Review Article

Association of CD4 T cell count and optimal timing of antiretroviral therapy initiation with immune reconstitution inflammatory syndrome and all-cause mortality for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis

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Abstract: Aims: CD4 T cell count and optimal timing of antiretroviral therapy (ART) during tuberculosis (TB) treatment are challenging. We conducted a meta-analysis to assess the association of CD4 T cell count and timing of ART initiation with immune reconstitution inflammatory syndrome (IRIS) and all-cause mortality of patients co-infected with HIV/TB. Methods: We conducted an electronic search of clinical studies dated from January 1980 to December 2019 in PubMed and EMBASE. Randomized, controlled trials evaluating low-base CD4 T cell count (< 50 cells/μL) versus high-base CD4 T cell count (≥ 50 cells/μL), and/or early ART initiation (1 to 28 days after starting TB treatment) versus delayed ART initiation (≥ 28 days after starting TB treatment) were included. The primary endpoints were all-cause mortality and TB-related immune reconstitution inflammatory syndrome (IRIS-TB). The risk ratio (RR) was calculated as a measure of intervention effect. Mantel-Haenszel method was used to estimate the RR. Results: Ten trials (n = 5226) were conducted in North America, Africa, and Asia. We found that low-baseline CD4 T cell count increased the incidence of TB-associated IRIS (RR, 1.47; 95% CI, 1.24-1.75; I² = 58%) and all-cause mortality (RR, 2.42; 95% CI, 1.71-3.42; I² = 41%) compared with high baseline CD4 T cell count, and early ART initiation increased the incidence of TB-associated IRIS compared with delayed ART initiation (RR, 1.80; 95% CI, 1.57-2.07; I² = 74%). However, early ART initiation did not reduce all-cause mortality (RR, 0.91; 95% CI, 0.74-1.12; I² = 49%) compared with delayed ART initiation. Conclusions: The present study demonstrates that low-baseline CD4 T cell count (< 50 cells/μL) in patients co-infected with TB-HIV increases the incidence of TB-associated IRIS and all-cause mortality. Early ART initiation (≤ 28 days) in patients co-infected with TB-HIV increases the incidence of TB-associated IRIS. However, evidence is insufficient to refute or support a survival benefit conferred by the comparison between early ART initiation (≤ 28 days) and delayed ART initiation.

Keywords: CD4 T cell count, antiretroviral therapy, immune reconstitution inflammatory syndrome, tuberculosis, human immunodeficiency virus

Introduction

Tuberculosis (TB) is a common cause of deaths in human immunodeficiency virus (HIV)-infected patients. In 2012, about one-third of the one million patients with new TB among those who were HIV-positive died [1]. Among the new cases, more than 70% were in resource-limited settings. Without the use of anti-retroviral therapy (ART), the risk of HIV-infected adults dying during TB treatment ranges from 16% to 37% among those with CD4 T cell counts greater than 350 cells/μL [2-6]. For many reasons, the basic time and optimal timing of CD4+ T cell count to start antiretroviral therapy with anti-TB drugs during the treatment for drug-resistant TB are still challenging [2-6].

The CD4 T-cell counts at baseline and optimal timing of ART initiation in TB-HIV co-infected...
patients who have begun TB therapy require further definition. The current World Health Organization (WHO) guidelines recommend that for severely immunosuppressed patients (CD4 T-cell counts < 50 cells/μL), TB therapy should be started first, and then retroviral therapy treatment should be initiated “within the first 8 weeks” of starting TB therapy. Further data are shown in various expert reviews [7-10]. To provide an up-to-date summary, we conducted a meta-analysis to assess the association of CD4 T cell count and timing of ART initiation with IRIS and all-cause mortality among TB-HIV co-infected patients.

Materials and methods

Search strategy

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement. An electronic search of clinical studies dated from January 1980 to December 2019 was independently conducted by two reviewers with English language restrictions in PubMed and EMBASE.

