, however in coinfection with opportunistic diseases such as tuberculosis, the initiation of ART can generate a greater risk of immune reconstitution inflammatory syndrome when associated with antituberculosis treatment, generating an exacerbated inflammatory response in tissues rich in Mycobacterium tuberculosis, characterized by the clinical worsening of the patient. The picture ranges from mild and self-limited symptoms to more severe effects and even death.Objectives: This systematic review aims to describe and evaluate the impact, incidence, severity and morbidity of immune reconstitution syndrome (IRRS) on the condition of HIV-positive patients, taking into account the time of ART initiation during antituberculosis treatment. Material and methods: Randomized clinical studies, case-control studies, prospective and retrospective cohorts of the last 11 years, in english, spanish and portuguese idioms, obtained from search bases such as PubMed, Cochrane, Embase, performed in adult humans co-infected with mycobacterium tuberculosis and human immunodeficiency virus (HIV) were evaluated. Results: A total of 22 scientific articles were selected and analyzed, 8 of which report that early, immediate and integrated ART of HIV in patients co-infected with TB improved survival despite the higher incidence of TB-SIRI, on the other hand 5 clinical studies affirm that integrated ART generated severe clinical pictures of SIRI-TB and increased mortality, however 5 studies observed that it is more beneficial to initiate ART at any time of anti-tuberculosis treatment, than not to initiate it. Conclusion:our analysis considers it necessary to implement antiretroviral treatment (ART) early in patients coinfected with HIV and TB regardless of the CD4 + cell / mm count, despite the risk of developing another complication such as LRTI associated with TB, taking into account the adequate management of prevention with the corresponding treatment of the opportunistic infection that precedes it, as well as the early diagnosis of LRTI-TB and its consequent treatment, which is not addressed in this review

KEYWORDS

Immune Reconstitution Syndrome, Tuberculosis-HIV coinfection, Antiretroviral therapy, Tuberculosis and AIDS-related opportunistic infections, Tuberculosis

Incidencia e impacto del síndrome de respuesta inflamatoria de reconstitución inmune asociado con tuberculosis con respecto al inicio del tratamiento antirretroviral durante la terapia antituberculosa en pacientes adultos coinfectados con tuberculosis y VIH: una revisión sistemática

RESUMEN

La terapia antirretroviral (ART) es clave fundamental para la lucha contra el VIH, permite que el paciente prolongue su vida con mejoría de la calidad de la misma. Sin embargo, en coinfección con enfermedades oportunistas como la tuberculosis, el inicio del TAR puede generar un mayor riesgo de presentar síndrome Inflamatorio de reconstitución inmune cuando se asocia a tratamiento antituberculoso generando una respuesta inflamatoria exacerbada en tejidos ricos en Mycobacterium Tuberculosis caracterizada por el empeoramiento clínico del paciente.

El cuadro muestra desde síntomas leves y autolimitados hasta efectos más graves e incluso la muerte. Objetivos: Esta revisión sistemática tiene como objetivo describir y evaluar el impacto, incidencia, gravedad y morbilidad que genera el Síndrome de Reconstitución Inmunitaria (SIRI) sobre la condición del paciente VIH positivo, teniendo en cuenta el momento de inicio del TAR durante el tratamiento antituberculoso.

Material y métodos: Se evaluaron ensayos clínicos aleatorizados, estudios de casos y controles, cohortes prospectivas y retrospectivas de los últimos 11 años, en idioma inglés, español y portugués obtenidos de bases de datos de búsqueda como Pubmed, Cochrane, Embase, realizados en humanos adultos coinfectados con mycobacteryum tuberculosis. y virus de inmunodeficiencia humana (VIH).

Resultados: Se seleccionaron y analizaron un total de 22 artículos científicos, 8 de los cuales informan que inicialmente, el TAR en pacientes HIV coinfectados con TB mejoró la supervivencia a pesar de la mayor incidencia de TB-SIRI. Por otro lado 5 estudios clínicos muestran que el TAR integrado generó cuadros clínicos graves de IBS-TB y aumento de la mortalidad. Sin embargo, 5 estudios mostraron que es más beneficioso iniciar el TAR en cualquier momento del tratamiento antituberculoso que no iniciarlo.

