

Does Early ART Initiation is Better than Later ART Initiation in TB/HIV Co-infected Patients? A Retrospective Cohort Study

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Research

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Abstract

Background: The co-infection of TB/HIV poses a significant burden in the health care system of developing countries like Ethiopia. There are conflicting results on the preference of the time to initiate antiretroviral therapy (ART) and hence assessing the survival experience and treatment outcomes associated with ART initiation is crucial to settle the controversies. The study compared the treatment outcomes in early versus later ART initiation in TB/HIV co-infected patients.

Methods: A retrospective cohort study was conducted in Ayder Comprehensive Specialized Hospital and Mekelle Referral Hospital on 77 and 105 patients that started ART early and lately, respectively. An assumption for proportional hazard was met. Kaplan-Meier and life-table analyses were used to compare survival curves; and an independent samples *t*-test was used to compare means of the continuous variables between the two cohorts. Moreover, incidence per 100 persons-years was employed to crudely determine new mortality rates, and Cox regression analysis was done to find out the effects of independent variables on the outcome variables.

Results: The mean survival time was 5.8 months after ART initiation. A 9.9 and 5.5 new incident mortality rates per 10,000 persons–years for the early and late ART initiation were observed, respectively. There was a statistically significant difference in mean CD4⁺ T cells between early (208.20 ± 11.94 cells/mm³) and late (245.94 ± 11.69 cells/mm³) ART initiators ($t_{180} = -2.213, p < 0.028$). Additionally, late initiators had a better survival chance at all levels of time (Log Rank $\chi^2=5.56, p<0.018$) than early initiators. Having normal body mass index [adjusted hazard ratio [AHR]=0.263; 95% confidence interval [CI]: 0.089–0.778] and having a ‘working’ baseline functional status [AHR=0.151; 95% CI: 0.054–0.427] were found to be preventive factors from death. However, patients with < 250 CD4⁺ T cells/mm³ were more likely to die earlier [AHR=12.023; 95%: 1.588–91.005] than their counterpart groups.

Conclusion: TB/HIV co-infected patients who had a CD4 count of below 250 cells/ul started ART regimen within two weeks of TB treatment initiation were found to have better survival outcomes than those who start ART beyond two weeks in the study settings. Moreover, female patients were more likely to die than males and, patients with the functional status of bedridden were more likely to die in contrast to working and ambulatory functional status. Moreover, body mass index, baseline functional status, and CD4 count were found to be independent predictors of mortality.

Background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* [1] and results in either a latent infection or a progressive active disease [2]. Human Immune Deficiency Virus (HIV) is an infection that targets the immune system and the resulting immunodeficiency leads to increased susceptibility to a wide range of infections and diseases including TB [3]. The disease remains the most common risk factor for active TB especially among people 25 to 44 years of age [2].

The existence of active TB is highly prevalent in HIV patients [4]. TB is the leading opportunistic infection (OI) in HIV infected patients and the most common cause of mortality among TB/HIV co-infected patients that accounted for one-third of deaths worldwide [5]. HIV is driving the TB epidemic in many countries and this appears more serious in sub-Saharan Africa [4]. Co-infection has increased the risk of death, treatment failure, and relapse [6]. It was estimated that about 1.2 million people living with HIV had TB co-infection worldwide in 2015. Africa accounted for 75% of all deaths. Globally, people living with HIV are 19 times more likely to fall ill with TB than those without HIV [7].

Ethiopia is one of the 22 high burden countries and TB remained one of the leading communicable diseases causing mortality in the country. According to the 2014 world health organization (WHO) report, the prevalence and incidence of all forms of TB were 211 and 224 per 100,000 populations, respectively. Excluding HIV related death, TB mortality was estimated to be 32 per 100,000 population in 2013. Among estimated all new TB cases, 13% of them were HIV co-infected [8].

ART has proven to have a great impact on the survival of HIV-infected patients with TB [5,9,10]. It can be initiated simultaneously or soon after the initiation of TB treatment. However, ART is often deferred until the intensive phase of TB treatment is completed because of concern about the immune reconstitution inflammatory syndrome (IRIS) [11,12], a high pill burden, and overlapping side effects [13]. These challenges may result in interruption or discontinuation of treatment for the acquired immunodeficiency syndrome (AIDS) or TB, which can lead to drug resistance and potentially limit future therapeutic options [14,15] but the disadvantages must be weighed against the risk of increased mortality early in the treatment of TB.

The current WHO guidelines recommend that ART should be initiated as soon as possible 'within the first 8 weeks' of starting TB treatment and 'within the first 2 weeks' for patients who have CD4 cell counts less than 50 cells/mm³ [16]. Furthermore, some factors likely determine the general outcome of the survival time of TB/HIV co-infected patients who start their ART treatment early and late after TB treatment. Concerns about early initiation of ART include a high pill burden, pharmacological interactions, overlapping toxicities, and the IRIS. Conversely, delayed initiation of ART may be associated with HIV disease progression and death. Even though different researches have conducted on TB/HIV co-infection there are controversies' on the timing of initiation of the ART regimen and there is no similar study conducted in the setting. Hence, considering its possible benefit to TB/HIV program planners, decision-makers, and project implementers, this particular study emphasized the direct and indirect effects on the overall survival experience of TB/HIV co-infected patients in early and late ART therapy in Ayder Comprehensive Specialized Hospital (ACSH) and Mekelle Referral Hospital (MRH).

