Time to Initiate Antiretroviral Therapy Between 4 Weeks and 12 Weeks of Tuberculosis Treatment in HIV-Infected Patients: Results From the TIME Study

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Background: Optimal timing for initiation of antiretroviral therapy (ART) among HIV-infected patients with tuberculosis (TB) is not well established.

Methods: HIV/TB-coinfected patients were randomized to initiate tenofovir/lamivudine/efavirenz at 4 weeks (4-week group) or 12 weeks (12-week group) of TB treatment. The primary outcome was 1-year all-cause mortality.

Results: Of 156 patients, 79 were in 4-week group and 77 in 12-week group. Overall, median (interquartile range) CD4 was 43 (47–106) cells per cubic millimeter and median (interquartile range) HIV-1 RNA was 5.8 (5.4–6.3) log copies per milliliter. Eleven (7%) mortalities occurred in a total follow-up period of 137 patient-years. Seven percent (6/79, 8.76 per 100 patient-years) mortalities were in 4-week group, and 6% (5/77, 7.25 per 100 person-years) mortalities were in 12-week group [relative risk (RR) = 0.845, 95% confidence interval (CI) = 0.247 to 2.893]. Twenty-eight (35%) patients in 4-week group and 25 (32%) patients in 12-week group were hospitalized (RR = 1.142, 95% CI = 0.588 to 2.217). Grade 2–4 adverse events were 39% (31/79) in 4-week group and 34% (26/77) in 12-week group (RR = 1.267, 95% CI = 0.659 to 2.435). In multivariate analysis, "low albumin" (RR = 2.695, 95% CI = 1.353 to 5.475) and "low baseline CD4 count" (RR = 4.878, 95% CI = 1.019 to 23.256) were the independent predictors of mortality. Immune reconstitution inflammatory syndrome was more frequent in 4-week group with an incidence of 8.86 versus 5.02 per 100 person-months in 12-week group over the first 6 months of ART ($P = 0.069$).

Conclusions: In middle-income countries where ART is initiated at CD4 count of <350 cells per cubic millimeter, immediate initiation of ART in HIV-infected patients with active TB was not associated with survival advantage when compared to initiation of ART at 12 weeks.

Key Words: HIV, tuberculosis, antiretroviral, treatment, Thailand

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INTRODUCTION

HIV infection and tuberculosis (TB) remain serious public health threat in many countries, particularly in the resource-constrained countries. The global incident cases of TB in 2010 were 8.8 million, and it resulted in almost 350,000 people with HIV died from TB.[1] Most of the cases of both diseases were coincided in Africa and Asia; however, the rate of coinfection of those varies in each geographical location.[1] Approximately half of the patients who coinfected with HIV and TB were on antiretroviral therapy (ART) in 2010. As a result of scaling up ART access program in such area, a significant number of advanced HIV-infected patients who enter ART programs are increasing.

Remarkable achievements in reducing mortality in HIV and TB–coinfected patients had been previously reported.[2,3] Nevertheless, treatment with antiretroviral drugs in this scenario is relatively complex. These issues included poor tolerability of concomitant treatment regimens, drug co-toxicities, pharmacokinetic drug interactions between rifampicin and antiretroviral drugs, and polypharmacy impacts on adherence.[4,5] This requires expertise and multidisciplinary approaches in the comanagement of both diseases. Delayed ART potentially allows better determination of a specific cause for adverse drug effects particularly severe drug hypersensitivity, decreasing the incidence and severity of TB-associated immune reconstitution inflammatory syndrome (TB IRIS). The major concern raised among many variables is that we mainly have to balance between mortality associated with delayed ART initiation versus mortality associated with TB IRIS and/or severe overlapping drug hypersensivity/toxicities with early ART.[4,5] Thus, attending physicians have to take several considerations for timely initiation of ART. Recent published reports demonstrated that mortality was substantially reduced in patients who initiated ART during 6 months of TB therapy rather than deferring until it was

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completed.[2,6–8] Nevertheless, data regarding precisely how early ART should be initiated and how lowest threshold of CD4 cutoff level should be deferred ART during TB treatment is still limited, especially in the different setting of resources, medical infrastructure, geographical location, severity of TB, and degree of immune deficiency. We therefore conducted the present study with aim to determine the optimal timing for initiation of ART to minimize the mortality among HIV-infected patients with active TB in the setting of a middle-income country.