Conclusión: Nuestro análisis considera necesario implementar el tratamiento antirretroviral (TAR) precozmente en los pacientes coinfectados por VIH y TB independientemente del recuento de CD4 + / mm a pesar del riesgo de desarrollar otra complicación como el SIRI asociado a la TB, teniendo en cuenta la manejo adecuado de la prevención con el correspondiente tratamiento de la infección oportunista que la precede, así como el diagnóstico precoz de IRIS-TB y su consecuente tratamiento, que no se aborda en esta revisión.

PALABRAS CLAVE

Immune Reconstitution Syndrome, Tuberculosis-HIV coinfection, Antiretroviral therapy, Tuberculosis and AIDS-related opportunistic infections, Tuberculosis

INTRODUCTION

Over the years and with the advancement of science, it has been possible to find effective treatments to reduce the mortality and complications of Tuberculosis (TB) and Acquired Immune Deficiency Syndrome (AIDS), however, the concomitance of both pathologies demands the need to associate treatments with the consequence of a complication: immune reconstitution inflammatory syndrome (IRIS) associated with TB. The immunopathogenesis of IRIS remains only partially understood. Qualitative and quantitative reconstitution of the immune system, host genetic susceptibility and mycobacterial load are supposedly involved in the pathogenesis of IRIS.

The role of the amount of mycobacteria in the pathogenesis is suggested by several observations. In patients with disseminated or extrapulmonary tuberculosis the increased risk of IRIS is attributed to a higher bacillary load. In HIV positive patients, the risk of IRIS is highest if the antiretroviral therapy is iniciated early during antimycobacterial treatment, when the mycobacterial load is considerable, as shown in trials trying to establish the correct time of ART initiation.

The hasty killing of mycobacteria by anti-TB therapy may determine the release of large amounts of mycobacterial antigens, which can stimulate an excessive inflammatory response.

A prospective study recently showed a correlation between sputum culture (indicating high antigenic load) and inflammatory monocyte activation markers (strongly predictive of development of paradoxical TB-IRIS) suggesting that high antigen loads and inflammation may act together in the pathogenesis. However host inflammatory responses (with the release of proinflammatory cytokines) may be stronger determinants of IRIS pathogenesis than mycobacterial factors. Other studies also indicate that immune reconstitution is involved in the pathogenesis of IRIS, and in particular the reconstitution of T helper 1 CD4+ immune responses, as shown by the conversion of tuberculin skin tests to positive after treatment start. ART initiation has been associated with a shift from T helper 2 to T helper 1 cytokine patterns, and with the restoration of T lymphocyte proliferative responses.

In conclusion, the immunopathogenesis of IRIS in both HIV infected and uninfected patients appears to involve T helper 1 driven immune responses in the presence of multibacillary disease and immunodeficiency. (1) Looking for the best time to start antiretroviral therapy (ART) in these patients, several large clinical trials such as CAMELIA (early versus late introduction of antiretroviral drugs in Cambodia(3),-SAPiT and ACTG 5221 (AIDS clinical trial group 5221), determined the optimal delay between the initiation of antituberculous treatment and ART (4).

A study with meta-analysis confirmed that early ART initiation was associated with a higher incidence of IRIS-TB compared with late initiation, regardless of CD4 + T cell count. (5),while some more recent studies have shown high incidence rates of TB-IRIS (19-57%) in adult patients with low CD4 + counts (<50 cells / mm3) (6)and that the early initiation of ART in patients with these low counts would be associated with a decrease in mortality (4)

On the other hand, the World Health Organization (WHO) recommends starting ART early regardless of the amount of CD4 + T cells (within the first 2 weeks in those with CD4 + <50cells / mm3), while a trial Randomized, placebo-controlled study conducted between January 1, 2008 and April 31, 2013 refuted that statement by recommending that the initiation of ART be delayed for up to 6 months after completing the treatment regimen.

tuberculosis in those who have CD4 cell counts above 220 cells / mm3 and it was shown that the incidence of IRIS-TB did not increase in this group, this could be explained by the high CD4 + T cell count(6).