Methods

Operational definitions

An ART was deemed to be initiated early if the ART is started within 2 weeks of TB treatment initiation and later if the ART is started after 2 weeks of TB treatment initiation [18].

Study Design, Period, and Area

This retrospective cohort study was conducted at ART and TB clinics of ACSH and MGH, which are the two largest governmental health institutions found in Mekelle, Ethiopia. Inpatient and outpatient medical records, pre-ART registers, follow-up forms, anti-TB record forms, ART intake forms, treatment outcome, and patient cards, SmartCare[®] as well as TB Information System documents of the eligible patients were reviewed retrospectively from 6-Feb-2017 to 24-April-2017, for six years ranging from index period (3-Jan-2012) until the occurrence of the outcome, date of administrative censoring, or 24-April-2017.

Study population

The study population was all TB/HIV co-infected individuals who received their primary care at the TB and ART clinics from the index period to the end of data collection. Cross-linking of TB clinics with ART clinics and crosschecking of the records were conducted to identify eligible patients. TB/HIV co-infected patients who had started their ART early were considered as cases whereas late initiators were considered as control groups. The source population was all TB/HIV co-infected patients who obtained services at TB and ART clinics of both hospitals.

Eligibility Criteria

TB/HIV co-infected individuals who received their primary care at the clinics were 15 years old, and older, and were diagnosed with TB at any time during pre-ART and/or ART follow-up since 3-Jan-2012 were included in the study. On the other hand, TB/HIV co-infected patients whose TB treatment was not initiated during the enrolment period; who were non-ART users; whose period (month and year) of starting ART and TB treatment was unknown; who were transferred to other health institution; who were lost and drop to follow-up; and with unknown/non-documented outcome variable were excluded from the study.

Sample Size and Sampling Technique

Kelsey samples size calculation method was employed in this study [17] [Appendix 1]. Accordingly, the sample (n) and the continuity corrected sample (n_c) were found to be 236 and 212, respectively. On actual data collection, 182 patients were enrolled in this study with 77 patients considered as early ART initiators and 105 patients enrolled as late ART initiators (with a ratio of about 1.3). These patients were selected based on a convenient sampling procedure. This selection procedure is summarized in Figure 1.

Data collection process

Data abstraction format was prepared and pre-tested conducted in 5% of the sample size (9 patients). Amendments of the data collection tool were considered based on the pretest. The staff members who had good work experience in the ART and TB clinics were recruited as data collectors. One day training was given to the data collectors by the principal investigator. Supervision was done daily basis by the principal investigator to assure the completeness of the data.

Data analysis and interpretation

The data abstraction format was Kaplan-Meier analysis was used to estimate the hazard ratios for survival status among TB/HIV co-infected patients who started their ART early versus lately after TB treatment. The assumption for proportional hazard was assessed graphically by log minus log survival curve [Supplementary Figure] and by the time-dependent Cox-model, and the assumption was met.

Because of the retrospective nature of data collection, sensitively analysis was performed to evaluate confounding by indication and the effect of loss to follow-up. To address the confounding by indication, a propensity score analysis was performed. Using logistic regression analysis, the expected probability of starting ART was calculated for each member of the group using a full list of covariates and interactions; this probability was considered the propensity score for starting ART. Using this score, patients who were on early ART were matched with patients who were on late ART treatment in a one-to-one manner according to the propensity scores. After matching the number of patients, the continuous outcome variables between the matched pairs were then compared to ensure balance. In this propensity-matched cohort, the Kaplan-Meier analysis was repeated to estimate the survival status between the groups. An adjusted Cox proportional hazards model was used to examine the overall effect of early and late ART initiation on survival status. An independent samples t-test was also used to compare the mean of the continuous variables between the two groups. Moreover, incidence rates of mortality per 100 person-years (PYs) of follow-up was employed to crudely determine mortality rates. Cox regression analysis and marginal structural model (MSM) were employed to find out the effects of socio-demographics, clinical characteristics, and treatment categories on the outcome variable. In all of the analyses, significance testing was done using two-sided p -values and 95% CI. A p -value < 0.05 was considered statistically significant.

Ethics approval and consent to participate

The study was formally approved by the Ethical Review Board of College of Health Sciences, Mekelle University. A letter of support was obtained from the medical director's office of the hospitals. All results of this research were based on the use of secondary data and the data collection was performed retrospectively. Therefore, obtaining informed written consent form from the study participants was not applicable in this study but the study was conducted following with the ethical standards of the institutional and national research committee. The study also adhered to the declarations of Helsinki and STROBE guidelines.

Results

Concerning the socio-demographic characteristics of the study participants, less than half (45%) of them were in the age group of 30–39 years, followed by 40–49 years (24%). The majority of the patients were males and were residing in urban for both groups [Table 1].

As shown in Table 2, about half (47.3%) of the patients were having extra-pulmonary TB during the TB diagnosis. Besides this, almost all of the patients were naïve to TB treatment, taking TDF/3TC/EFV and 2RHZE/4RH as their HIV and TB management, respectively.

