Therapeutic effectiveness on early and delayed treatment of antiretroviral in TB-HIV patients: a literature review

Dian Natasya Rahardjo1,2, Stefannie Sherine Santoso2, Retnosari Andrajati1, Ratu Ayu Dewi Sartika3, Mariana Wahjudi4*

ABSTRACT

Introduction: Indonesia is one of the countries with a high TB-HIV prevalence. Antiretroviral treatment (ART) is only being administered to approximately 42% of TB-HIV patients. The low utilization of ART can be attributed, in part, to the delayed initiation of treatment. Nonetheless, starting ART in these people at an early stage poses risks, owing to the increased likelihood of drug-drug interactions and the manifestation of Immune Reconstitution Inflammatory Syndrome (IRIS) side effects when combined with anti-TB medication. Postponing ART, on the other hand, can hasten illness progression and increase the risk of death.

Methods: A literature review was conducted to assess the effects of early ART (within four weeks of getting anti-TB) against delayed ART initiation (at least eight weeks after receiving anti-TB) in individuals co-infected with TB and HIV. The data was obtained by a comprehensive electronic search using the PubMed and Science Direct databases.

Results: The findings of our study suggest that there was no statistically significant disparity in mortality rates between the early ART group and the delayed ART group. The initial ART cohort had a markedly elevated susceptibility to encountering an IRIS occurrence, particularly among individuals with a CD4 count below 50 cells per cubic millimeter.

Conclusion: In summary, the strategy of delaying the initiation of ART in patients co-infected with TB-HIV is seen as preferable when compared to the approach of early treatment. The frequency of IRIS events is a significant determinant in determining the optimal timing of ART initiation in individuals co-infected with TB-HIV.

Keywords: antiretroviral therapy, effectiveness, initiation time, TB-HIV co-infection.


INTRODUCTION

Globally, 7.0 million new TB cases were reported in 2018 (an increase from 6.4 million in 2017 and a significant increase from the 5.7-5.8 million reported annually from 2009 to 2012). TB affected an estimated 10.0 million persons worldwide in the same year, with an estimated 251,000 fatalities among HIV-positive TB patients. Indonesia has a high prevalence of tuberculosis, MDR-TB, and TB-HIV. Despite this, only approximately 42% of TB-HIV patients receive antiretroviral medication (ART).1,2

One of the key strategies to reduce morbidity and mortality associated with opportunistic infections such as tuberculosis (TB) in HIV patients is the timely delivery of antiretroviral medication (ART). According to WHO, TB-HIV co-infected individuals who have not begun medication must begin anti-tuberculosis treatment promptly, followed by ART within 8 weeks of beginning anti-tuberculosis treatment. HIV patients with a CD4 cell count of fewer than 50 cells/mm3 should begin anti-tuberculosis medication as soon as 2 weeks. ART-supported TB treatment in HIV-positive TB patients saved 10 million lives. However, according to global data from 2018, 11% of HIV-positive TB patients died during therapy.1

Nonetheless, the issue of initiating ART in TB-HIV co-infected individuals remains debatable. Early ART treatment (within 4 weeks of anti-tuberculosis medication) can decrease patient adherence due to the number of drugs that must be eaten (high-burden pills), probable adverse effects from Immune Reconstitution Inflammatory Syndrome (IRIS), and drug interaction risk.

A retrospective meta-analysis of 54 cohorts of TB-HIV co-infected patients revealed that the incidence of TB-IRIS (tuberculosis - immune reconstitution inflammatory syndrome) in patients on ART was 15.7%, with a death rate of 3.2%.3 TB-IRIS is an excessive and aberrant immune response to either live or dead Mycobacterium tuberculosis germs. There are two types of TB-IRIS: paradoxical and unmasking. When a previously confirmed TB infection responds to tuberculosis treatment but is aggravated by ART-induced immunological reconstitution,
this is known as paradoxical TB-IRIS. Unmasking TB-IRIS is also characterized as a circumstance in which asymptomatic infection is not identified until ART-induced immune reconstitution results in an overly inflammatory condition. The combined incidence of paradoxical TB-IRIS in co-infected individuals starting ART is estimated to be 18%, with 25% requiring hospitalization. The risk factors for TB-IRIS are a low baseline CD4 T cell count prior to ART beginning and a short delay between TB therapy and ART initiation.4