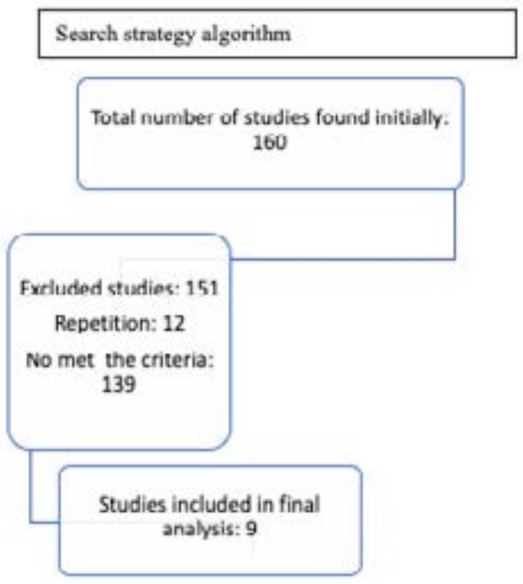
Thus, patients with low levels of CD4 + T cells who start ART early benefit from the decrease in mortality, but are more likely to suffer IRIS-TB, taking into account that the level of mortality associated with this complication is low, In this systematic review, we hypothesized that starting ART early would not generate a greater negative impact with respect to IRIS-TB in the patient regardless of the number of CD4 + T cells at the time of initiation of treatment.

MATERIALS AND METHODS

The present study is a systematic review made with searches on digital platforms, in English, Spanish and Portuguese idioms. The following Mesh terms were consulted: “Inflamatory immune reconstitution syndrome “,” tuberculosis “,” HIV-1 infection”, “ acquired immunodeficiency syndrome ”in three different

databases: PUBMED, EMBASE, and COCHRANE. Inclusion criteria: Clinical studies, randomized controlled trials, case-control studies, prospective and retrospective cohorts of the last 11 years in English, Spanish and Portuguese idioms, were selected that describe HIV-positive adult patients co-infected with TB and with confirmed or probable Immune Reconstitution Inflammatory Syndrome (IRIS) and who They were assigned to an early ART initiation group, a late ART initiation group, or a delayed initiation group during TB treatment, regardless of any combination of ART and TB drugs used. Exclusion criteria: Those HIV + patients with more than one coinfection in addition to TB, those with Extra pulmonary TB, patients with comorbidities that reflect a poor prognosis such as: uncontrolled autoimmune diseases, long-standing cancer patients, and patients with terminal illnesses or poor prognosis were excluded from this study.

The selected studies should report the clinical effects of IRIS in the different groups of patients taking into account: the initiation of ART and the number of CD4 + T cells of the patient at the time of initiation of ART. In addition, the median time from the start of antiretroviral therapy to the development of IRIS, among others.



RESULTS

Early, immediate and integrated HIV ART in TB co-infected patients improved survival despite the higher incidence of TB-IRIS

Some studies selected for this systematic review justify the integrated, early and / or immediate implementation of ART in HIV-positive patients co-infected with tuberculosis. (7), (8), (3), (9), (10), (11), (12), (13) (table 1), conclude that, although the incidence is higher compared to the late / sequential and / or delayed initiation of ART, the survival and quality of life benefits are more relevant, especially for patients with CD4 + counts <50 cells/ mm 3.