The average weight and body mass index (BMI) (in absolute kg and kg/m^2 , respectively) were increased by 9.72 and 3.00 over the six-year, interpreting into 20.3% and 17.5% increase from 2012 to 2017, respectively [Figure 2].

The mean CD4 cells for patients who had less than 200 cells per mm^3 decreased by 73.5% from 2012 to 2017. On the contrary, the mean CD4 cells increased by 120% and 1466.7% for the same period for patients with CD4 between 200 and 350 cells, and more than 350 cells per mm^3 , respectively. The CD4⁺ T cells increased (by 181.42%) over the past six years, with an average of 320.25 cells per mm^3 in 2017, up from a mean of 113.80 mm^3 in 2012 [Figure 3].

Among the deaths, the mean survival time for patients whose outcome was registered as ‘death’ was found to be 5.8 months commencing from the TB treatment start date. In the crude Cox-regression analysis, sex, BMI, CD4⁺ T cells (in cells/ mm^3), and the functional status at baseline were found to be statistically significant factors associated with death. Thus, male patients at any time during the study period were 63.5% [AHR=0.365; 95% CI: 0.147–0.905] less likely to die than female patients. Moreover, without adjustment of the factors, the difference in risk of death between participants with normal BMI and abnormal BMI remains statistically significant, with approximately a 72.7% decrease [AHR=0.263; 95% CI: 0.089–0.778] in the risk of death among participants with normal BMI compared abnormal BMI. On the contrary, at any particular time, about twelve times [AHR=12.023; 95%: 1.588–91.005] as many patients with CD4⁺ T cells < 250 cells/ mm^3 were experiencing death compared to CD4⁺ T cells \geq 250 cells/ mm^3 . Lastly, patients with ‘working’ functional status at baseline were 84.9% [AHR=0.151; 95% CI: 0.054–0.427] less likely to die at any time point during the study period than patients with ‘bedridden’ functional status at baseline [Table 3].

There was a statistically significant difference in mean CD4⁺ T cells between early and late ART initiators ($t_{180} = -2.213$, $p < 0.028$). The average CD4 count for early ART initiators (mean=208.196 cells/ mm^3 ; SEM=11.943 cells/ mm^3) was 37.747 cells/ mm^3 lower than the average CD4 count for late ART initiators (mean=245.943 cells/ mm^3 ; SEM=11.688 cells/ mm^3). However, a statistically significant difference was not observed in the mean BMI for the two groups [Table 4].

Another finding illustrated in this study was that patients with late ART initiation had a better survival chance than patients with early ART initiation at all levels of time ($p < 0.018$). The test of equality of survival distributions for the different levels of survival status showed Chi-Square results of 5.56, 6.07, and 6.08 for the Log Rank (Mantel-Cox) ($p < 0.018$), Breslow (Generalized Wilcoxon) ($p < 0.014$), and Tarone-Ware ($p < 0.014$) respectively [Figure 4].

Discussions

The mean survival time was 5.8 months and the incidence mortality rate was 9.9 per 10,000 PYs for early ART initiators compared to 5.5 new death rates per 10,000 persons–years for late ART initiators. There was also a statistically significant difference in mean CD4+ T cells between the cohorts and patients with late ART initiation had a better survival chance than patients with early ART initiation at all levels of time. Four randomized controlled trials have examined the question of the optimal timing of ART in TB/HIV co-infected patients. In 2010, the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT trial) demonstrated no overall difference in the primary endpoint of AIDS-defining illness or death between the early integrated therapy arm (ART commenced < 4 weeks of TB treatment) and late integrated therapy arm (ART commenced < 4 weeks after completing intensive TB treatment) [19]. A second international multicenter randomized controlled trial, the AIDS Clinical Trials Group (ACTG 5221) study, reported that immediate ART (<2 weeks) did not reduce the primary endpoint of AIDS-defining illness or death compared with early ART (8 to 12 weeks) [18]. However, both studies found that in patients with baseline CD4 counts < 50 cells/mm³, early ART initiation was associated with a significant reduction in AIDS or death. A third randomized controlled trial, the [Cambodian Early versus Late Introduction of Antiretrovirals] CAMELIA trial conducted in Cambodia, reported improved survival in predominantly pulmonary TB patients initiating ART at 2 weeks compared with 8 weeks [20].

In contrast, a Vietnamese randomized controlled trial of immediate (within 7 days of TB treatment) versus deferred (after 8 weeks TB treatment) ART initiation in patients with HIV-associated TB meningitis showed no survival benefit, and an increase in severe adverse events, in the immediate ART arm [21]. Collectively, the results of these four trials suggest that ART should be started early in TB/HIV co-infected patients with advanced immunosuppression, apart from those with TB meningitis [22]. The finding of the present study, however, differs from the above studies. The result of this study showed that initiating ART after two weeks (later) of starting TB therapy significantly increase survival among TB/HIV co-infected patients with newly diagnosed TB and with mean CD4⁺ T-cell counts of about 130 cells/mm³ compared with the initiation of ART before two weak (early). The difference of the current study from the previous findings could be explained by variation in the timing of ART initiation and study design. The high likelihood of drug-to-drug interaction, overlapping toxicities of TB and ART regimens, and the higher prevalence of immune reconstitution inflammatory syndrome (IRIS) during early initiation might be the contributing factors for the increased mortality.