On the other hand, according to WHO guidelines, a delay in initiation of ART (≥ 8 weeks after administration of anti-tuberculosis therapy) can lead to increased morbidity and mortality in TB-HIV co-infected.5 Early initiation of ART in patients with CD4 counts below 50 /mm³ reduces AIDS-related comorbidity and mortality, but increases the risk of IRIS events compared to patients who begin treatment later.6

As a result, this study was conducted to review the literature on the effect of early ART initiation (4 weeks after antituberculosis therapy) versus delayed ART treatment (8 weeks after antituberculosis therapy), which is expected to provide an optimal time in administering ART in patients with TB-HIV co-infection. This study looked at the prevalence of TB-IRIS and the death rate in TB-HIV co-infected patients.

METHODS
Data collection
We performed a systematic article search from PubMed and ScienceDirect databases to identify relevant articles published between 2010 and 2020. Studies were retrieved using keywords 'TB', 'tuberculosis', 'HIV', 'human immunodeficiency virus', 'antiretroviral therapy', 'ART', 'initiation time', 'timing', 'immediate treatment', 'delayed treatment', 'mortality', 'IRIS', 'immune reconstitution inflammatory syndrome'.

Inclusion and exclusion criteria
We use the PICO Strategy, namely Population, Intervention, Comparator, and Outcome, to include all relevant articles. The population is TB-HIV co-infected patients, the intervention is early ART treatment (four weeks after antituberculosis therapy), the comparator is delayed ART treatment (eight weeks after antituberculosis therapy), and the outcomes are TB-IRIS and mortality among TB-HIV co-infected patients. We collect any RCT and cohort studies published in the period 2010-2020 that have a Scopus reputation (Q1, Q2, Q3) for international journals or meet good article quality according to the CASP checklist critical review. The articles were excluded if the study involved children and pregnant women as a research sample, if no full text was available, if the full text was not available in English or Bahasa Indonesia, or if the articles were not original research.

Data selection
The initial search using predefined keywords generated 2,981 articles, consisting of 512 articles from PubMed and 2,469 from the ScienceDirect database. Data selection goes through duplication checks, screening title, abstract, and full-text articles according to inclusion and exclusion criteria, as well as checking journal reputation and critical studies. The data selection is briefly described in Figure 1.

RESULTS
After the selection process based on the scheme in Figure 1, nine articles have met the specified criteria and will be analyzed to answer the study objectives. A summary of the articles and their findings are listed in Table 1. The impact of the initiation time of ART on TB-IRIS and death events are summarized in Table 2 and Table 3.

According to the findings of 9 articles, five articles (Abdool Karim et al., 2011; Blanc et al., 2011; Havlir et al., 2011; Yang et al., 2011; Yang et al., 2011) indicate that early ART initiation (4 weeks after antituberculosis therapy) reduces the prevalence of TB-IRIS and mortality among TB-HIV co-infected patients.
Table 1. Summary of studies on the impact of early versus delayed ART in TB-HIV patients