A randomized trial of earlier ART (within 2 weeks of initiation of TB treatment) versus subsequent ART (8-12 weeks after TB treatment) found IRIS TB to be mild (no hospitalization / procedures / steroids) in 27.9%, moderate (use of cortico-steroids / invasive procedure) in 41.0% and severe in 31.1% (hospitalization / death). There were no deaths associated with TB IRIS (12).According to a randomized clinical study, shortening the delay between the start of tuberculosis treatment and the start of ART to 2 weeks was associated with an increased risk of developing TB-IRIS. However, this event was easily manageable, therefore the fear of IRIS-TB should not be an impediment to early ART in adults with advanced immunodeficiency in high burden settings and with limited resources.(13).

The integrated ART of TB and HIV generated severe clinical pictures of IRIS-TB and increased mortality. Several studies, including randomized controlled trials, prospective observational studies, and retrospective cohort studies, concluded that the early initiation of ART in patients coinfected with HIV and TB generated a higher risk of severe clinical symptoms of IRIS-TB and the consequent increase in mortality. (14), (15), (16), (17), (18).

In a secondary analysis of the SAPiT trial, IRIS was evaluated in patients randomized to start ART in three groups, the incidence of IRIS-TB was higher in early ART initiation, specifically in patients with CD4 + <50 cells /mm 3(table 2). SIRI cases in the early integrated treatment group were more severe (34.9% versus 18.9%); had significantly higher hospitalization rates (18/43 vs. at 5/37) and longer resolution time (70.5 vs 29.0 days) compared to IRIS cases in the other two arms (14).A randomized trial conducted in Mozambique concluded that the appearance of IRIS-TB within 12 weeks after initiating ART was associated with patient mortality at 48 weeks later. Was included573 coinfected patients, with a median CD4 count of 92 cells / mm 3 and a median time to start anti-TB treatment and ART of 4.9 weeks, where 9.2% of patients had IRIS-TB in the 12 weeks after ART initiation and mortality at week 48 was 6.1%.(15).

A multicenter study conducted in the city of Dar es Salaam, Tanzania reported that the risk of mortality for TB / HIV coinfected patients was lowest when ART was started after 14 days of anti-TB treatment and highest when ART started 90 days or less before TB therapy and within the first 14 days of TB therapy. It recommended delaying the start of ART until the third week of anti-TB treatment for coinfected patients without previous treatment.(16).In the Central Hospital of Yaoundé, Cameroon, they conducted a prospective study that resulted in 49 deaths in the intensive initiation phase (early death), thus lThe incidence of mortality during this phase of TB treatment was high, however; it was not possible to determine how many patients had IRIS-related mortality. (17)A retrospective cohort study in Cape Town analyzed 60,482 HIV-positive TB patients, of whom 19.4% were on ART at the start of TB treatment, while 80.6% were not. Survival per year for

Patients receiving ART at the start of TB treatment was not much different over the 5-year period, but for patients who did not receive ART at the start of TB treatment, the year-over-year improvement in survival was significant. (18)

The absence of ART and a delayed therapeutic regimen increases the risk of death in HIV-positive patients coinfected with Regardless of the time of initiation of ART in patients coinfected with HIV and TB, several studies have shown that it is more beneficial, with respect to mortality, to include an integrated plan in the therapeutic treatment than not to include it. A An observational cohort study in Rio de Janeiro, Brazil compared the survival of HIV patients coinfected with TB who received simultaneous ART ST (up to 60 days after TB diagnosis) vs Deferred DT (> 60 and <360 days). Of the 437 patients included, 13% died during follow-up: 10% in the TS patients and 16% in the DT group. This study concluded that delaying treatment on a delayed ART regimen increased the risk of death by 45%.(19)

A retrospective cohort analyzed 337 HIV-TB co-infected patients with CD4 + T cells by above 350 cells / mm3, of these 76% started ART during TB treatment and 24% never started ART. The risk of

Death among ART patients was reduced by 78% compared to patients who did not receive ART. (20)

On the other hand, in South Africa, 797 patients were retrospectively analyzed, 42.5% received ART while 17.7% did not receive ART and it was associated with a higher mortality and rate of therapeutic non-compliance. (21)