Another plausible explanation for this discrepancy could be the cut-off point used in this study (two weeks), unlike the aforementioned trials that used different classification systems of ART initiation. This

difference in the timing of ART initiation may affect the outcome of this study and may attribute to the differences observed in the present study and the other findings. The late ART initiation is too delayed in the previous studies, compared to the current study, and hence the patients may have a greater deterioration in their immunity in these studies and maybe a reason for the greater mortality.

The interactions between rifampin and the Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are particularly important because NNRTIs are recommended as components of initial ART in countries with a high burden of HIV infection [23]. The concentrations of all of the available NNRTIs are significantly reduced because of CYP2B6 and CYP3A4 induction by rifampin [24]. The effect of rifampin on nevirapine concentrations is greater than its effect on efavirenz concentrations. Reductions of 20%–55% in nevirapine concentrations have been reported [25,26], with a greater proportion of co-treated patients having trough levels of nevirapine below the target ranges [25,27,28]. Concomitant rifampin treatment results in reductions of ~20%–25% in efavirenz peak and trough concentrations [29,30]. Among patients not receiving TB treatment, lower trough concentrations of efavirenz are associated with an increased risk of virological failure and selection of drug-resistant viral strains [31,32]. This drug interaction may be one of the causes that increase mortality at early ART initiation.

Most of the adverse effects due to the TB treatment and ART occurs within the first months of therapy [33]. HIV-infected patients receiving TB treatment commonly experience drug toxicity [33,34]. Most studies suggest that adverse events are more common among HIV-infected patients than among HIV-uninfected patients being treated for TB. For example, a retrospective study of patients treated for TB in Canada found that HIV-infected patients were 3.8 times more likely to experience a significant drug-related adverse event (defined as one resulting in hospitalization or in modification or discontinuation of treatment) [35]. Thus, due to overlapping toxicities of TB treatment and ART occur frequently, pushing discontinuation of therapy and increasing the risk of non-adherence. This is may also be one of the causes of increased mortality among patients with early ART initiation.

Paradoxically, IRIS occurs within 6 weeks of the initiation of ART but it has been reported to occur many months after the commencement of ART [36,37]. Data from retrospective and observational studies indicated that TB-associated IRIS occurs in approximately 11% to 71.4% of TB/HIV co-infected patients starting ART [38]. Reports of high IRIS rates from various settings is a key reason for delaying the initiation of ART in patients receiving TB treatment [17,18,20]. This is maybe also another reason for the higher death during early ART initiation.

In this study, the majority of TB/HIV co-infected patients had a CD4⁺ T cell count of less than 250 cells/mm³. Most TB infections had occurred in those whose CD4⁺ cell count was < 250 cell/mm³. About twelve times as many patients with CD4⁺ T cells < 250 cells/mm³ were experiencing death compared to CD4⁺ T cells [≥] 250 cells/mm³. These findings revealed that mortality upsurges as CD4⁺ T cells count decreases because the TB/HIV co-infection leads to severe immune suppression. Co-infection is associated with lower CD4⁺ T count than those with HIV alone, which could translate into an increased morbidity and progression of HIV to AIDS. Several other studies are consistent with this finding and they

also pointed to the fact that CD4⁺ T cell count is lower among co-infected patients as compared to HIV infected alone and severe immune suppression is seen in those with CD4⁺ T cell count below 200 cells/mm³ [39,40]. Institutional based cross-sectional study conducted in Ethiopia on the magnitude and correlates of TB among HIV patients found that 79.5% of TB infection occurred in low CD4 level (< 200 cells/mm³), which could translate into increased morbidity, the progression of HIV to AIDS, and mortality [41].

Patients with 'working' baseline functional status were having an 84.9% of protection from death than patients with 'bedridden' baseline functional status, in which the former patients may have a better immunity status [42] and the later patients may present with an advance immunocompromised state and with many opportunistic infections.

The study has certain limitations. The investigators' rely on the record-keeping of others, which has an effect in accurate comparison of the exposure and outcome. The investigators have also less control over variables including over exposure and outcome variables.

Conclusions

TB/HIV co-infected patients who had a CD4 count of below 250 cells/ul started ART regimen within two weeks of TB treatment initiation were found to have better survival outcomes than those who start ART beyond two weeks in the study settings. Moreover, female patients were more likely to die than males and, patients with the functional status of bedridden were more likely to die in contrast to working and ambulatory functional status. Hence, multiple efforts should be in place for patients with these predictors. These findings call for greater research attention in TB/HIV co-infected patients and strengthening efforts in managing these patients.

