Times of initiation of antiretroviral therapy in patients with tuberculosis and human immunodeficiency virus co-infection with CD4 count less than 350 cells/mm^3

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Kunthida Phromlor[1], M.D.; Chawalit Prakrongyat[2], M.D.; Nonchaya Jaitrong[3], M.D.

[1]The 50th Anniversary Mahavajiralongkorn Hospital, Thailand; [2]Pra Arjarnphun Arjaro Hospital, Thailand; [3]Dontan Hospital, Thailand.

Accepted: Jun 2020
Latest revision: Sep 2020
Printed: Sep 2020

Correspondence to: Kunthida Phromlor; **kunthida.kp**@gmail.com

ABSTRACT

OBJECTIVE

To examine the mortality rates of various initiation times of antiretroviral therapy (ART) after starting tuberculosis treatment.

METHODS

We conducted a retrospective cohort study using medical records of outpatients with the diagnosis of TB/HIV co-infection in Khon Kaen Hospital, Thailand between January 2007 and August 2017. We included the patients who started tuberculosis treatment and various times of starting ART with CD4 count less than 350 cells/mm^3. We separated patients into 3 groups by the time of initiated ART starting within the first 4 weeks, 5 to 8 weeks, and 9 to12 weeks after starting tuberculosis treatment. We compared the risk of all-cause mortality within 1 year after start tuberculosis treatment among three groups as our primary outcome. Our secondary outcomes were sputum conversion at 2 months after starting tuberculosis treatment and rate of CD4 count increasing in 1 year after tuberculosis treatment.

RESULTS

A total of 132 patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3 were included in the study; 62 patients started ART within the first 4 weeks after TB treatment, 45 patients started in 5 to 8 weeks and 25 patients started in 9 to 12 weeks. The primary outcome was reached by 1 (2%) patient in the first group, 2 (8%) patients in the second group, and 1 (4%) patient in the third group. (relative risk [RR], 2.76, 95% CI, 0.26 to 29.47 and RR, 2.48, 95% CI, 0.16 to 38.13). Only 28 of 132 patients (21%) had been recorded data on sputum conversion at 2 months after tuberculosis treatment, the result showed no significant difference in improving sputum conversion between starting ART at 5 to 8 weeks and starting ART within the first 4 weeks (RR, 1.30, 95% CI, 0.77 to 2.21). CD4 level increasing rates among the three groups were not significantly different (mean difference (MD), 2556.79, 95% CI, -1011.56 to 6125.14 and MD, 86.67, 95% CI, -1333.69 to 1507.04).

CONCLUSION

The study showed no significant difference between mortality rate and various initiation time of ART after start tuberculosis treatment.

INTRODUCTION

Tuberculosis (TB) is a leading cause of morbidity and mortality among people living with human immunodeficiency virus (HIV) infection worldwide, it was estimated that about one-third of new HIV patients infected with TB were death in 2014.[1] Using of antiretroviral therapy (ART) decreased a large number of the morbidity and mortality of patients with TB/HIV co-infection.[2,3] A systematic review study in 2015 including 8 trials with 4,368 patients with TB/HIV co-infection showed starting ART within 4 weeks after starting TB treatment improved survival in those with CD4 count less than 50 cells/mm^3, and it associated with a 2-fold higher frequency of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS), and it also stated that there is not enough evidence to support or refute a survival benefit for starting ART within 4 weeks compared with starting within 8 to 12 weeks after starting TB treatment or starting after finished TB treatment in patients with CD4 count more than 50 cells/mm^3.[4] There is a randomized controlled trial study in four countries of Africa in 2014 including 1,538 patients with TB/HIV co-infection with CD4 count more than 220 cells/mm^3, it showed no difference of mortality rate between starting ART after 2 weeks of starting TB treatment and starting at the end of TB treatment.[5] There is another randomized controlled trial study in 2011 in Cambodia include 661 patients with CD4 count less than 200 cells/mm^3 showed starting ART at 2 weeks after the starting TB treatment significantly improved survival rate compared with starting ART at 8 weeks after starting TB treatment.[6] Furthermore, there is a randomized controlled trial study in Thailand in 2012 including 156 patients with TB/HIV co-infection, and CD4 count less than 350 cells/mm^3 showed no difference in mortality rate in starting ART at 4 weeks compared with 12 weeks after tuberculosis treatment.[7] However, no study showed the risks or benefits of starting ART in a different period during 1 to 12 weeks after tuberculosis treatment in patients with CD4 count less than 350 cells/mm^3. Thus, we aim to identify the risks and benefits of ART in various starting times; within the first 4 weeks, 5 to 8 weeks, and 9 to 12 weeks in patients with TB/HIV co-infection.