METHODS

The present study was designed as an open-label, randomized, controlled trial involving 156 HIV-infected patients at the Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand. This institute is a 300-bed tertiary HIV-referral center located directly northwest to Bangkok. A primary objective was to compare 1-year all-cause mortality between coinfected patients with HIV and TB who received ART at 4 weeks (4-week group) and 12 weeks (12-week group) of TB treatment. Secondary objectives were to compare (1) the rate of hospitalization, (2) the rate of adverse events related to anti-TB and antiretroviral drugs, (3) composite endpoint of mortality, hospitalization, and grade 3–4 adverse events, (4) the rate of TB IRIS, and (5) to identify the risk factors of death.

All eligible patients were randomly assigned using computer-generated numbers to 1 of 2 treatment groups in a 1:1 ratio with no stratification, and all patients remained in their randomized arm until the end of study. Enrollment was from October 2009 to May 2011. Inclusion criteria for both groups were as follows: (1) HIV-infected patients who were 18–65 years of age, (2) had CD4 cell count of $<$350 cells per cubic millimeter, (3) having a diagnosis of active TB by clinical features, positive acid-fast staining and/or positive culture for *Mycobacterium tuberculosis*, and (4) participated and provided an informed consent. Exclusion criteria for both groups were as follows: (1) prior receiving of any antiretroviral drug, (2) being pregnant, (3) having serum aspartate aminotransferase and alanine aminotransferase levels $>$5 times the upper limit of the normal range, (4) having serum creatinine level $>$2 times the upper limit of the normal range, and (5) moribund patients. A once-daily antiretroviral regimen of tenofovir, lamivudine, and efavirenz was initiated at 4 weeks and 12 weeks of TB treatment. The patients had follow-up visits at week 2, week 6, week 12, and every 12 weeks after initiation of ART until 96 weeks, at which time they were assessed clinically, and blood samples were taken.

All patients were instructed to report by phone call and present to the institute for any suspected symptoms. Information of the mortality was based on justification of attending physicians and investigators; and all had been reviewed by the ethical committee. Adverse events related to antiretroviral drugs and anti-TB drugs were graded using the division of AIDS table for grading of severity of adult and pediatric adverse events. Regarding TB IRIS definition, patients were classified as having definite TB-IRIS if they met criteria from a case definition previously described by the International Network for the Study of HIV-associated IRIS.[9] Medication adherence was assessed by study questionnaire.

Extrapulmonary TB was defined as a case of TB involving organs other than the lung, such as involved lymph node, pleura, gastrointestinal tract, central nervous system, skeletal tissue, genitourinary tract, and skin. Anti-TB regimen consisted of isoniazid, rifampicin, ethambutol, and pyrazinamide were administered in the first 2 months followed by isoniazid and rifampicin for the subsequent 4–7 months based upon clinical response. The dosage of rifampicin was 450 mg per day for patients with a body weight $<$50 kg and 600 mg per day for patients with a body weight $\geq$50 kg. Oral trimethoprim/sulfamethoxazole prophylaxis was given for primary prophylaxis of *Pneumocystis jiroveci* pneumonitis in case of CD4 cell count $<$200 cells per cubic millimeter. The general baseline clinical characteristics (eg, gender, age, body weight, body mass index, previous opportunistic infections, and site of TB infection) were recorded. Laboratory parameters, including complete blood cell count, liver enzymes, kidney enzyme, serum cryptococcal antigen, serology of viral hepatitis, and lipid profiles, were assessed at baseline visit. Blood samples were obtained to study CD4 cell counts by flow cytometry and plasma HIV-1 RNA by real-time polymerase chain reaction using a COBAS AmpliPrep/COBAS TaqMan HIV-1 test (Roche Molecular Systems Inc, Branchburg, NJ) in which plasma HIV-1 RNA can be measured in a range of 40–10,000,000 copies per milliliter.