In Botswana, 300 patients coinfected with HIV-TB were retrospectively studied, they concluded that those who did not use ART during tuberculosis treatment were more likely to die in the first 2 months. There were 45 deaths (45/300; 15%) during the study period, 14% made up of those who had received ART for ≥3 months at the time of TB diagnosis, meanwhile 10% of the patients who had recently started ART (had TB within 3 months of starting ART or had started ART after TB treatment) and those who had no ART experience during TB treatment accounted for 35% of death. (22)

A recent study in 2020 retrospectively analyzed 292 patients and divided them into two groups: patients who experienced TB-IRIS and those with uncomplicated immune recovery (group without IRIS). IRIS-TB occurred in 28% of the participants and of them 20.7% obtained an unfavorable response to anti-TB treatment, while in the group without IRIS only 13.3% obtained unfavorable responses. (23)

TABLE 1. EARLY, IMMEDIATE AND INTEGRATED TREATMENT OF TB AND HIV IMPROVED PATIENT SURVIVAL DESPITE THE HIGHER INCIDENCE OF TB-IRIS

Type of study - Year of publication	No. of patients	SIRI- TBC incidence		SIRI-TB mortality		CD4 +	Median time from ART initiation to SIRI-TB	
		TAR IT	TAR TDS	TAR IT	TAR TDS		TAR IT	TAR TDS
ECA -2010 (6)	642	12.4%	3.8%	-	-	<500 mm 3	Does not describe	
Open EA -2011 (7)	806	eleven%	5%	-	-	<250 / mm 3	4.6 weeks	11.7sem.
ECA-2011 (2)	429	20.2%	7.7%	-	-	150 / mm 3	15 days	15.5 days
Prospective-2011 (8)	661	16.6%	6.8%	6	-	<200 / mm 3	14 days	16 days
Prospective-2014 (9)	229	36.8%	19.5%	-	5	-	10 days	10 days
Retrospective-2020 (10)	275	-	-	14	35	66 / mm 3	-	-
ECA 2014 -A5221 (11)	806	10.4%	4.7%	-	-	> and <50 mm 3	29 days	82 days
ECA- 2013 (12)	597	36%	16%	6	-	<200 / mm	14 days	14 days

*TAR. IT =EARLY / IMMEDIATE INTEGRATED ANTIRETROVIRAL TREATMENT *TAR TD S = DELAYED, DELAYED, OR SEQUENTIAL ANTIRETROVIRAL TREATMENT
*ECA = RANDOMIZED CONTROLLED TRIAL, * EA OPEN = OPEN RANDOMIZED TRIAL

TABLE 2

642 PATIENTS	Early ART	Late TAR	Sequential ART
<50 CD4 + / mm 3	19.5%	7.5%	8.1%
> 50 CD4 + / mm 3	34.9%	22.2%	15.8%
Median time	17.5 days	17 days	28 days

* EARLY ART = ART WITHIN THE FIRST 4 WEEKS OF THE START OF ANTI-TB TREATMENT, * LATE ART = 4 WEEKS AFTER THE INTENSIVE PHASE OF ANTI-TB TREATMENT, * SEQUENTIAL ART = 4 WEEKS AFTER THE END OF ANTI-TB TREATMENT, * THE MEDIAN TIME = SIRI SINCE THE START OF ART IN DAYS

The data available of this review does not allow to perform a metaanálisis.

DISCUSSION

The need arises to evaluate the impact generated by IRIS in the patient coinfected with HIV and TB with respect to the time of initiation of ART, taking into account that it is considered one of the risk factors for its appearance.

Although it is true that a delay in the initiation of ART delays the events of TB-IRIS, it is nevertheless associated with clinical deterioration and in few cases catastrophic prognosis. Thus, the therapeutic conduct for these patients is the subject of intense debate.