METHODS

STUDY DESIGN

This was a retrospective cohort study to determine the optimal initiation time of ART during tuberculosis treatment and to identify the association between the initiation time of ART and mortality rate in patients with TB/HIV co-infection. The present study was approved by the Khon Kaen Hospital Institutional Review Board (IRB). All patient's data will be kept confidentially without disclosed. All patient's data were collected in a closed system that people cannot access to patients' data except the researcher team.

PATIENTS

We included patients who have diagnosed with both TB and HIV infection by using ICD A15 to A19 and B20 to B24. Inclusion criteria as follows (i) tuberculosis was confirmed by a positive smear for acid-fast bacilli (AFB) stain or positive mycobacterial culture or positive polymerase chain reaction (PCR) for tuberculosis in any body fluid or confirmed by clinical symptoms and radiological findings, (ii) HIV infection was confirmed by any tests. Exclusion criteria as follows (i) age<18 years, (ii) previous treatment by ART, (iii) patients with CD4 count more than 350 cells/mm^3, (iv) patients who died before start ART, (v) previous TB treatment more than 12 weeks before starting ART.

INTERVENTION

We separated time to initiate ART during tuberculosis treatment into three groups (within

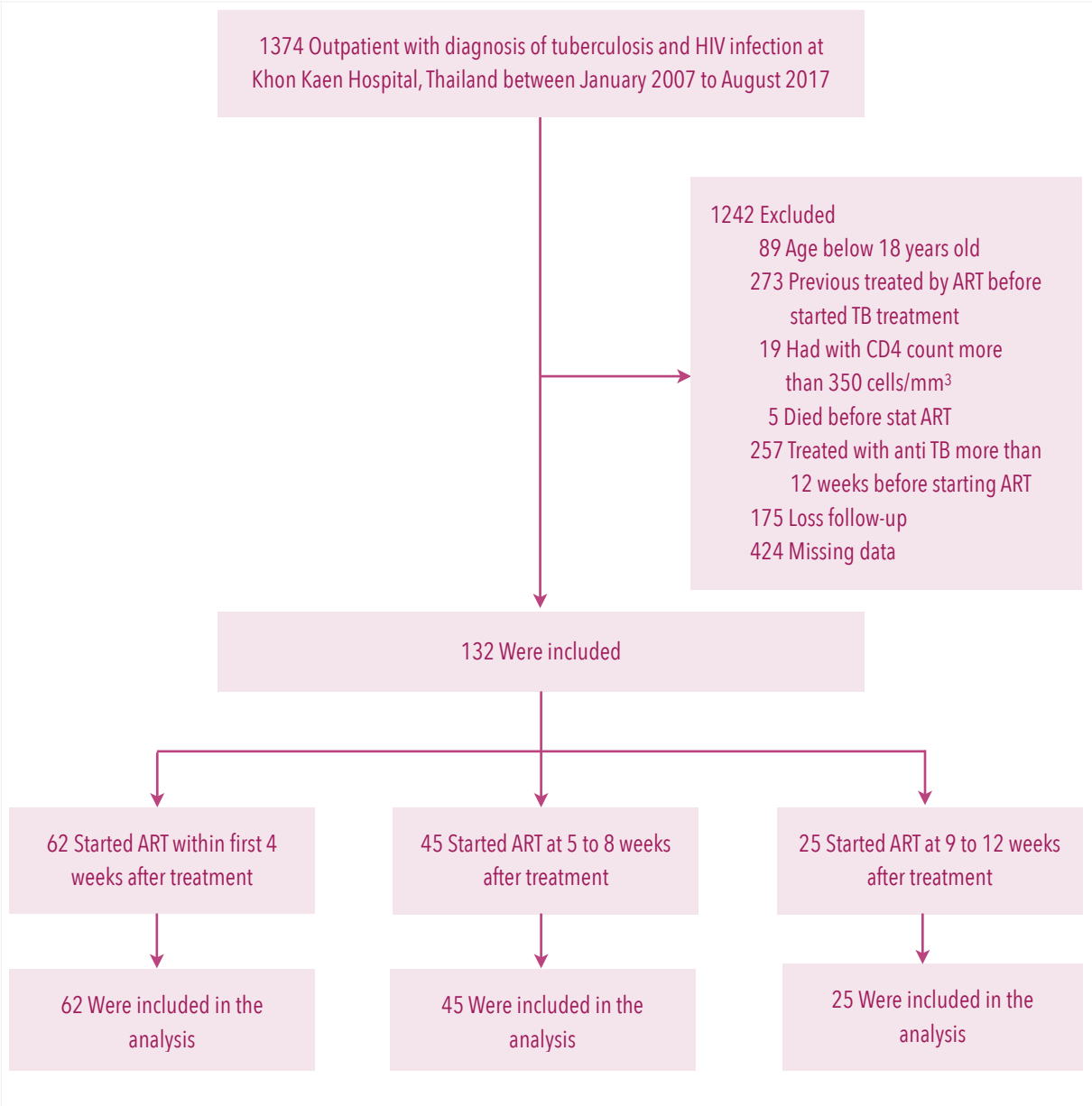

Figure 1. Study flow

the first 4 weeks, 5 to 8 weeks, and 9 to 12 weeks after start tuberculosis treatment) collected by reviewing the medical record of the patients.

OUTCOMES

The primary outcome was all-cause mortality within 1 year after start tuberculosis treatment. The secondary outcomes were sputum conversion rate at 2 months after starting tuberculosis treatment in patients with pulmonary tuberculosis confirmed by positive sputum AFB and percent change of CD4 level in 1 year after tuberculosis treatment.

DATA COLLECTION

We confirmed the medical record of outpatients with the diagnosis of tuberculosis and HIV infection