Sample size was calculated by testing for the proportion of death after 48 weeks of TB treatment between the 2 study groups. The difference of proportion of death was a 2.5-time difference of the 2 treatment groups on the basis of a predicted rate of 10% in either one of the study group. Type 1 and type 2 errors were 0.05 and 0.20, respectively. Sample size needed to include in the study was 210 patients. After the interim analyses in December 2010 and May 2011, this study was ended prematurely in May 2011 by ethical committees of the Department of Disease Control, Ministry of Public Health, with a reason that the final primary outcome was achieved. The further recruitment was not needed due to enough power of the test. Mean (±SD), median [interquartile range at 25th and 75th, (IQR)] and frequencies (%) were used to describe patients' characteristics. The χ^2 test and Kruskal–Walis test were used to compare categorical and continuous variables, respectively. Death-free probabilities due to any reason at 1 and 2 years after TB diagnosis and the median time to ART discontinuation were calculated by the Kaplan–Meier method and compared between groups by the log rank test. The Cox proportional hazard model was used to explore the probability of death after TB diagnosis by adjusting for confounding factors and factors of interest. The factor which had P value of less than 0.10 by univariate analysis and factors of interest were included into the multivariate analysis. The relative risk (RR) for variable and its 95% confidence interval (CI) were estimated. All statistical analyses were conducted using SPSS version 15.0 (SPSS Inc, Chicago, IL). All reported P values were 2-sided and were statistical significant if P $<$0.05. This study was reviewed

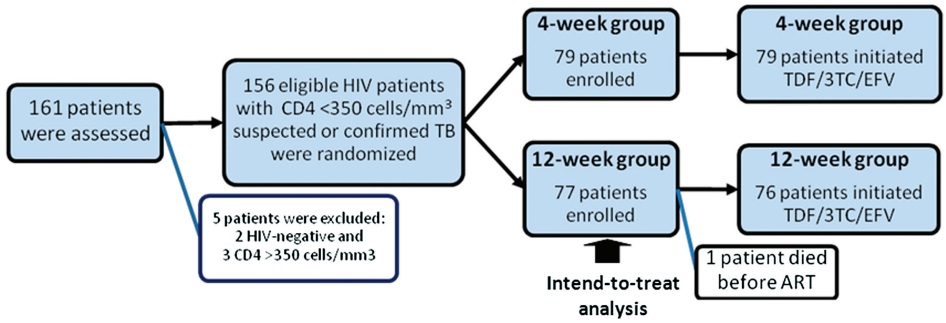

FIGURE 1. Schematic of study enrollment.

and approved by ethical committee for research in human subjects of the Department of Diseases Control, Ministry of Public Health, and by the institutional review board.

RESULTS

The study scheme is shown in Figure 1. A total of 156 patients were eligible and randomized. Overall mean ± SD age was 38 ± 9 years; 121 (77.6%) were male, median (IQR) CD4 cell count was 43 (47–106) cells per cubic millimeter; and median (IQR) plasma HIV-1 RNA was 5.8 (5.4–6.3) log copies per milliliter. Eighty-three (53%) patients were diagnosed extrapulmonary or disseminated TB; and the remaining patients were isolated pulmonary TB. One hundred one (65%) patients had positive acid-fast staining or positive TB culture and 55 (35%) patients were identified by clinical symptoms and radiological findings. All patients were ethnically Thai. Seventy-nine patients were randomized into the 4-week group and 77 patients were in the 12-week group. There were no significant differences in terms of patients' demographic features and baseline laboratory parameters ($P > 0.05$), except total cholesterol, as shown in Table 1.

During the study period, 11 (7%) mortalities occurred in a totaling of 137 patient-years of follow-up. Seven percent (8.76 per 100 patient-years) mortalities were in the 4-week group and 6% (7.25 per 100 person-years) mortalities were in