Trial selection

Two reviewers evaluated the eligibility of trials. Disagreements were resolved by negotiation. Randomized, controlled trials that compared low-baseline CD4 T cell count (less than 50 cells/μL) with high-baseline CD4 T cell count (greater or equal to 50 cells/μL), and those that compared TB-HIV co-infected patients who had early ART initiation (≤ 28 days after the initiation of TB therapy) with delayed ART initiation (> 28 days after the initiation of TB therapy) were included in the present study.

Data extraction

Two reviewers independently extracted the data. Trial design, demographic characteristics, and outcome indicators were extracted and the bias was evaluated for each trial. Discrepancies were resolved by reaching consensus through discussion. The primary outcomes considered included IRIS-TB and all-cause mortality.

Data synthesis and analysis

Heterogeneity of trials was assessed by forest plots and tau2 test, and I² statistic. The results of individual trials were assessed by R (version 3.3.2 “meta” package).

Results

Basic features

Figure 1 shows the process of research identification and selection. The main outcomes of four trials were not related to IRIS-TB [11-14].
The main outcomes of fifteen trials could not be classified by “low CD4/high CD4” or “early/delayed” [15-29]. Four trials were repeated research [30-33]. All of these trials were excluded. A total of 10 studies were included in this meta-analysis [34-43], and their characteristics are listed in Table 1. The studies were conducted in North America, Africa, and Asia and published between 2011 and 2018. The mean length of follow-up of the participants ranged from 8 to 528 days, the mean age ranged between 32 and 38 years, the mean BMI ranged between 17 and 26 kg/m², the median CD4 T cell count ranged between 25 and 367 cells/μL, and the median log₁₀ HIV-1 RNA viral load ranged from 5.0 to 5.7 copies/mL. Five studies compared low CD4 T cell count with high CD4 T cell count in IRIS-TB. Nine studies compared early ART with delayed ART in IRIS-TB. Three studies compared low CD4 T cell count with high CD4 T cell count regarding all-cause deaths. Six studies compared early ART with delayed ART regarding all-cause deaths. In addition, 827 patients (16%) developed IRIS, and 333 patients (9%) died.

Bias of included studies

A bias evaluation of the included studies is shown in Figure 2. The trials showed a relatively low risk of bias.

Heterogeneity assessment

Figures 3-6 show the heterogeneity among the included trials. I² ranged from 41% to 74%. There was no heterogeneity among the studies.

IRIS-TB

Low CD4 T cell count versus high CD4 T cell count at base

Among 917 participants with low CD4 T cell count at baseline, 238 (26.0%) developed IRIS-TB compared with 176 of 1232 (14.3%) in high CD4 group [5 studies; relative risk, RR, 1.47 (95% CI, 1.24-1.75); I² = 58%] (Figure 3). As shown in Figure 3, low CD4 T cell count at baseline was associated with a higher incidence of IRIS-TB than a high CD4 T cell count at baseline for patients.

Early ART initiation versus delayed ART initiation

Among 2663 participants with early ART, 488 (18.3%) became IRIS-TB compared with 259 of 2443 (10.6%) in the delayed ART set [9 studies; RR, 1.80 (95% CI, 1.57-2.07); I² = 74%] (Figure 4). As shown in Figure 4, early ART was associated with a higher incidence of IRIS-TB than delayed ART for patients.

All-cause mortality

Low CD4 versus high CD4 T cell count at base

Patients with low CD4 T cell count at baseline [18.3% (56 of 306 patients)] had a higher all-cause mortality than those with high CD4 T cell count at baseline [7.1% (57 of 798 patients)] at the end of follow-up [3 trials; RR, 2.42 (95% CI, 1.71-3.42); I² = 41%] (Figure 5).