Table 1. Characteristics of the patients

Characteristic	Initiation time of ART after tuberculosis treatment			P Value
	The first 4 weeks (N=62)	5-8 weeks (N=25)	9-12 weeks (N=25)	
Age–yr				0.08
Median	35.1	32.5	37.8	
Interquartile range	29.3–39.1	27.7–38.6	33.3–39.6	
Male sex–no. (%)	45 (72.6)	37 (82.2)	14 (56.0)	0.06
BMI–kg/m^2	18.7 3.2	18.5 2.5	19.0 2.5	0.76
Range of CD4 count level at time of diagnosis–cells/mm^3				0.91
50	32 (51.6)	20 (44.4)	14 (56.0)	
51– 200	22 (35.5)	18 (40.0)	8 (32.0)	
201–350	8 (12.9)	7 (15.1)	3 (12.0)	
CD4 count level at time of diagnosis–cells/mm^3				0.89
Median	45.5	59.0	30.0	
Interquartile range	20.8–119.3	14.0–136.0	15.0–147.0	
Opportunistic infections–no. (%)				
Pneumocystis jiroveci pneumonia	7 (11.3)	4 (8.9)	2 (8.0)	0.93
Candidiasis	1 (1.6)	5 (11.1)	0	0.05
Cryptococcosis	2 (3.2)	5 (11.1)	1 (4.0)	0.21
Herpes virus infection	4 (6.5)	4 (8.9)	0	0.36
Toxoplasmosis	1 (1.6)	2 (4.4)	1 (4.0)	0.53
Cytomegalovirus infection	1 (1.6)	5 (11.1)	3 (12.0)	0.06
Histoplasmosis	0	0	1 (4.0)	0.19
Hemoglobin level–g/dl	10.12.5	10.2 2.2	9.52.2	0.48
Positive AFB smear–no. (%)	26 (47.3)	22 (48.9)	10 (43.5)	0.91
Positive culture for TB–no. (%)	7 (46.7)	4 (44.4)	2 (33.3)	0.90

Table 1. (Continued)

Characteristic	Initiation time of ART after tuberculosis treatment			P Value
	The first 4 weeks (N=62)	5-8 weeks (N=25)	9-12 weeks (N=25)	
Type of tuberculosis–no. (%)				
Pulmonary	45 (72.6)	32 (71.1)	19 (76.0)	0.91
Spine	0	1 (2.2)	0	0.53
Lymphadenitis	21 (33.9)	14 (31.1)	7 (28.0)	0.86
Pleura	0	4 (8.9)	1 (4.0)	0.03
Meningitis	1 (1.6)	5 (11.1)	1 (4.0)	0.08
Pericarditis	1 (1.6)	0	0	1.00
Colitis	2 (3.2)	2 (4.4)	0	0.82
Peritonitis	3 (4.8)	1 (2.2)	1 (4.0)	0.85
Miliary	1 (1.6)	0	0	1.00

and follow-up at Khon Kaen Hospital, Thailand between January 2007 and August 2017. The primary outcome was the mortality of patients identified by reviewing the medical records and searching the database of Civil registration.