TABLE 1. Baseline Characteristics of 156 HIV-Infected Patients

Characteristics	4-Week Group (n = 79)	12-Week Group (n = 77)	*P*
Demographics			
Male gender	62 (78.4%)	59 (76.6%)	0.849
Age, years, mean ± SD	38 ± 9	38 ± 8	0.745
Body weight, Kg, mean ± SD	53 ± 10	55 ± 9	0.074
Sites of TB			
Lung	40 (50.6%)	33 (42.9%)	0.569
Cervical lymph node	10 (12.6%)	9 (11.7%)	
Disseminated TB	26 (32.9%)	33 (42.9%)	
Meninges	1 (1.3%)	2 (2.5%)	
Colon	2 (2.6%)	0 (0%)	
Duration of TB treatment, months, mean ± SD	7.2 ± 2.0	7.9 ± 2.5	0.164
Laboratory parameters			
Microbiological diagnosis of TB	54 (68.3%)	47 (61.0%)	0.403
CD4 cell count, cells/mm^3, median (IQR)	38 (17–96)	53 (19–130)	0.155
Percentage of CD4 cell count, %, median (IQR)	5 (2–10)	7 (3–13)	0.079
Log plasma HIV-1 RNA, Log copies/mL, median (IQR)	5.83 (5.38–6.38)	5.71 (5.42–6.11)	0.259
Hemoglobin, g/dL, mean ± SD	12.8 ± 14.1	12.3 ± 12.4	0.822
Serum alkaline phosphatase, mg/dL, mean ± SD	160 ± 132	139 ± 126	0.314
Alanine aminotransferase, U/L, mean ± SD	37 ± 24	36 ± 26	0.806
Albumin, mg/dL, mean ± SD	3.3 ± 0.6	3.3 ± 0.7	0.490
Total bilirubin, mg/dL, mean ± SD	0.56 ± 0.38	0.62 ± 0.43	0.346
Direct bilirubin, mg/dL, mean ± SD	0.33 ± 0.37	0.36 ± 0.37	0.661
Serum creatinine, mg/dL, mean ± SD	0.72 ± 0.18	0.74 ± 0.19	0.621
Hepatitis B virus antigen: positive	6 (7.6%)	2 (2.6%)	0.276
Hepatitis C antibody: positive	10 (12.7%)	9 (11.7%)	1.000
Total cholesterol, mg/dL, mean ± SD	187 ± 46	168 ± 46	0.012
Triglyceride, mg/dL, mean ± SD	173 ± 75	147 ± 52	0.880

the 12-week group (RR = 0.845, 95% CI = 0.247 to 2.893) as shown in Table 2. The same trends were found in the subgroup of patients with baseline CD4 count <100 cells per cubic millimeter and <50 cells per cubic millimeter ($P > 0.05$). Six attributed causes of mortalities in the 4-week group were 1 sepsis, 1 pulmonary TB with IRIS-associated acute respiratory distress syndrome, 1 upper gastrointestinal hemorrhage, 1 hemolytic anemia and acute renal failure, 1 wasting syndrome, and 1 murder. Five mortalities in the 12-week group included 2 wasting syndromes, 1 sepsis, 1 pneumonitis and urosepsis, and 1 acute renal failure and pulmonary edema. After considering only infectious causes, 3 mortalities were in 4-week group and 4 mortalities were in 12-week group ($P = 0.718$). Figure 2 compared the cumulative probabilities of mortality after TB treatment between the 2 treatment groups ($P = 0.772$, log rank test).

The rates and incidences of hospitalization and adverse events that related to ART and TB treatment were not different between the 2 groups ($P > 0.05$) as shown in Table 2. There were no differences in terms of composite endpoint (45.5% vs. 40.2%, RR = 1.242, 95% CI = 0.658 to 2.345) and rate of opportunistic infections (13.9% vs. 23.4%, RR = 0.530, 95% CI = 0.232 to 1.213) between the 2 groups. Reasons for the hospitalizations included 14 TB IRIS, 13 adverse events related to anti-TB drugs or antiretroviral drugs, 12 opportunistic infections, 5 wasting syndrome, 3 TB-related complications, and 6 others. Table 3 shows the multivariate analysis adjusting for timing to initiating ART. The analysis showed that the factors "low baseline serum albumin" (RR = 2.695, 95% CI = 1.353 to 5.475) and "low baseline CD4 count" (RR = 4.878, 95% CI = 1.019 to 23.256) were the independent predictors of all-cause mortality. TB IRIS was more frequent in the 4-week group with an incidence of 8.86 vs. 5.02 per 100 person-months in the 12-week group over the first 6 months of ART ($P = 0.069$) as shown in Table 4. The clinical features of TB IRIS included 15 worsening of chest x-ray and/or chest symptoms, 11 enlarging lymph nodes, 1 worsening of meningitis, 1 worsening of colitis, 1 worsening of pleuritis, and 12 worsening of more than 1 affected site. Median (IQR) duration of TB IRIS symptoms was 44 (30–72) days. Of 41 patients, 32 (78%) patients had received corticosteroids and 9 (22%) patients had received symptomatic supportive treatment only. Over the study period, 9 patients in 4-week group and 14 patients in 12-week group developed major opportunistic infections and/or AIDS-related malignancy ($P = 0.264$). These infections in 4-week group were as follow: 3 pneumocystis pneumonitis, 2 cryptococcosis, 2 cytomegalovirus retinitis, 1 toxoplasmosis, and 1 Kaposi sarcoma. The 12-week group included 7 cryptococcosis, 4 cytomegalovirus retinitis, 2 pneumocystis pneumonitis, and 1 cytomegalovirus colitis. Over the study period, 5 of 156 (3.2%) patients had adherence of less than 80%.