List Of Abbreviations

ACSH=Ayder Comprehensive Specialized Hospital; AHR=Adjusted hazard ratio; AIDS Clinical Trials Group (ACTG); AIDS=Acquired immune deficiency syndrome; ART=Antiretroviral Treatment; BMI=Body mass index; CAMELIA=Cambodian Early versus Late Introduction of Antiretrovirals; CD4=Cluster of differentiation 4; CHR=Crude hazard ratio; CI= Confidence interval; CPT=Cotrimoxazole Preventive Treatment; DOT= Directly observed therapy; HAART= Highly active antiretroviral therapy; HIV=Human Immune deficiency Virus; IRIS=Immune reconstitution inflammatory syndrome; MR=Mortality rates; OI=Opportunistic infection; OR=Odds ratios; Person-years (PYs); PI=Protease Inhibitor; SAPIt=Starting Antiretroviral Therapy at Three Points in Tuberculosis; SD=Standard deviation; SEM=Standard error of mean; SPSS=Statistical Package for Social Sciences; TB=Tuberculosis; WHO=World Health Organization.

Declarations

Consent to publish

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of the study are included in the article. Any additional data will be available on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

TMA and FG were involved in the conception and design of the study, developed data collection tools, supervised data collection, analyzed data, and wrote the manuscript. SWA, KBT, AKG, HG, MK, HHG, and DMD involved in the writing, and editing of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Socio-demographic characteristics of TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

Variables	Time difference between TB and ART initiation		p-value	
		Early ART initiation N (%)		Late ART initiation N (%)
Sex	Male	45 (43.3)	59 (56.7)	0.762
	Female	32 (41.0)	46 (59.0)	
Residency	Rural	10 (50.0)	10 (50.0)	0.460
	Urban	67 (41.4)	95 (58.6)	
Age in years (mean \pm SD, 37.3 \pm 9.3)	< 30	13 (36.1)	23 (63.9)	0.847
	30–39	36 (44.4)	45 (55.6)	
	40–49	18 (41.9)	25 (58.1)	
	\geq 50	10 (45.5)	12 (54.5)	

ART: Antiretroviral therapy; SD: Standard deviation; TB: tuberculosis

Table 2. Status and classification of TB at diagnosis stage, type of ART, and TB treatment regimen among TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

Variables	Frequency (%)
Status and classification of TB at the diagnosis stage	
Extra pulmonary	86 (47.3)
Smear negative	43 (23.6)
Smear positive	53 (29.1)
Retreatment	3 (1.6)
New	179 (98.4)
Type of ART treatment regimen	
AZT + 3TC + EFV	4 (2.2)
TDF + 3 TC + EFV	178 (97.8)
Type of TB treatment regimen	
2 RHZE/10RH	5 (2.7)
2RHZES/RHZE/5RHE	3 (1.6)
2RHZE/4RH	174 (95.6)

3TC=Lamivudine; AZT=Zidovudine; E=Ethambutol; EFV=Efavirenz; H=Isoniazid; R=Rifampin; S=Streptomycin; TDF=Tenofovir; Z=Pyrazinamide

Table 3. Factors associated with survival status among TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

Variable		Survival status		CHR [95% CI]	p-value	AHR [95% CI]	p-value
		Alive, n (%)	Dead, n (%)				
Sex	Male	97 (93.3)	7 (6.7)	0.334 [0.136–0.819]	0.017*	0.365 [0.147–0.905]	0.030*
	Female	63 (80.8)	15 (19.2)	1.00	—	1.00	—
Body mass index (BMI)	Normal BMI	76 (95.0)	4 (5.0)	0.263 [0.089–0.778]	0.016*	0.364 [0.118–1.125]	0.079
	Abnormal BMI	84 (82.4)	18 (17.6)	1.00	—	1.00	—
CD4+ T cells (per mm ³)	< 250	99 (82.5)	21 (17.5)	12.500 [1.679–93.060]	0.014*	12.023 [1.588–91.005]	0.016*
	≥ 250	61 (98.4)	1 (1.6)	1.00	—	1.00	—
Functional status	Working	75 (96.2)	3 (3.8)	0.070 [0.020–0.244]	0.001	0.146 [0.039–0.541]	0.004*
	Ambulatory	64 (92.8)	5 (7.2)	0.136 [0.049–0.380]	0.001	0.151 [0.054–0.427]	0.001*
	Bedridden	21 (60.0)	14 (40.0)	1.00	—	1.00	—

Abbreviations: AHR=Adjusted hazard ratio; CD4 = Cluster of differentiation; CI=Confidence interval; CHR=Crude hazard ratio, BMI=Body mass index,

*Statistically significant at $p < 0.05$

Table 4. Mean values of CD4 and BMI by the status of ART initiation among TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

Variable	Status	Mean	T	Df	p-value (two-tailed)	Mean Difference [95% CI]
Average BMI (kg/m ²)	Early ART initiation	18.753	0.828	180	0.409	0.335 [-0.464-1.134]
	Late ART initiation	18.418				
Average CD4 ⁺ T cells (cells/mm ³)	Early ART initiation	208.196	-2.213	180	0.028	-37.747 [-71.406-4.088]
	Late ART initiation	245.943				

Abbreviation: BMI=Body mass index; CD4+ T cells=Cluster of Differentiation 4 positive T-lymphocyte cells