STATISTICAL ANALYSIS

We compared the characteristics of the included patients that could be potentially confounded to our primary and secondary outcomes. We used descriptive statistics to summarize the characteristics of the patients. Number and percentage were used for categorical variables. Mean with standard deviation (SD) were used for summarizing normally distributed scale variables while median and interquartile range (IQR) for non-normally distributed scale variables. For inferential statistics, we used either Pearson's chi-squared test, Fisher's exact test, ANOVA, or Kruskal-Wallis test which appropriate to compare the characteristic of the patients among the three groups. We used relative risk (RR) to compare outcomes among the three groups. Also, to identify the factors that might affect our primary outcome, we used binary logistic regression analysis and Cox proportional hazard regression together with crude odds ratio, adjusted odds ratio, the crude hazard ratio (CHR), and adjusted hazard ratio (AHR). All tests were interpreted together with either P-Value or a 95% confidence interval (CI). $P<0.05$ and 95% CI do not include 1.00 were considered as statistically significant. We also used the Kaplan-Meier plot to demonstrate time against cumulative survival within 1 year after tuberculosis treatment among the three groups. All analyses were performed with SPSS.

Table 2. Treatment outcomes

Outcome	Initiation time of ART after tuberculosis treatment			Relative risk (95% CI) *	Relative risk (95% CI)†	Mean difference (95% CI)‡	Mean difference (95% CI)§
	The first 4 weeks (N=62)	5-8 weeks (N=25)	9-12 weeks (N=25)				
1-Year mortality-no. (%)	1 (2)	2 (8)	1 (4)	2.76 (0.26– 29.47)	2.48 (0.16–38.13)		
Sputum conversion at 2 months-no. (%)	8 (13)	8 (32)	5 (20)	1.30 (0.77–2.21)	N/A *		
Percent change of CD4 level in 1 year							
Median	336.4	230.1	480.1			2556.79	86.67
Interquartile range	147.2–796.9	106.5–1066.3	27.3–1418.6			-1011.56 to 6125.14	-1333.69 to 1507.04

* Relative risk from the comparison between the group of 5-8 week compared to the first 4 weeks
† Relative risk from the comparison between the group of 9-12 week compared to the first 4 weeks
‡ Mean difference from the comparison between the group of 5-8 week compared to the first 4 weeks
§ Mean difference from the comparison between the group of 9-12 week compared to the first 4 weeks

RESULTS

CHARACTERISTICS OF THE PATIENTS

Among 1,374 patients who diagnosed with tuberculosis and HIV infection at Khon Kaen Hospital, Thailand between January 2007 to August 2017, a total of 132 patients were included in the study; 62 patients who started ART within the first 4 weeks after TB treatment, 45 patients who started in 5 to 8 weeks and 25 patients who started in 9 to12 weeks (Figure 1). Most of them were male with an average age of 35 years old and average body mass index (BMI) of 18.7 kg/m^2. The median of CD4 count level at the time of diagnosis was 45.5 cells/mm^3 in the first 4 weeks group, 59.0 cells/mm^3 in the 5 to 8 weeks group and 30.0 cells/mm^3 in the 9 to 12 weeks. There were no statistically significant differences among the three groups regarding to baseline characteristics (Table 1). In addition, clinical characteristics including opportunistic infections, hemoglobin level, positive AFB, positive culture for TB, positive PCR for TB in any fluid and types of tuberculosis were relatively similar among three groups except pleural tuberculosis; no pleural tuberculosis in the first 4 weeks group, 4 patients (8.9%) with pleural tuberculosis in the 5 to 8 weeks group while only one patient (4%) with pleural tuberculosis in the 9 to 12 weeks group.

ALL-CAUSE MORTALITY

Overall, there are 4 patients died in 10 years among 3 groups, 1 (2%) patient who started ART within the first 4 weeks, 2 (8%) patients who started at 5 to 8 weeks, and 1 (4%) patient who started at 9 to 12 weeks. Our study showed no significant difference in one-year all-cause mortality (RR, 2.76; 95% CI, 0.26 to 29.47 and RR, 2.48; 95% CI, 0.16 to 38.13) as shown in Table 2.

SPUTUM CONVERSION AT 2 MONTHS.

Only 28 of 132 patients (21.2%) had been recorded data on sputum conversion at 2 months after tuberculosis treatment, the result showed no significant difference in improving sputum conversion between starting ART at 5 to 8 weeks and starting ART within the first 4 weeks (RR, 1.30; 95% CI, 0.77 to 2.21) as shown in Table 2.

