Int J Clin Exp Pathol 2021;14(6):670-679
www.ijcep.com /ISSN:1936-2625/IJCEP0121856

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

Lifang Li[1], Jianqiang Li[1], Chunwei Chai[2], Tanzhen Liu[1], Pingping Li[1], Mengrui Qu[1], Hui Zhao[1]

[1]Department of Respiratory Medicine, The Second Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, P. R. China; [2]Department of Internal Medicine, The Fourth People's Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, P. R. China

Received September 7, 2020; Accepted March 7, 2021; Epub June 15, 2021; Published June 30, 2021

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; I^2 = 58%) and all-cause mortality (RR, 2.42; 95% CI, 1.71-3.42; I^2 = 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; I^2 = 74%). However, early ART initiation did not reduce all-cause mortality (RR, 0.91; 95% CI, 0.74-1.12; I^2 = 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

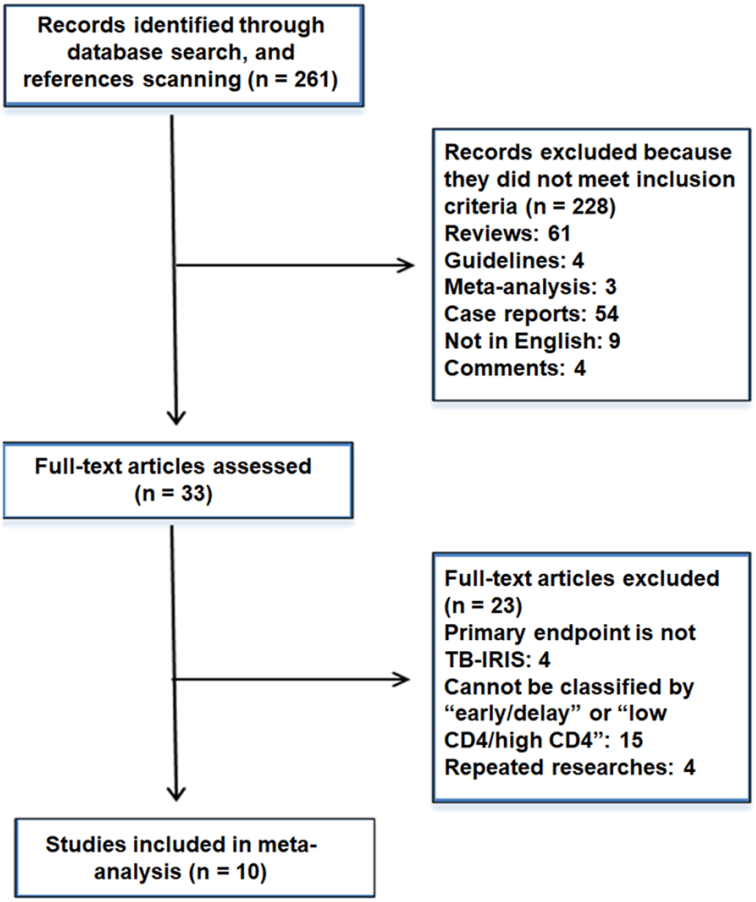

Figure 1. Summary of evidence search and selection. The main outcomes of four trials were not related to IRIS-TB. The main outcomes of fifteen trials cannot be classified by "low CD4/high CD4" or "early/delayed". Four trials were repeated research. All of these trials were excluded. A total of 10 studies were included in this meta-analysis.