Figures

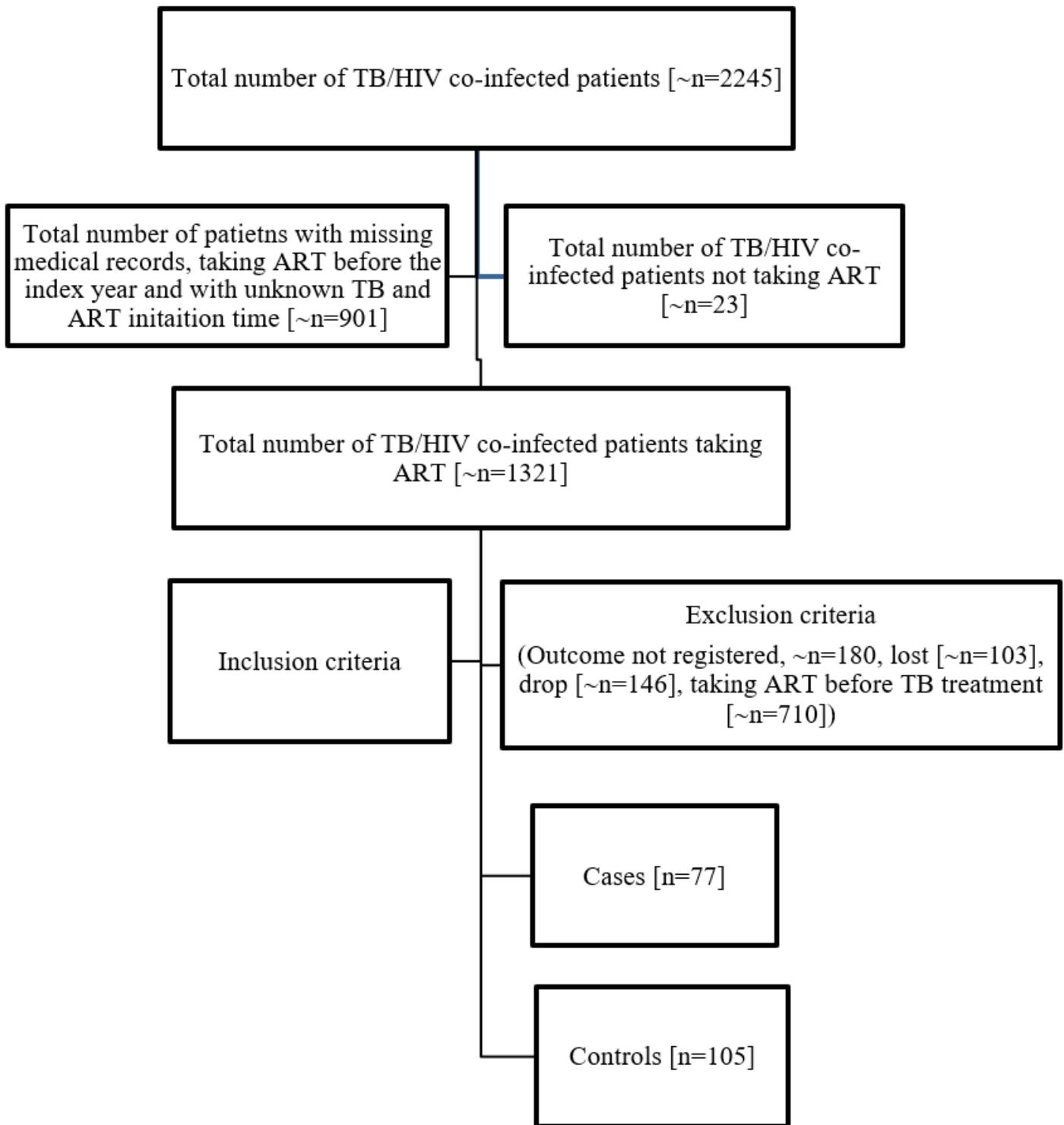


Figure 1

A diagram that shows eligible patients' selection process.