RATE OF CD4 LEVEL INCREASING IN 1 YEAR.

The result shows CD4 level increasing rate medians 336.4% (IQR, 147.2 to 796.9%) inpatient who started ART within the first 4 weeks, 230.1% (IQR, 106.5 to 1066.3%) inpatient who started at 5 to 8 weeks, and 480.1% (IQR, 27.3 to 1418.6%) inpatient who started at 9 to 12 weeks. However, there is no significant difference among 3 groups (Mean difference, 2556.79; 95% CI, -1011.56 to 6125.14 and Mean difference, 86.67; 95% CI, -1333.69 to 1507.04)

FACTORS DETERMINE OUTCOME

The result of the binary logistic regression analysis and the Cox regression analysis of the outcome were summarized in Table 3. We found no factors significantly associated with a 1-year mortality rate in patient with TB/HIV co-infection and CD4 count less than 350 cells/mm^3 including various initiation time of ART during tuberculosis treatment, age group (age<40 yr. vs. age≥ 40yr.), sex, BMI (BMI<18 kg/m^2 vs. BMI≥18 kg/m^2) and hemoglobin level (Hb<8 g/dL vs. ≥ 8 g/dL). Figure 2 Kaplan-Meier showed that the three groups of various initiation times of ART during tuberculosis treatment had no statistical difference in the survivors within 1 year.

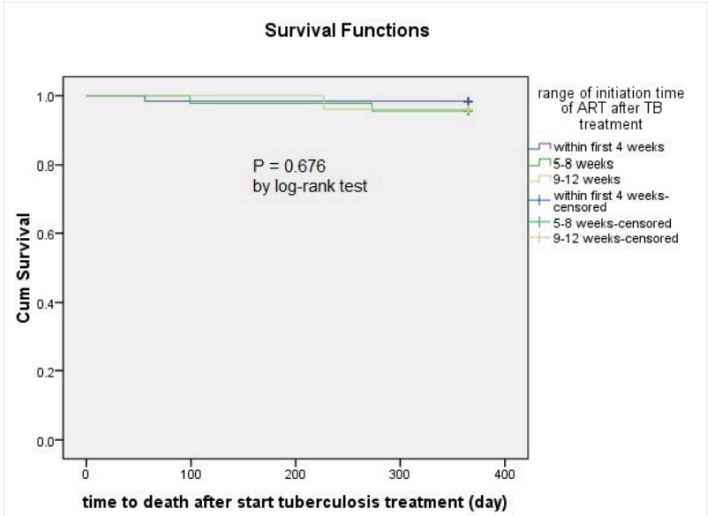

Figure 2. Kaplan-Meier comparing mortality in various initiation time of ART during tuberculosis treatment .

DISCUSSION

MAIN FINDINGS

In this retrospective cohort study based on 132 patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3, we found that one year all-cause mortality rate were not significantly difference among three groups of various initiation time of ART after starting tuberculosis treatment. The other outcomes including sputum conversion in two months and rate of CD4 count increasing in one year after tuberculosis treatment were no significantly difference as well.

COMPARISON WITH OTHER STUDIES

Our findings showed no difference in mortality in patients who initiated ART within the first 4 weeks group compared with 5 to 8 weeks group and 9 to12 weeks group. The first previous study showed no difference in mortality rate in starting ART at 4 weeks compared with 12 weeks after TB treatment in patients with CD4 count less than 350 cells/mm^3.[7] So, our result goes along with this study. However, this study did not mention.

LIMITATIONS OF STUDY

We collected data by the reviewed medical record of outpatients within ten years retrospectively. Thus, there are some limitations to our study. First,

Table 3. Factor determining death

Factor	Odds ratio (95% CI)		Hazard ratio (95% CI)	
	Crude analysis	Adjusted analysis	Crude analysis	Adjusted analysis
Initiation time of starting ART after tuberculosis treatment				
Within first 4 weeks	Reference	Reference	Reference	Reference
5-8 weeks	2.84 (0.25–32.29)	5.01 (0.32–78.10)	2.75 (0.25–30.36)	5.10 (0.35–75.17)
9-12 weeks	2.54 (0.15–42.29)	2.19 (0.12–39.88)	2.48 (0.16–39.57)	2.12 (0.13–34.65)
Age 40 year	4.12 (0.55–30.69)	4.71 (0.58–38.39)	3.93 (0.55–27.87)	4.61 (0.62–34.46)
Male sex	0.36 (0.05–2.67)	0.21 (0.02–2.46)	2.65 (0.37–18.82)	0.23 (0.02–2.40)
BMI 18 kg/m^2	2.12 (0.22–20.94)	5.11 (0.33–77.92)	2.12 (0.22–20.36)	5.18 (0.36–73.91)
Hemoglobin level 8 g/dL	0.66 (0.07–6.61)	0.43 (0.04–5.03)	0.66 (0.07–6.33)	0.39 (0.04–4.13)