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 I^2 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/m^2, the median CD4 T cell count ranged between 25 and 367 cells/μL, and the median $\log_{10}$ 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. I^2 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); I^2 = 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); I^2 = 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); I^2 = 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); I^2 = 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

Authors	Publication year	Country	Study design	No. of patients	Length of follow-up (wk)	Mean age (y)	No. of male	No. of female	Mean BMI	Median CD4 cell count (cells/μL)	Median HIV-1 RNA viral load-log_{10} (copies/ml)	Patients with TB at enrolment	Days on tuberculosis therapy at ART start	Incidence of TB-Associated IRIS	Deaths of all-cause
Abdool Karim SS et al.	2011	South Africa	Randomized clinical trial, RCT	429	18	34	209	220	26	152	5	429	28	61	30
Havlir DV et al.	2011	USA	Randomized clinical trial, RCT	806	48	34	501	305	19	76	5.4	374	14	61	
Blanc FX et al.	2011	Cambodia	Randomized clinical trial, RCT	661	50	35	425	236	17	25	5.7	661	14/56	155	149
Manosuthi W et al.	2012	Thailand	Randomized clinical trial, RCT	156	54	38	121	35	19	45	5.7	156	28/84	81	11
Sinha S et al.	2012	India	Randomized clinical trial, RCT	150	54	35	126	24	18	140	5.3	150	14-28/56-84	15	16
Laureillard D et al.	2013	Cambodia	Randomized clinical trial, RCT	597	48	36	385	212	18	26	5.6	530	14/56	155	
Mfinanga SG et al.	2014	South Africa	Randomized clinical trial, RCT	1675	24	32	922	616	19	367		1675	14/180	171	63
Amogne W et al.	2015	Ethiopia	Randomized clinical trial, RCT	478	8	36	245	233	19	72	5.2	478	7/28/56	22	64
Haridas V et al.	2015	Cambodia	Randomized clinical trial, RCT	154	48							154	14/56	50	
Meintjes G et al.	2018	South Africa	Randomized clinical trial, RCT	120	12	36	73	47	21	49	5.6	89	30	56	

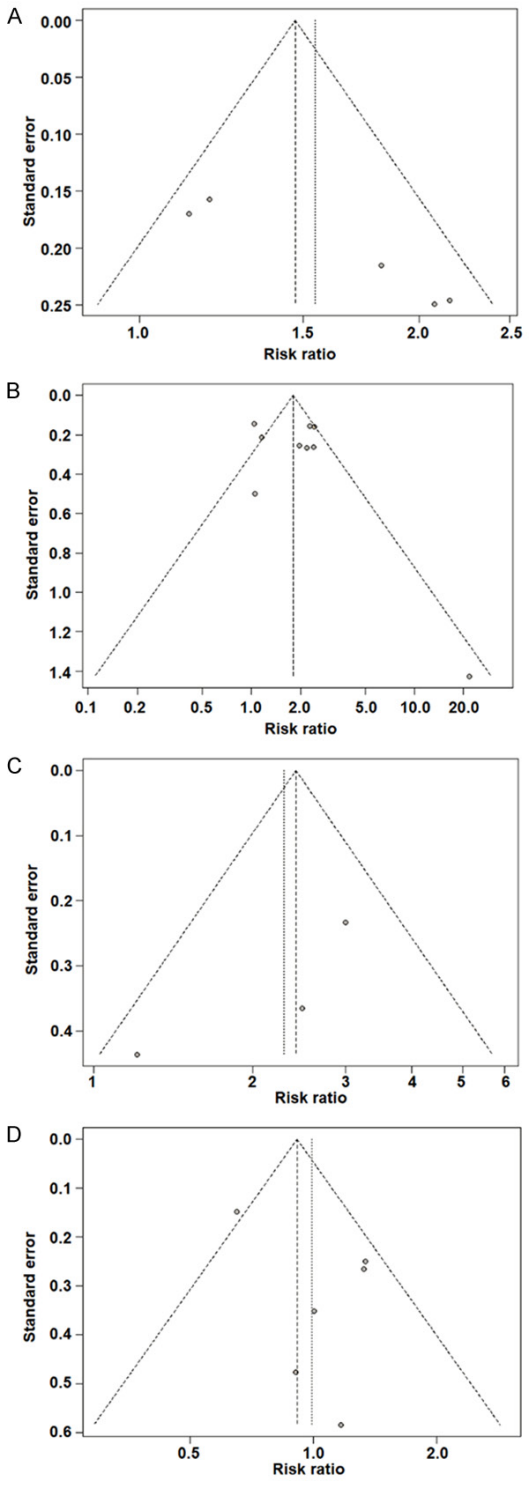

Figure 2. Risk-of-bias assessments of the included studies. A. IRIS-TB comparison between low CD4 T cells and low CD4 T cells at baseline. B. IRIS-TB comparison between early ART initiation and delayed ART initiation. C. All-cause mortality comparison between low CD4 T cells and low CD4 T cells at baseline. D. All-cause mortality comparison between early ART initiation and delayed ART initiation.