<table>
<thead>
<tr>
<th>Article No.</th>
<th>Author, year</th>
<th>Location</th>
<th>Study purpose</th>
<th>Design study and Sample</th>
<th>Findings on IRIS</th>
<th>Findings on mortality</th>
</tr>
</thead>
</table>
| 1           | (Abdool Karim et al., 2011) | South Africa | To determine the clinical impact based on the timing of ART initiation in patients with HIV infection and tuberculosis | **Design**: randomized controlled trial, open-label  
**Sample**: 429 ambulatory patients with TB-HIV, 214 in the early ART group and 215 in the delayed ART group | **Early ART**: 43 events from 214 patients, 20.1 event rate/100 person-year  
**Delayed ART**: 18 events from 215 patients, 7.7 event rate/100 person-year  
**P value** <0.001 | **Early ART**: 15 events from 214 patients, 5.7 event rate/100 person-year  
**Delayed ART**: 15 events from 215 patients, 6.0 event rate/100 person-year  
**P value** = 0.91 |
| 2           | (Blanc et al., 2011) | Cambodia | To compare the impact of earlier initiation with later initiation of ART in mortality rate among patients with advanced immunodeficiency | **Design**: prospective, randomized controlled trial, open-label  
**Sample**: 661 outpatients and inpatients with TB-HIV from five hospitals, 332 in the early ART group and 329 in the delayed ART group | **Early ART**: 110 events from 332 patients, 3.76 event rate/100 person-months  
**Delayed ART**: 45 events from 329 patients, 1.53 event rate/100 person-months  
**P value** <0.001 | **Early ART**: 59 events from 332 patients, 8.28 event rate/100 person-year  
**Delayed ART**: 90 events from 329 patients, 13.77 event rate/100 person-year  
**P value** = 0.006  
There was no difference in the effect of starting ART earlier between the groups with CD4 count <50/mm3 compared with 51-200/mm3 (p-value = 0.49) |
| 3           | (Havlir et al., 2011) | 26 clinical research sites in Africa, Asia, North America, and South America | To evaluate the timing of ART during tuberculosis therapy | **Design**: randomized controlled trial, open-label  
**Sample**: 806 patients with TB-HIV, 405 in the early ART group and 401 in the delayed ART group | **Early ART**: 43 events from 405 patients (11%)  
**Delayed ART**: 19 events from 401 patients (5%)  
**P value** =0.002 | **Early ART**: 31 events from 405 patients (8%)  
**Delayed ART**: 37 events from 401 patients (9%)  
21 of 31 deaths (68%) in the early ART and 21 of 37 deaths (57%) in the delayed ART were related to HIV-TB illness. |
| 4           | (Manosuthi et al., 2012) | Thailand | To determine the optimal time to initiate ART in order to minimize mortality among HIV-infected patients with active TB in middle-income countries | **Design**: randomized controlled trial, open-label  
**Sample**: 156 patients with TB-HIV, 79 in the early ART group and 77 in the delayed ART group | **Early ART**: 26 events from 79 patients, 8.86 event rate/100 person-months  
**Delayed ART**: 15 events from 77 patients, 5.02 event rate/100 person-months  
**P value** = 0.069 | **Early ART**: 6 events from 79 patients, 8.6 event rate/100 person-year  
**Delayed ART**: 5 events from 77 patients, 7.25 event rate/100 person-year  
**P value** >0.99 |
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<th>Findings on mortality</th>
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| 5          | (Sinha et al., 2012) | India | To compare early (2-4 weeks) and delayed (8-12 weeks) ART initiation after starting anti-tuberculosis treatment in HIV-TB-infected adults in North India against HIV mortality and disease progression | **Design:** randomized controlled trial, open-label  
**Sample:** 150 patients with TB-HIV, 88 in the early ART group and 62 in the delayed ART group | **Early ART:** 9 events from 88 patients (10.2%)  
**Delayed ART:** 6 events from 62 patients (9.7%)  
**P value = 0.571** | **Early ART:** 9 events from 88 patients (10.2%)  
**Delayed ART:** 7 events from 62 patients (11.3%)  
**P value = 0.773** |
| 6          | (Kendon et al., 2012) | Durban, South Africa | To describe some baseline demographic variables of adults with HIV-associated TB accessing ART in an urban hospital in KwaZulu-Natal (KZN) and to compare the clinical outcomes based on the duration of TB therapy received before commencement of ART | **Design:** retrospective cohort study  
**Sample:** 458 patients with TB-HIV, 303 in the immediate ART group, 85 in the early ART group and 70 in the delayed ART group | **Immediate ART:** 31 events from 303 patients (10.2%)  
**Early ART:** 7 events from 85 patients (8.2%)  
**Delayed ART:** 6 events from 70 patients (7.1%)  
**P value = 0.670** | **Immediate ART:** 47 events from 303 patients (15.5%)  
**Early ART:** 7 events from 85 patients (8.2%)  
**Delayed ART:** 1 events from 70 patients (1.4%)  
**P value = 0.002** |
| 7          | (Mfinanga et al., 2014) | 26 health centers in South Africa, Tanzania, Uganda, and Zambia | To determine the impact of early versus delayed ART on tuberculosis treatment outcomes for HIV-positive people with CD4 counts of at least 220 cells per μL with newly diagnosed, smear-positive, culture-confirmed tuberculosis | **Design:** randomized, placebo-controlled trial, double-blind  
**Sample:** 1,538 patients with TB-HIV, 767 in the early ART group and 771 in the delayed ART group | **Early ART:** 87 events from 767 patients (11.3%)  
**Delayed ART:** 84 events from 771 patients (10.9%)  
**P value = 0.56** | **Early ART:** 36 events from 767 patients (3%)  
**Delayed ART:** 27 events from 771 patients (2.2%) |
et al., 2014; Amogne et al., 2015) showed that early initiation of ART (≤4 weeks after initiation of anti-tuberculosis therapy) significantly increased the incidence of IRIS in TB-HIV co-infected patients when compared with delayed ART (p-value < 0.05).7,11 Meanwhile, four articles (Kendon et al., 2012; Manosuthi et al., 2012; Sinha et al., 2012; Mfinanga et al., 2014) showed that there was no significant difference in the occurrence of IRIS between the groups receiving early ART and delayed ART.12-15 For the incidence of death, seven articles (Abdool Karim et al., 2011; Havlir et al., 2011; Manosuthi et al., 2012; Sinha et al., 2012; Mfinanga et al., 2014; Yang et al., 2014; Amogne et al., 2015) showed that there was no statistically significant difference between the group receiving early ART and the group receiving delayed ART.7,9-11,13-15 However, (Blanc et al., 2011) and (Kendon et al., 2012) showed a significant difference in the incidence of death between groups receiving early ART and delayed ART.8,12