Early initiation versus delayed initiation of ART

Patients randomly assigned to the early ART group [9.5% (172 of 1803 patients)] had insignificantly lower all-cause mortality than those receiving delayed ART [10.0% (161 of 1609 patients)] at the end of follow-up [6 trials; RR, 0.91 (95% CI, 0.74-1.12); I² = 49%] (Figure 6).

Discussion

The present systematic review included 10 trials with 5226 participants to assess the association of timing of ART initiation and CD4 T cell count with IRIS and all-cause mortality among TB-HIV co-infected patients receiving TB therapy.

Overall, patients with baseline CD4 T cell count < 50 cells/μL had a higher incidence of IRIS-TB than those with baseline CD4 T cell count ≥ 50 cells/μL. Patients commencing ART within 28 days after starting TB therapy had a higher incidence of IRIS-TB than those commencing ART more than 28 days after starting TB therapy. Compared to IRIS-TB, mortality benefit is a more important consideration in treating TB-HIV co-infected patients. Overall, patients with baseline CD4 T cell count < 50 cells/μL had higher all-cause mortality than those with baseline CD4 T cell count ≥ 50 cells/μL. By contrast, patients commencing ART within 28 days after starting TB therapy had statistically
## Table 1. Characteristics of the 10 studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication year</th>
<th>Country</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Length of follow-up (wk)</th>
<th>Mean age (y)</th>
<th>No. of male</th>
<th>No. of female</th>
<th>Mean BMI</th>
<th>Median CD4 cell count (cells/μL)</th>
<th>Median HIV-1 RNA viral load-log(_{10}) (copies/ml)</th>
<th>Patients with TB at enrolment</th>
<th>Days on tuberculosis therapy at ART start</th>
<th>Incidence of TB-Associated IRIS</th>
<th>Deaths of all-cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdool Karim SS et al.</td>
<td>2011</td>
<td>South Africa</td>
<td>Randomized clinical trial, RCT</td>
<td>429</td>
<td>18</td>
<td>34</td>
<td>209</td>
<td>220</td>
<td>26</td>
<td>152</td>
<td>5</td>
<td>429</td>
<td>28</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>Havlir DV et al.</td>
<td>2011</td>
<td>USA</td>
<td>Randomized clinical trial, RCT</td>
<td>806</td>
<td>48</td>
<td>34</td>
<td>501</td>
<td>305</td>
<td>19</td>
<td>76</td>
<td>5.4</td>
<td>374</td>
<td>14</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Blanc FX et al.</td>
<td>2011</td>
<td>Cambodia</td>
<td>Randomized clinical trial, RCT</td>
<td>661</td>
<td>50</td>
<td>35</td>
<td>425</td>
<td>236</td>
<td>17</td>
<td>25</td>
<td>5.7</td>
<td>661</td>
<td>14/56</td>
<td>155</td>
<td>149</td>
</tr>
<tr>
<td>Manosuthi W et al.</td>
<td>2012</td>
<td>Thailand</td>
<td>Randomized clinical trial, RCT</td>
<td>156</td>
<td>54</td>
<td>38</td>
<td>121</td>
<td>35</td>
<td>19</td>
<td>45</td>
<td>5.7</td>
<td>156</td>
<td>28/84</td>
<td>81</td>
<td>11</td>
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<tr>
<td>Sinha S et al.</td>
<td>2012</td>
<td>India</td>
<td>Randomized clinical trial, RCT</td>
<td>150</td>
<td>54</td>
<td>35</td>
<td>126</td>
<td>24</td>
<td>18</td>
<td>140</td>
<td>5.3</td>
<td>150</td>
<td>14-28/56, 56-84</td>
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<td>16</td>
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<tr>
<td>Laureillard D et al.</td>
<td>2013</td>
<td>Cambodia</td>
<td>Randomized clinical trial, RCT</td>
<td>597</td>
<td>48</td>
<td>36</td>
<td>385</td>
<td>212</td>
<td>18</td>
<td>26</td>
<td>5.6</td>
<td>530</td>
<td>14/56</td>
<td>155</td>
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<tr>
<td>Mfinanga SG et al.</td>
<td>2014</td>
<td>South Africa</td>
<td>Randomized clinical trial, RCT</td>
<td>1675</td>
<td>24</td>
<td>32</td>
<td>922</td>
<td>616</td>
<td>19</td>
<td>367</td>
<td>1675</td>
<td>14/180</td>
<td>171</td>
<td>63</td>
<td></td>
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<tr>
<td>Amogne W et al.</td>
<td>2015</td>
<td>Ethiopia</td>
<td>Randomized clinical trial, RCT</td>
<td>478</td>
<td>8</td>
<td>36</td>
<td>245</td>
<td>233</td>
<td>19</td>
<td>72</td>
<td>5.2</td>
<td>478</td>
<td>7/28/56</td>
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<td>64</td>
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<tr>
<td>Haridas V et al.</td>
<td>2015</td>
<td>Cambodia</td>
<td>Randomized clinical trial, RCT</td>
<td>154</td>
<td>48</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>154</td>
<td>14/56</td>
<td>50</td>
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<tr>
<td>Meintjes G et al.</td>
<td>2018</td>
<td>South Africa</td>
<td>Randomized clinical trial, RCT</td>
<td>120</td>
<td>12</td>
<td>36</td>
<td>73</td>
<td>47</td>
<td>21</td>
<td>49</td>
<td>5.6</td>
<td>89</td>
<td>30</td>
<td>56</td>
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</table>
insignificantly lower all-cause mortality than those commencing ART more than 28 days after starting tuberculosis therapy. Although the present meta-analysis strongly supported timely treatment in patients with CD4 T cell counts less than 50 cells/μL, it had insufficient evidence to support or refute a survival benefit conferred by the comparison between early ART initiation (≤ 28 days) and delayed ART initiation (> 28 days). This indicates that we need more nuanced data to better define the time threshold for early ART.