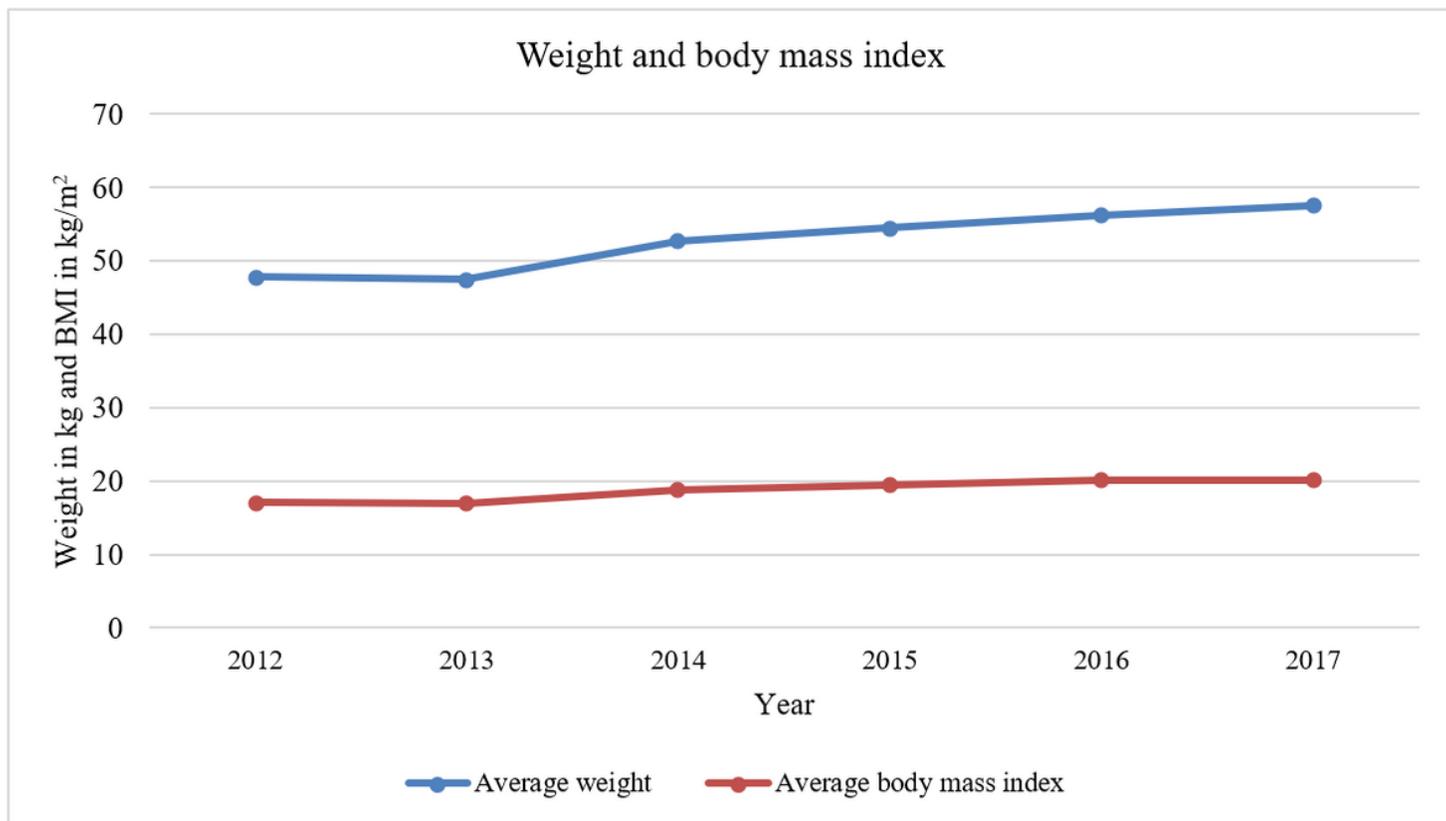


Figure 2

Trend of weight and body mass index among TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