We calculated the risk ratio (RR) for the incidence of TB-IRIS and mortality in patients with TB-HIV with early ART and delayed ART. The summary of RR based on the type of research can be found in Table 4 and Table 5. The impact of early and delayed ART in patients with CD4 count <50/mm³ and patients with CD4 count ≥50/mm³ is also summarized in Table 6.

**DISCUSSION**

This review shows that early ART significantly increased the incidence of IRIS in TB-HIV co-infected patients when compared with delayed ART (Abdool Karim et al., 2011; Blanc et al., 2011; Havlir et al., 2011; Yang et al., 2014; Amogne et al., 2015).7,11 Nevertheless, there are still some studies that do not show a statistically significant increase in the incidence of IRIS early (Kendon et al., 2012; Manosuthi et al., 2012; Sinha et al., 2012; Mfinanga et al., 2014).12-15 It could be due to several factors. The incidence of TB-IRIS is more prone to be experienced by patients with low CD4 cell counts, while research subjects in Mfinanga et al., 2014, have a CD4 cell count ≥220/mm³.15 In the other studies, Kendon et al., 2012 and Sinha et al., 2012, there were research
subjects who were diagnosed with TB not based on bacteriological confirmation so that it could cause bias in the results of the study. Subjects in early ART in Kendon et al.'s 2012 study also used traditional medicines. Meanwhile, in Manosuthi et al., 2012, patients in the research study were not fully included in the calculation as described in the research method. The type-2 error (false negative) of this study was initially set at 20%, but due to the lower-than-expected number of participants, the value for detecting the smallest beneficial effect was lower at 70%. This can affect the calculation of the p-value of the study.