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/

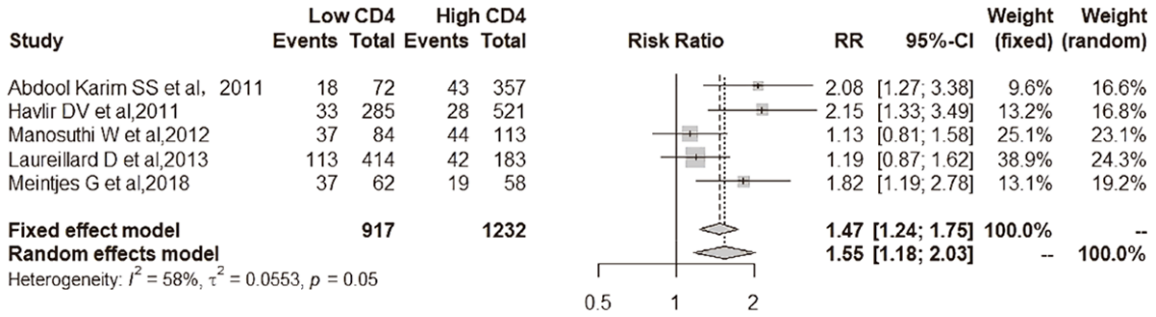

Figure 3. IRIS-TB comparison between low CD4 T cell and low CD4 T cell at baseline. Among 917 participants with low CD4 T cell count at baseline, 238 (26.0%) developed IRIS-TB compared with 176 of 1232 (14.3%) in high CD4 group [5 studies; relative risk, RR, 1.47 (95% CI, 1.24-1.75); I^2 = 58%].

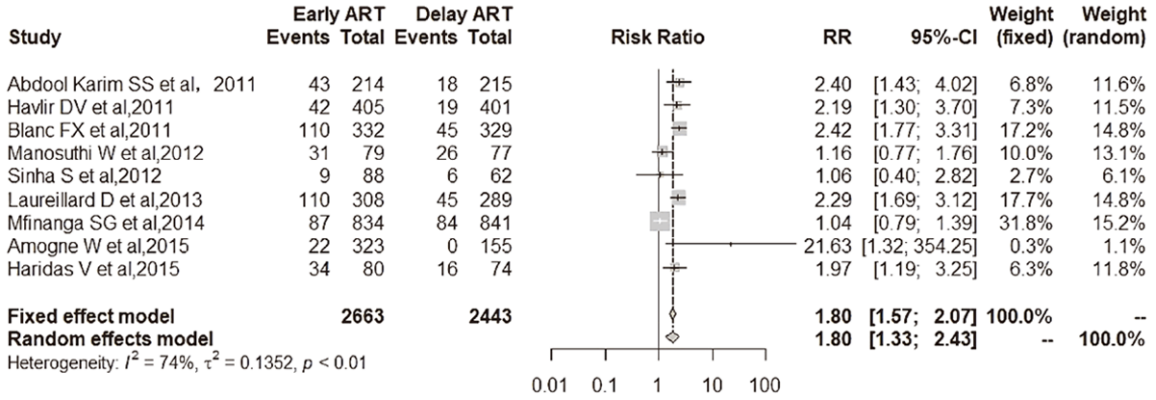

Figure 4. IRIS-TB comparison between early ART initiation and delayed ART initiation. Among 2663 participants with early ART, 488 (18.3%) became IRIS-TB compared with 259 of 2443 (10.6%) in the delayed ART set [9 studies; RR, 1.80 (95% CI, 1.57-2.07); I^2 = 74%].