DISCUSSION

The present study demonstrates a nonsignificant difference in the survival outcome, and hospitalization and adverse

TABLE 2. Mortality, Hospitalization, and Grade 2–4 Adverse Events that Related to ART and TB Treatment

	Overall Cohort	4-Week Group		12-Week Group			
Outcomes	Event Rate	Event Rate	Incidence Per 100 Patient-Years	Event Rate	Incidence Per 100 Patient-Years	RR (95% CI)	*P*
All-cause mortality							
All patients	7.0% (11/156)	7.6% (6/79)	8.8	6.5% (5/77)	7.2	0.845 (0.247 to 2.893)	>0.99
CD4 counts <50 cells/mm^3	10.7% (9/84)	8.7% (4/46)	10.2	13.1% (5/38)	14.3	1.591 (0.396 to 6.397)	0.725
CD4 counts <100 cells/mm^3	8.8% (10/113)	8.1% (5/62)	9.9	9.8% (5/51)	11.4	1.239 (0.338 to 4.542)	0.753
Hospitalization							
All patients	33.9% (53/156)	35.4% (28/79)	56.1	32.5% (25/77)	45.3	1.142 (0.588 to 2.217)	0.737
CD4 counts <50 cells/mm^3	39.3% (33/84)	39.1% (18/46)	66.4	39.5% (15/38)	58.8	0.986 (0.409 to 2.376)	0.576
CD4 counts <100 cells/mm^3	36.3% (41/113)	37.1% (23/62)	45.3	35.3% (18/51)	51.6	1.081 (0.500 to 2.339)	>0.99
Grade 2–4 adverse events							
All patients	36.5% (57/156)	39.2% (31/79)	72.5	33.8% (26/77)	53.6	1.267 (0.659 to 2.435)	>0.99
CD4 counts <50 cells/mm^3	40.0% (37/84)	43.5% (20/46)	80.1	44.7% (17/38)	87.5	0.950 (0.400 to 2.257)	>0.99
CD4 counts <100 cells/mm^3	38.9% (44/113)	40.3% (25/62)	77.5	37.2% (19/51)	65.5	1.138 (0.531 to 2.437)	0.847
Grade 3–4 adverse events							
All patients	24.3% (38/156)	24.0% (19/79)	34.8	24.7% (19/77)	35.5	0.967 (0.465 to 2.008)	>0.99
CD4 counts <50 cells/mm^3	30.9% (26/84)	32.6% (15/46)	52.0	28.9% (11/38)	47.5	1.188 (0.467 to 3.021)	0.814
CD4 counts <100 cells/mm^3	27.4% (31/113)	30.6% (19/62)	51.9	23.5% (12/51)	39.7	1.292 (0.563 to 2.961)	0.657

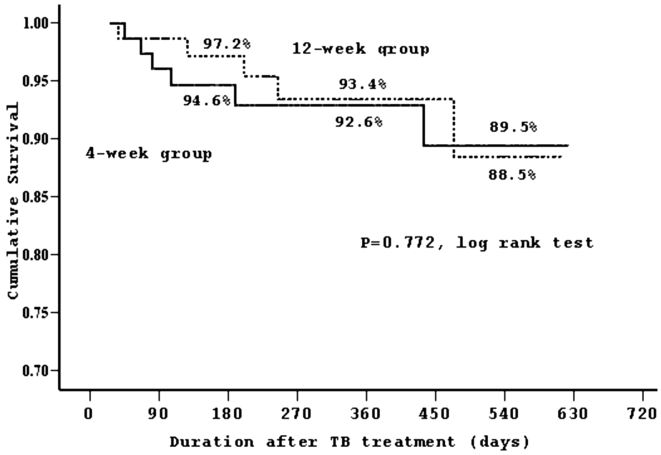

FIGURE 2. Comparing cumulative probability of death after TB treatment between 4-week group and 12-week group.