Overall, the incidence of death from this review showed that there was no statistically significant difference between the group receiving early ART and delayed ART. However, Blanc et al., 2011 and Kendon et al., 2012 show a significant difference in the incidence of death between these two groups. In Blanc et al., 2011, the mortality rate was significantly higher in the group on delayed ART compared to early ART. The research subjects in this study had a small difference where the body mass index (BMI) was 16 (median = 16.7). The study states that BMI is one of the independent risk factors associated with increased mortality. In addition, 70% of the subjects in the study had a CD4 cell count <50/mm3, where the CD4 cell count is one of the main risk factors for causing death. Therefore, the patient’s condition in the initial period of TB treatment has an important role in predicting a patient’s outcome in terms of mortality. In the Kendon et al., 2012, there are different results on the incidence of IRIS and the incidence of death. This was caused by several factors, where the early ART group had lower CD4 cell counts, GFR, and Hb cells compared to other groups.

The calculated Risk Ratio (RR) between the early ART group and the delayed ART group in RCT studies (Table 4) is 1.50 and 2.09 in the cohort studies (Table 5), which means that early initiation likely increases the risk of IRIS occurrence in TB-HIV co-infected patients compared with delayed ART. The Risk Ratio (RR) on the incidence of death between the early ART group and the delayed ART group in RCT studies was caused by several factors, where the early ART group had lower CD4 cell counts, GFR, and Hb cells compared to other groups.

<table>
<thead>
<tr>
<th>Article No.</th>
<th>Author, Year</th>
<th>Number of Patients</th>
<th>Number of Patients</th>
<th>Events</th>
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<th>Events</th>
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<th>Risk Ratio (RR)</th>
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<tbody>
<tr>
<td>1</td>
<td>(Abdool Karim et al., 2011)</td>
<td>214</td>
<td>43</td>
<td>215</td>
<td>18</td>
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<tr>
<td>2</td>
<td>(Blanc et al., 2011)</td>
<td>332</td>
<td>110</td>
<td>329</td>
<td>45</td>
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<td></td>
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<tr>
<td>3</td>
<td>(Havlir et al., 2011)</td>
<td>405</td>
<td>43</td>
<td>401</td>
<td>19</td>
<td></td>
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<tr>
<td>4</td>
<td>(Manosuthi et al., 2012)</td>
<td>79</td>
<td>26</td>
<td>77</td>
<td>15</td>
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<td></td>
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</tr>
<tr>
<td>5</td>
<td>(Sinha et al., 2012)</td>
<td>88</td>
<td>9</td>
<td>62</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>(Kendon et al., 2012)</td>
<td>303</td>
<td>38</td>
<td>70</td>
<td>6</td>
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<tr>
<td>7</td>
<td>(Mfinanga et al., 2014)</td>
<td>767</td>
<td>87</td>
<td>841</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>(Yang et al., 2014)</td>
<td>144</td>
<td>53</td>
<td>19</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>(Amogne et al., 2015)</td>
<td>323</td>
<td>22</td>
<td>155</td>
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<th>Events</th>
<th>Events</th>
<th>Events</th>
<th>Risk Ratio (RR)</th>
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<tbody>
<tr>
<td>IRIS</td>
<td>2208</td>
<td>340</td>
<td>15.40</td>
<td>2010</td>
<td>187</td>
<td>9.30</td>
<td>1.50</td>
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<tr>
<td>Death</td>
<td>2208</td>
<td>196</td>
<td>8.88</td>
<td>2010</td>
<td>199</td>
<td>9.90</td>
<td>0.9</td>
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<th>Risk Ratio (RR)</th>
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<tbody>
<tr>
<td>IRIS</td>
<td>447</td>
<td>84</td>
<td>18.79</td>
<td>89</td>
<td>8</td>
<td>8.99</td>
<td>2.09</td>
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<tr>
<td>Death</td>
<td>447</td>
<td>71</td>
<td>15.88</td>
<td>89</td>
<td>6</td>
<td>6.74</td>
<td>2.36</td>
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<th>Risk Ratio (RR)</th>
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<tbody>
<tr>
<td>IRIS</td>
<td>148</td>
<td>36</td>
<td>24.32</td>
<td>74</td>
<td>4</td>
<td>5.41</td>
<td>4.5</td>
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<tr>
<td>CD4 &lt;50/mm³</td>
<td>389</td>
<td>29</td>
<td>7.46</td>
<td>296</td>
<td>14</td>
<td>4.73</td>
<td>1.57</td>
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<tr>
<td>CD4 ≥50/mm³</td>
<td>389</td>
<td>32</td>
<td>8.23</td>
<td>296</td>
<td>15</td>
<td>5.07</td>
<td>1.6</td>
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<th>Events</th>
<th>Risk Ratio (RR)</th>
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<tbody>
<tr>
<td>IRIS</td>
<td>148</td>
<td>30</td>
<td>20.27</td>
<td>74</td>
<td>17</td>
<td>22.97</td>
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<td>CD4 &lt;50/mm³</td>
<td>389</td>
<td>32</td>
<td>8.23</td>
<td>296</td>
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<td>5.07</td>
<td>1.6</td>
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(Table 4) is 0.9, which means the risk of death with early ART is 0.9 times the risk with delayed ART. This result is in line with most of the studies reviewed. There was no statistically significant difference between the group receiving early ART and the group receiving delayed ART (p-value > 0.05),7-9,11,13,15