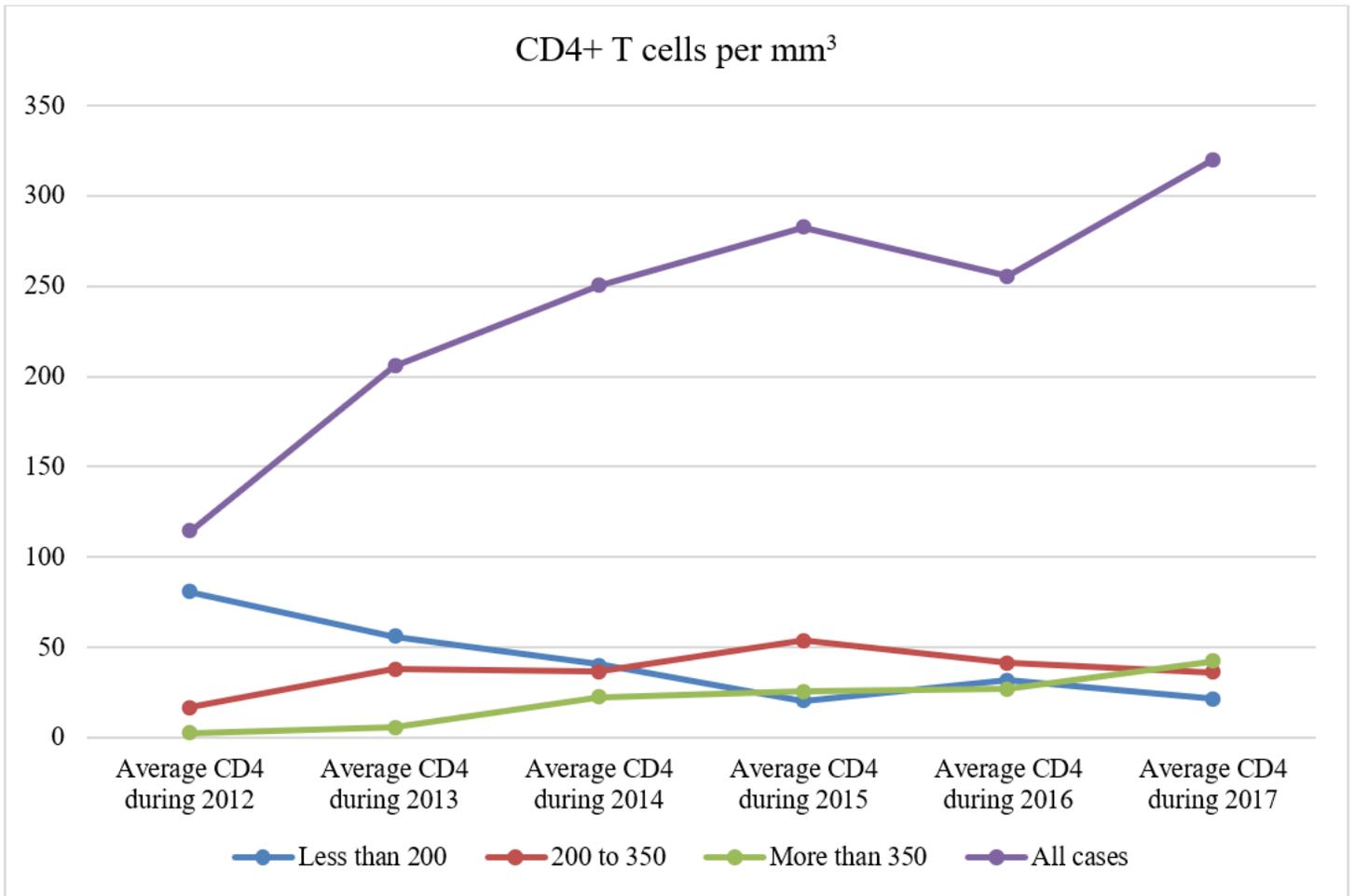


Figure 3

Trend of CD4+ T cells per millimeter cubic among TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

Survival function

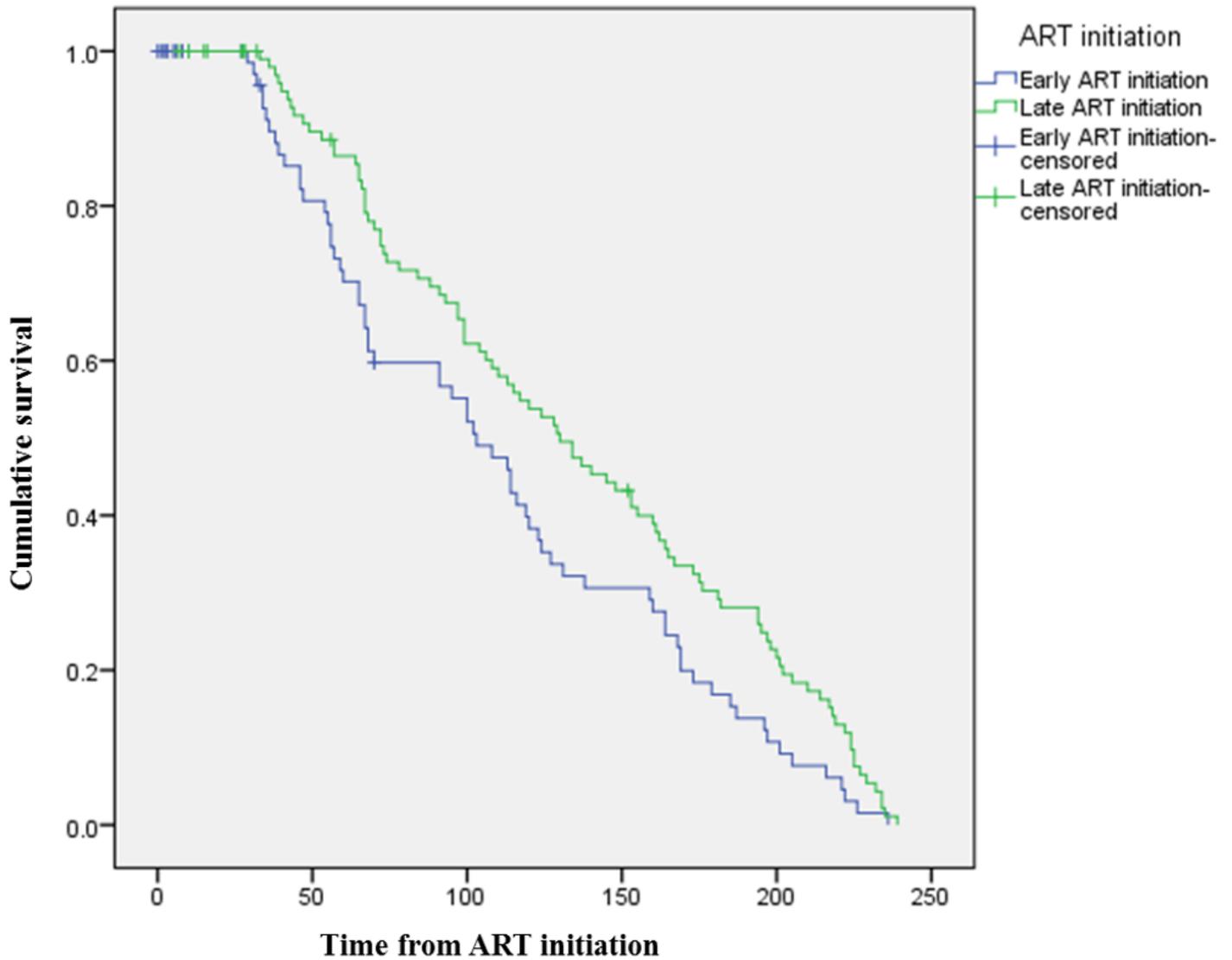


Figure 4

Comparison of survival status of early and late ART initiation among TB/HIV co-infected patients in two governmental hospitals of Mekelle, Ethiopia, 2012–2017.

Supplementary Files

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