events, among HIV and TB–coinfected patients between those who had received ART at 4 weeks and 12 weeks after starting TB treatment in a middle-income country. This finding is still consistent after adjusting for other potential predictors, that is, serum albumin and CD4 cell counts. A previous observational cohort in more than 1000 coinfected HIV and TB Thai patients, which demonstrated that survival benefit was diminished only if delayed ART until the completion of TB treatment.[2] A randomized controlled trial in South Africa demonstrated that the initiation of ART during TB therapy reduced mortality by 56% compared with delay ART until completion of 6-month TB treatment.[6] The same trend was found in Cambodians that compared mortality of ART initiation between 2 weeks versus 8 weeks after beginning TB therapy but in a lesser magnitude.[10] In contrast, an earlier ART initiation does not show survival benefit in our setting. A study of TB meningitis in Vietnam showed that survival benefit was also not better from early ART intervention.[11] An observational study in African pediatric patients also reported a nonsignificant difference of mortality between initiating ART before and after 2 months of TB treatment.[12] These different findings may be partly explained by the difference of geographical locations, different medical infrastructure among settings, different severity of HIV-associated immunodeficiency, different forms of TB, and different opportunistic infections. On the other hand, overall mortality rate in the current study is relatively low (7%) compared with that of almost 20% in other recent reports from South Africa and Cambodia where the proportion of severe cases was higher.[10,13] Our relatively low mortality rate in coinfected HIV and TB patients receiving ART is not different from previous cohorts in our setting, which ranged from 7% to 12%.[2,14–16] Therefore, this low mortality could not be due to selection bias.

With regard to the question that how low threshold of CD4 cutoff level should be safe for deferring ART until TB treatment has been given for a period of time, this study showed that overall mortality rate is relatively higher in the patients who had CD4 count of <50 cells per cubic millimeter and the magnitude of difference was greater when compared with the patients with higher CD4 stratum. A preliminary outcome of ACTG 5221 STRIDE study and the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) substudy also demonstrated that the survival benefit of immediate ART strategy were revealed only in the subgroup of the patients with CD4 counts of <50 cells per cubic millimeter.[6,13] The Cambodian Early Versus Late Introduction of Antiretrovirals (CAMELIA) study showed that CD4 threshold to improve survival was gained at CD4 count of 200 cells per cubic millimeter in Cambodian.[10] In addition, we also found that low baseline CD4 cell count and low serum albumin level at the time of ART initiation were the significant risk factors for mortality regardless of the time period of ART initiation. In multivariate analysis, HIV-infected patients with CD4 count of <50 cells per cubic millimeter was associated to almost 5 times at increased risk of mortality. Low CD4 cell count at TB diagnosis consistently predicted poorer survival in these studies.[6,13] Therefore, this may indicate that condition of the patient in the early period of TB treatment is probably more important than the interval between commencing TB treatment and starting ART in predicting the likely outcome for the patient in this setting.

Anti-TB drugs can cause a significant number of adverse reactions, especially in HIV-infected patients.[17] Most of them are overlapping toxicities with antiretroviral drugs, included liver toxicities and skin rashes.[18] In this study, the overall rate of moderate to severe adverse events was relatively high, but no significant differences in rate were observed between the 2 treatment groups as same as other studies in non-TB meningitis patients.[6,10,13] In contrast, adverse events were more frequently found in the early treatment group among patients who diagnosed with TB meningitis, especially during the first few months of ART.[5] Thus, close clinical monitoring is still emphasized during the early period of concurrent HIV and TB treatment.