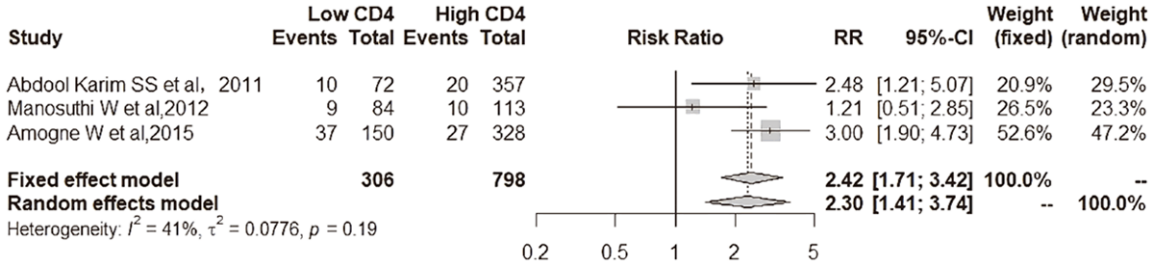

Figure 5. All-cause mortality comparison between low CD4 T cells and low CD4 T cells at baseline. Patients with low CD4 T cell count at baseline [18.3% (56 of 306 patients)] had a higher all-cause mortality than those with high CD4 T cell count at baseline [7.1% (57 of 798 patients)] at the end of follow-up [3 trials; RR, 2.42 (95% CI, 1.71-3.42); I^2 = 41%].

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.

Acknowledgements

The authors thank all member of their team for help and dedication. International Science and

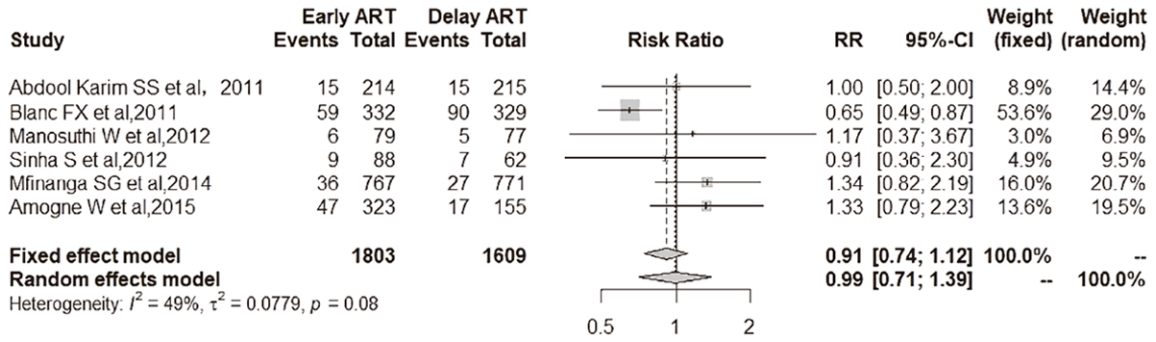

Figure 6. All-cause mortality comparison between early ART initiation and delayed ART initiation. Patients randomly assigned to early ART group [9.5% (172 of 1803 patients)] had insignificantly lower all-cause mortality than those receiving delayed ART [10.0% (161 of 1609 patients)] at the end of follow-up [6 trials; RR, 0.91 (95% CI, 0.74-1.12); I^2 = 49%].

technology cooperation project of Shanxi Province (2015081033).

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.

Address correspondence to: Hui Zhao, Department of Respiratory Medicine, The Second Hospital of Shanxi Medical University, No. 382 Wuyi Road, Taiyuan 030001, Shanxi Province, P. R. China. Tel: +86-351-3365393; E-mail: hui_zhao@sxmu.edu.cn

References

[1] Lawn SD, Myer L, Bekker LG and Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS 2006; 20: 1605-1612.