Except for the incidence of IRIS-TB and mortality, concurrent treatment of HIV and TB still requires consideration of adherence and drug interactions for both infections [44, 45]. These considerations highlight the need for more in-depth research to conduct rigorous controlled trials through the use of anti-inflammatory drugs (such as glucocorticoids or non-steroidal anti-inflammatory drugs) in an environment where TB and HIV co-infection are highly prevalent. Such trials are under way in high-burden settings, including South Africa [46].

Our search for reviews on the association of CD4 T cell count and timing of ART initiation with IRIS and mortality among patients co-infected with TB-HIV was updated in December 2019 and identified 2 reviews. Being consistent with our findings, Müller et al. [10] conclude that the risk of IRIS is related to CD4 cell count at the beginning of ART, with a high risk in patients with less than 50 cells/μL. Uthman and colleagues [47] conclude that early ART in HIV-infected adults with newly diagnosed TB improves survival in those with CD4 T cell counts fewer than 50 cells/μL, which is not comparable to our results. This is possibly because that we did not perform a subgroup analysis.

The strengths of our meta-analysis include rigorous methods to control bias during the review process and a exhaustive search for multiple databases to identify eligible randomized, controlled study. However, the present study still had limitations in bias in our analyses. For example, only 3 trials that compared early ART with delayed ART provided enough data to analyze mortality.

In conclusion, the present study demonstrates that low baseline CD4 T cell count (< 50 cells/
μL) in TB-HIV co-infected patients increases the incidence of TB-associated IRIS and all-cause mortality. Early ART (≤ 28 days) in TB-HIV co-infected patients increases the incidence of TB-associated IRIS. However, evidence is not enough to refute or support a survival benefit conferred by the comparison between early ART initiation (≤ 28 days) and delayed ART initiation.

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The current study was approved by the Ethics Committee of Shanxi Medical University. Informed consent was obtained from all patients.

Disclosure of conflict of interest

None.

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References


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