Based on the patient’s CD4 cell count data described in detail by the studies of Abdool Karim et al., 2011 and Amogne et al., 2015, patients with CD4 cell count <50/mm3 are much more susceptible to the incidence of IRIS, especially in the group receiving early ART.7,11 This is also supported by other studies which state that the overall incidence of IRIS is relatively higher in patients with CD4 cell count <50 cells/mm3 compared to patients with CD4 cell count ≥50/mm3 with RR=4.5 (Table 6). The mechanism of occurrence of TB-IRIS in co-infected patients is related to the suppression of viral replication and immune restoration induced by highly active antiretroviral therapy (ART), with the resultant TB-specific immune-restoring response. This response provides a positive benefit in most patients, but in certain hosts there can be an exaggerated response that can lead to paradoxical TB-IRIS.

The mortality rate between the group with CD4 count <50/mm3 receiving early ART and the group with CD4 count <50/mm3 receiving delayed ART did not show any significant difference. The RR results in the CD4 cell count <50/mm3 = 0.88 showed that the risk of death with early ART was 88% of the risk with delayed ART. The RR results in the group with CD4 T cell count ≥50/mm3 = 1.6, which means that early initiation increases the risk of death in TB-HIV co-infected patients. It can be concluded that, early ART initiation increases the risk of death compared to delayed ART in the group with CD4 cell count <50/mm3 and ≥50/mm3.

According to the findings, early ART initiation (four weeks after starting anti-tuberculosis therapy) did not result in a significant difference in the incidence of death when compared to the group that received delayed ART initiation (eight weeks after starting anti-tuberculosis therapy). Furthermore, patients in the early ART group had a higher risk of TB-IRIS than those in the delayed ART group, and TB-IRIS could be one of the reasons for death in TB-HIV co-infected patients.

The included articles in this review encompassed a combination of randomized controlled trials (RCTs) and cohort studies, introducing inherent variability in methodologies. This diversity in study designs may contribute to variations in results, limiting the ability to draw uniform conclusions. Additionally, variability in patient characteristics, including CD4 cell counts, comorbidities, and nutritional status, among the selected studies poses a potential influence on the generalizability of the findings. The absence of detailed information on these factors in some studies further obscures the impact of these variables on the outcomes, adding complexity to the interpretation of the results.

CONCLUSIONS

(i) When compared to the group receiving delayed ART, early ART initiation significantly increased the incidence of IRIS in TB-HIV co-infected patients with CD4 cell counts below 50/mm3 and above 50/mm3; (ii) Early ART initiation increases the risk of death in TB-HIV co-infected patients with CD4 cell counts 50/mm3 and 50/mm3. However, the difference in increased risk was not statistically significant. In conclusion, delayed ART is the better method in TB-HIV patients over early treatment. An increased incidence of IRIS episodes is one of the key criteria evaluated when deciding whether to start ART in TB-HIV patients.

AUTHOR CONTRIBUTION

All authors have contributed to this research process, including conception and design, analysis and interpretation of the data, article drafting, critical revision of the article for important intellectual content, and final approval.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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