Although the rate of TB IRIS in either previous studies or this study was more common in the patients who had initiated ART earlier but it was not a great impact on mortality, except in the case of central nervous system involvement,[4,19] indicating it is a relative rare life-threatening condition. One (2.4%)

TABLE 3. Cox Regression of Possible Risk Factors for Death in 156 Coinfected HIV and TB Patients

	Univariate Analysis			Multivariate Analysis		
Risk Factors	**RR**	**95% CI**	***P***	**RR**	**95% CI**	***P***
Low baseline serum albumin	2.188	1.210 to 3.952	0.009	2.695	1.353 to 5.475	0.005
Baseline CD4 counts <50 vs. ≥ 50 cells/mm^3	4.048	0.873 to 18.867	0.074	4.878	1.019 to 23.256	0.047
4-week group vs. 12-week group	1.192	0.256 to 2.751	0.773	1.464	0.421 to 5.076	0.548

TABLE 4. Rate of TB IRIS Between the 2 Treatment Groups

Parameters	Overall Cohort	4-Week Group	12-Week Group	RR (95% CI)	*P*
All patients	26.2% (41/156)	32.9% (26/79)	19.4% (15/77)	2.028 (0.974 to 4.223)	0.069
CD4 counts <50 cells/mm^3	27.3% (23/84)	32.6% (15/46)	17.4% (8/46)	1.815 (0.671 to 4.903)	0.326
CD4 counts <100 cells/mm^3	27.4% (31/113)	33.9% (21/62)	19.6% (10/51)	2.100 (0.881 to 5.005)	0.137

TB IRIS–associated mortality was observed in the present study. A recent systematic review reported a TB IRIS–associated mortality of 3.2%.[20] Mild or moderate symptoms of IRIS can be managed symptomatically or treated with corticosteroid, nonsteroidal anti-inflammatory drugs, or surgical intervention.[21] One of the important predictors of occurring IRIS after ART is a low baseline CD4 cell count at time of ART initiation.[20] Thus, although delaying the initiation of ART may reduce the incidence and severity of TB IRIS, but this strategy can not outweigh the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality related to opportunistic infections. Further study in less advanced HIV-infected patients is needed.

A number of limitations should be acknowledged. First, the study patients were not completely included as previously calculated. Type-2 error rate of this study was initially set at 20%. Given the lower number of present participating patients, it results in a lower power of test from 80% to 70% to detect the smallest worthwhile effect. Nonetheless, this figure is still acceptable. Second, the magnitude of mortality reduction difference of <2.5 times due to intervention could not be excluded. Third, only two-third of patients were confirmed TB based on enrollment criteria of this study. However, the remaining of cases with clinical diagnosis had clinical response after receiving TB treatment and it reflects HIV-infected patients who are diagnosed as having active TB in real-life situation. Ultimately, 48-week virologic and immunologic outcomes could not be assessed as previously planned; however, favorable HIV treatment outcome in coinfected HIV and TB patients who had received efavirenz-based ART have previously been reported.[14,22,23] Although controversy somewhat remains over the appropriate timing to initiate ART, remarkable progress has been made over the past few years in the aspect of HIV and TB comanagement. The results from this study revealed useful information regarding HIV and TB management to further guiding public health programs. To date, data were still derived from different circumstances as aforementioned. We expect that a number of ongoing studies that have been conducting in various geographical locations and in the patients with different degree of immune deficiency will be coming out soon. However, strengths of the current study include its randomized design, and its use of tenofovir in the nucleoside reverse transcriptase inhibitor (NRTI) backbone regimen, the preferred NRTI, which is being used increasingly in the resource-limited countries. Although tenofovir was not used in the NRTI regimen in SAPIT and CAMELIA study.[6,10] In addition, this study included approximately 50% of patients who had extrapulmonary TB disease, which also distinguishes it from SAPIT and ACTG 5221 STRIDE, which focused on pulmonary TB only.

In summary, the present study which conducted in a middle-income country shows the evidence that immediate initiation of ART in HIV-infected patients with active TB was not associated with survival advantage when compared with initiation of ART at 12 weeks. Some trends were found in only the patients with very low CD4 cell count. In addition, patients with low baseline CD4 count and low albumin at TB diagnosis predicted poorer survival. Adverse events due to anti-TB drugs and antiretroviral drugs and hospitalization were not reduced by either strategic treatment. Integration and collaboration between TB and HIV care are necessary to improve survival of these patients.

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