[2] Lucas SB, De Cock KM, Hounnou A, Peacock C, Diomande M, Hondé M, Beaumel A, Kestens L and Kadio A. Contribution of tuberculosis to slim disease in Africa. BMJ 1994; 308: 1531-1533.

[3] Perriëns JH, St Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, Portaels F, Willame JC, Mandala JK, Kaboto M, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. N Engl J Med 1995; 332: 779-784.

[4] Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY and Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. PLoS Med 2010; 7: e1000296.

[5] Chu R, Mills EJ, Beyene J, Pullenayegum E, Bakanda C, Nachega JB, Devereaux PJ and Thabane L. Impact of tuberculosis on mortality among HIV-infected patients receiving antiretroviral therapy in Uganda: a prospective cohort analysis. AIDS Res Ther 2013; 10: 19.

[6] Nachega JB, Morroni C, Chaisson RE, Goliath R, Efron A, Ram M and Maartens G. Impact of immune reconstitution inflammatory syndrome on antiretroviral therapy adherence. Patient Prefer Adherence 2012; 6: 887-891.

[7] Boulle A, Van Cutsem G, Cohen K, Hilderbrand K, Mathee S, Abrahams M, Goemaere E, Coetzee D and Maartens G. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA 2008; 300: 530-539.

[8] Cohen K and Meintjes G. Management of individuals requiring antiretroviral therapy and tuberculosis therapy. Curr Opin HIV AIDS 2010; 5: 61-69.

[9] Uthman OA, Okwundu C, Gbenga K, Volmink J, Dowdy D, Zumla A and Nachega JB. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis. Ann Intern Med 2015; 163: 32-39.

[10] Müller M, Wandel S, Colebunders R, Attia S, Furrer H and Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 2010; 10: 251-261.

[11] Silva CAM, Graham B, Webb K, Ashton LV, Harton M, Luetkemeyer AF, Bokatzian S, Almubarak R, Mahapatra S, Hovind L, Kendall