Some more recent studies from 2016(20), 2019 (22) and 2020 (15) respectively, they suggest that starting antiretroviral treatment (ART) in all TB coinfected patients regardless of the time of onset, is more beneficial in terms of quality of life and clinical prognosis vs not starting any ART. However, several studies support the early initiation of ART with respect to anti-TB treatment, especially in patients with CD4 + counts <50 cells / mm because they resulted in optimal survival rates.(5), (7).Meanwhile, some studies recommend starting ART later than anti-TB treatment, especially in patients with higher CD4 + counts.

A recent systematic review published in 2018 concludes that the IRIS-TB causes significant morbidity in resource-limited settings and the risk of mortality may be underestimated (3. 4), In this study we consider that although IRIS-TB contributes to increasing the risk of mortality in patients coinfected with HIV and TB - as well as other intercurrences generated by the same advance of the disease -, each specialist doctor in charge of these complex cases You must know in depth the clinical condition of your patients, from the associated comorbidities to the way to evolve and respond to previous treatments, in a way that allows you to make the best possible decision taking into account that they are highly trained to handle these cases. .

That said, it is necessary to highlight that few studies were found in this regard carried out in Latin America, which is why we found limitations in the issuance of our judgment and it prevents us from generalizing. However, it was found a “real life” evaluation carried out in Latin America in 2016, in which they analyzed the management of HIV positive patients from Argentina, Brazil, Honduras and Mexico co-infected with opportunistic infections (OI),determined that the factors associated with initiating ART within 4 weeks of OI diagnosis was a lower CD4 count, however, patients diagnosed with TB were less likely to start early ART than patients diagnosed with other IO. (25) Although the time from diagnosis of an OI to the initiation of ART has decreased in recent years, the results of the previous study briefly show the possible therapeutic intervention and the limitations that still exist in this part of the globe, the reason for this is not clear. ART delay in these patients, but we infer that it happens due to the fear of a high mortality rate that IRIS supposes, lack of experience in this regard in hospital services, low budget, so they prefer to prioritize patients with more probable survival, among others possible reasons. The recommendation of another study conducted in South Africa indicates that, To reduce the probability of IRIS due to opportunistic infections (OI), it is necessary to optimize OI treatment before ART and at the time of ART, thus a shorter duration of OI / TB therapy before ART was SIRI-TB predictive (26).

It is necessary to know how to prevent the serious effects of IRIS-TB while considering the inclusion of early ART during TB treatment, since starting ART late or delayed entails higher rates of non-adherence and losses during follow-up(27),which could also explain the increase in associated mortality.

On the other hand, an early diagnosis could avoid unfavorable outcomes for these patients, so in 2019 a pilot study of metabolic profile suggests a tool for early diagnosis of IRIS-TB, stating that arachidonic acid metabolism, sphingolipid glycerophospholipids and linoleic acid were the most affected pathways during the SIRI –TB window (29).Betting on the same concept of prevention and early diagnosis, a genetic study published in 2020 reveals markers associated with TB, HIV and IRIS, they indicatethat these patients carry the KIR2DS2 gene, the HLA-B * 41 allele, the KIR2DS1 + HLA- pair; and they do not carry the KIR2DL3 + HLA-C1 / pair, and the KIR2DL1 + HLA-C1 / C2 pair(29),It is evident that in day-to-day professional practice it is little possible and even of little use to put this last tool into practice due to the time and expense involved. However, it is not a minor fact to take into account that helps to broaden the panorama and change the concept of “avoiding integrated ART to avoid IRIS-TB” to “I consider more options to prevent, diagnose and treat complications such as IRIS -TB during the integrated treatment of ART and TB ”.

In conclusion, despite the limitations found in the present review, our analysis considers it necessary to implement antiretroviral treatment (ART) from early in patients coinfected with HIV and TB regardless of the CD4+ cell count/mm3. This despite the risk of developing another complication such as IRIS associated with TB and also taking into account the clinical status of the patient.

Proper management of preventive measures must be carried out, with the corresponding treatment of the opportunistic infection that precedes it, as well as, the early diagnosis of IRIS-TB and its consequent treatment

Which is not addressed in this review.

CONFLICTS OF INTEREST

The authors declare not to have any interest conflicts.

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