there are a lot of incomplete and missing medical records and it probably missed some variables. Second, we studied only in one hospital. So, we had a small sample size, only four patients died through ten years. Third, we did not study the specific cause of death, so non TB/HIV associated cause of death might be included in this study. Due to the limitations, using our results in clinical practice should be considered.

CONCLUSION AND IMPLICATION

Our study showed no association between the various initiation time of ARV during tuberculosis treatment and mortality rate in patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3. So, ART can be delayed until 12 weeks after start tuberculosis treatment in patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3. However, our study has several limitations including small sample size, missing data due to a retrospective study in nature, and study design as a retrospective study. Thus, further studies with larger sample size and prospective study design to determine precise results are required.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his supervision, guidance, and all of his support to help us complete the present study. We also would like to thank Khon Kaen Medical Education Center for all resources offered to us and Department of Medical Information System, Khon Kaen Hospital for data accessing.

COMPETING INTERESTS: This study has no competing on interest.

FUNDING:None

REFERENCES

1. World Health Organization (WHO). Global Tuberculosis Report 2015.www.who.int/tb/publications/global_report/en/
2. Lawn SD, Myer L, Edwards D, Bekker L-G, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS Lond Engl. 2009 Aug 24;23(13):1717–25.
3. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011 Apr;24(2):351–76.
4. Uthman OA, Okwundu C, Gbenga K, Volmink J, Dowdy D, Zumla A, et al. 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 Jul 7;163(1):32.
5. Mfinanga SG, Kirenga BJ, Chanda DM, Mutayoba B, Mthiyane T, Yimer G, et al. Early versus delayed 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 Jul 1;14(7):563–71.
6. Blanc F-X, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis. N Engl J Med. 2011 Oct 20;365(16):1471–81.
7. Manosuthi W, Mankatitham W, Lueangniyomkul A, Thongyen S, Likanonsakul S, Suwanvattana P, et al. Time to initiate antiretroviral therapy between 4 weeks and 12 weeks of tuberculosis treatment in HIV-infected patients: results from the TIME study. J Acquir Immune Defic Syndr 1999. 2012 Aug 1;60(4):377–83.
8. Velasco M, Castilla V, Sanz J, Gaspar G, Condes E, Barros C, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. J Acquir Immune Defic Syndr 1999. 2009 Feb 1;50(2):148–52.
9. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodefi ciency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis 2011;52: 1374–83.
10. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 2011; 365: 1482–91.
11. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006; 367: 817–24.
12. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of Antiretroviral Therapy with Tuberculosis Treatment. New England Journal of Medicine. 2011 Oct 20;365(16):1492–501.
13. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. Lancet 2002; 359:2059–64.
14. Kirk O, Gatell JM, Mocroft A, et al. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. Am J Respir Crit Care Med 2000; 162:865–72.
15. Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS 2002; 16:75–83.
16. Pedral-Sampaio DB, Alves CR, Netto EM, Brites C, Oliveira AS, Badaro R. Efficacy and safety of efavirenz in HIV patients on rifampin for tuberculosis. Braz J Infect Dis 2004; 8:211–6.
17. Lawn SD, Bekker L-G, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005; 5:361–73.
18. Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin or rifabutin-based regimens in New York City, 1997–2000. Clin Infect Dis 2005; 41:83–91.
19. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Lancet 1999; 353: 1843–7.
20. McIlleron H, Wash P, Burger A, Norman J, Folb PI, Smith P. Determinants of rifampicin, isoniazid, pyrazinamide and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother 2006; 50:1170–7.
21. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. Clin Infect Dis 2005; 40:1481–91.
22. Perriens JH, St. Louis ME, Mukadi YB, 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; 332:779–84.
23. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009; 360: 1815–26.
24. Whalen C, Nsubuga P, Okwera A, et al. Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. AIDS 2000; 14: 1219–28.
25. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohorts Study. JAMA 1999; 282: 2220–26.