MA, Havlir D, Belisle JT and De Groote MA. A pilot metabolomics study of tuberculosis immune reconstitution inflammatory syndrome. Int J Infect Dis 2019; 84: 30-38.
[12] Crump JA, Wu X, Kendall MA, Ive PD, Kumwenda JJ, Grinsztejn B, Jentsch U and Swindells S. Predictors and outcomes of Mycobacterium tuberculosis bacteremia among patients with HIV and tuberculosis co-infection enrolled in the ACTG A5221 STRIDE study. BMC Infect Dis 2015; 15: 12.
[13] Grant PM, Komarow L, Andersen J, Sereti I, Pahwa S, Lederman MM, Eron J, Sanne I, Powderly W, Hogg E, Suckow C and Zolopa A. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of previously vs. deferred ART during an opportunistic infection. PLoS One 2010; 5: e11416.
[14] Shao HJ, Crump JA, Ramadhani HO, Uiso LO, Ole-Nguyaine S, Moon AM, Kiwera RA, Woods CW, Shao JF, Bartlett JA and Thielman NM. Previously versus postpone fixed dose combination abacavir/lamivudine/zidovudine in patients with HIV and tuberculosis in Tanzania. AIDS Res Hum Retroviruses 2009; 25: 1277-1285.
[15] Bourgarit A, Carcelain G, Martinez V, Lascoux C, Delcey V, Gicquel B, Vicaut E, Lagrange PH, Sereni D and Autran B. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. AIDS 2006; 20: F1-7.
[16] Breton G, Duval X, Estellat C, Poaletti X, Bonnet D, Mvondo Mvondo D, Longuet P, Leport C and Vildé JL. 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.
[17] da Silva TP, Giacoia-Gripp CBW, Schmaltz CA, Sant'Anna FM, Saad MH, Matos JA, de Lima ESJCA, Rolla VC and Morgado MG. Risk factors for increased immune reconstitution in response to mycobacterium tuberculosis antigens in tuberculosis HIV-infected, antiretroviral-naïve patients. BMC Infect Dis 2017; 17: 606.
[18] Kumarasamy N, Chaguturu S, Mayer KH, Solomon S, Yepthomi HT, Balakrishnan P and 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; 37: 1574-1576.
[19] Lawn SD, Myer L, Bekker LG and Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 2007; 21: 335-341.
[20] Manosuthi W, Kiertiburanakul S, Phoorisri T and Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. J Infect 2006; 53: 357-363.
[21] Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR and Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. Antivir Ther 2005; 10: 417-422.
[22] Musselwhite LW, Andrade BB, Ellenberg SS, Tierney A, Belaunzaran-Zamudio PF, Rupert A, Lederman MM, Sanne I, Sierra Madero JG and 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; 4: 115-123.
[23] Narita M, Ashkin D, Hollender ES and Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med 1998; 158: 157-161.
[24] Park WB, Choe PG, Jo JH, Kim SH, Bang JH, Kim HB, Kim NJ, Oh MD and Choe KW. Tuberculosis manifested by immune reconstitution inflammatory syndrome during HAART. AIDS 2007; 21: 875-877.
[25] Serra FC, Hadad D, Orofino RL, Marinho F, Lourenço C, Morgado M and Rolla V. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. Braz J Infect Dis 2007; 11: 462-465.
[26] Tadokera R, Meintjes GA, Wilkinson KA, Skolimowska KH, Walker N, Friedland JS, Maartens G, Elkington PT and Wilkinson RJ. Matrix metalloproteinases and tissue damage in HIV-tuberculosis immune reconstitution inflammatory syndrome. Eur J Immunol 2014; 44: 127-136.
[27] Tieu HV, Ananworanich J, Avihingsanon A, Apateerapong W, Sirivichayakul S, Siangphoe U, Klongugkara S, Boonchokchai B, Hammer SM and Manosuthi W. Immunologic markers as predictors of tuberculosis-associated immune reconstitution inflammatory syndrome in HIV and tuberculosis coinfected persons in Thailand. AIDS Res Hum Retroviruses 2009; 25: 1083-1089.
[28] Wendel KA, Alwood KS, Gachuhi R, Chaisson RE, Bishai WR and Sterling TR. Paradoxical worsening of tuberculosis in HIV-infected persons. Chest 2001; 120: 193-197.
[29] Bonnet M, Baudin E, Jani IV, Nunes E, Verhoustraten F, Calmy A, Bastos R, Bhatt NB and Michon C. Incidence of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome and impact on patient outcome. PLoS One 2013; 8: e84585.

[30] Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, Gengiah T, Nair G, Bamber S, Singh A, Khan M, Pienaar J, El-Sadr W, Friedland G and Abdool Karim Q. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010; 362: 697-706.

[31] Naidoo K, Yende-Zuma N, Padayatchi N, Naidoo K, Jithoo N, Nair G, Bamber S, Gengiah S, El-Sadr WM, Friedland G and Abdool Karim S. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. Ann Intern Med 2012; 157: 313-324.

[32] Luetkemeyer AF, Kendall MA, Nyirenda M, Wu X, Ive P, Benson CA, Andersen JW, Swindells S, Sanne IM, Havlir DV and Kumwenda J. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. J Acquir Immune Defic Syndr 2014; 65: 423-428.

[33] Meintjes G, Wilkinson RJ, Morroni C, Pepper DJ, Rebe K, Rangaka MX, Oni T and Maartens G. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. Aids 2010; 24: 2381-2390.

[34] Amogne W, Aderaye G, Habtewold A, Yimer G, Makonnen E, Worku A, Sonnerborg A, Aklillu E and Lindquist L. Efficacy and safety of antiretroviral therapy initiated one week after tuberculosis therapy in patients with CD4 T cell counts < 200 cells/μL: TB-HAART study, a randomized clinical trial. PLoS One 2015; 10: e0122587.

[35] Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, Gengiah T, Gengiah S, Naidoo A, Jithoo N, Nair G, El-Sadr WM, Friedland G and Abdool Karim Q. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011; 365: 1492-1501.

[36] Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, Madec Y, Marcy O, Chan S, Prak N, Kim C, Lak KK, Hak C, Dim B, Sin CI, Sun S, Guillard B, Sar B, Vong S, Fernandez M, Fox L, Delfraissy JF and Goldfeld AE. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011; 365: 1471-1481.

[37] Haridas V, Pean P, Jasenosky LD, Madec Y, Laureillard D, Sok T, Sath S, Borand L, Marcy O, Chan S, Tsitsikov E, Delfraissy JF, Blanc FX and Goldfeld AE. IRIS-TB, T-cell activation, and remodeling of the T-cell compartment in highly immunosuppressed HIV-infected patients with TB. Aids 2015; 29: 263-273.

[38] Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, Luetkemeyer AF, Hogg E, Rooney JF, Wu X, Hosseinipour MC, Lalloo U, Veloso VG, Some FF, Kumarasamy N, Padayatchi N, Santos BR, Reid S, Hakim J, Mohapi L, Mugyenyi P, Sanchez J, Lama JR, Pape JW, Sanchez A, Asmelash A, Moko E, Sawe F, Andersen J and Sanne I. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 2011; 365: 1482-1491.

[39] Laureillard D, Marcy O, Madec Y, Chea S, Chan S, Borand L, Fernandez M, Prak N, Kim C, Dim B, Nerrienet E, Sok T, Delfraissy JF, Goldfeld AE and Blanc FX. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome after previously initiation of antiretroviral therapy in a randomized clinical trial. Aids 2013; 27: 2577-2586.

[40] Manosuthi W, Mankatitham W, Lueangniyomkul A, Thongyen S, Likanonsakul S, Suwanvattana P, Thawornwan U, Suntisuklappon B, Nilkamhang S and Sungkanuparph S. Time to initiate antiretroviral therapy between 28 days and 12 weeks of tuberculosis treatment in HIV-infected patients: results from the TIME study. J Acquir Immune Defic Syndr 2012; 60: 377-383.

[41] Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, Ravinetto R, van Loen H, Nair A, Jackson A, Colebunders R, Maartens G, Wilkinson RJ and Lynen L. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. N Engl J Med 2018; 379: 1915-1925.

[42] Mfinanga SG, Kirenga BJ, Chanda DM, Mutayoba B, Mthiyane T, Yimer G, Ezechi O, Connolly C, Kapotwe V, Muwonge C, Massaga J, Sinkala E, Kohi W, Lyantumba L, Nyakoojo G, Luwaga H, Doulla B, Mzyece J, Kapata N, Vahedi M, Mwaba P, Egwaga S, Adatu F, Pym A, Joloba M, Rustomjee R, Zumla A and Onyebujoh P. Previously versus postpone initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. Lancet Infect Dis 2014; 14: 563-571.

[43] Sinha S, Shekhar RC, Singh G, Shah N, Ahmad H, Kumar N, Sharma SK, Samantaray JC, Ranjan S, Ekka M, Sreenivas V and Mitsuyasu RT. Previously versus postpone initiation of antiretroviral therapy for Indian HIV-Infected individuals with tuberculosis on antituberculosis treatment. BMC Infect Dis 2012; 12: 168.

[44] Nachega JB, Rosenkranz B, Simon G, Chaisson RE, Diacon A and Taljaard J. Management of adult active tuberculosis disease in era of HIV pandemic, current practices and future perspectives. Infect Disord Drug Targets 2011; 11: 134-143.

[45] Maartens G, Decloedt E and Cohen K. Effectiveness and safety of antiretrovirals with rifampicin: crucial issues for high-burden countries. Antivir Ther 2009; 14: 1039-1043.
[46] Lawn SD and Meintjes G. Pathogenesis and prevention of immune reconstitution disease during antiretroviral therapy. Expert Rev Anti Infect Ther 2011; 9: 415-430.
[47] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.