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Survival rate and mortality risk factors among TB–HIV co-infected patients at an HIV-specialist hospital in Myanmar: A 12-year retrospective follow-up study

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ABSTRACT

Background: Myanmar is listed as one of the countries with the highest burden of tuberculosis and HIV infections (TB–HIV) in the world. However, the survival rate and risk factors for mortality among TB–HIV co-infected patients in the country remain unstudied. Therefore, the purpose of this study was to examine these factors.

Methods: A 12-year retrospective follow-up study was conducted among 3598 TB–HIV co-infected patients (2452 male and 1146 female) aged 15 years and above, enrolled on antiretroviral therapy (ART) from July 1, 2005 to December 31, 2016. Hazard ratios (HR) were estimated using the Cox proportional hazards model. Survival rates at the beginning of ART were calculated using the Kaplan–Meier method.

Results: A total of 494 (13.7%) patients died during this period. The survival rate of TB–HIV co-infected patients was 82.0% at 5 years and 58.1% at 10 years. The risk factors for mortality were being bedridden (adjusted hazard ratio (aHR) 2.70, 95% confidence interval (CI) 2.13–3.42), having a low baseline CD4 count (aHR 1.53, 95% CI 1.25–1.87), and being on a second-line ART regimen (aHR 8.12, 95% CI 3.56–18.54).

Conclusions: Two out of five TB–HIV patients died within 10 years after ART initiation. Current HIV prevention and treatment programs should focus more on bedridden patients, those on second-line ART, and those with low baseline CD4 counts.

Introduction

The global estimated number of people living with HIV in 2015 was 36.7 million, with 5.1 million of these people living in the Asia and Pacific regions. The scaling up of antiretroviral therapy (ART) has been the main contributor to the 45.0% reduction in global deaths among people living with HIV (PLHIV) (UNAIDS, 2016). However, tuberculosis (TB) remains the leading opportunistic infection among PLHIV (WHO, 2015; Kwan and Ernst, 2011). In 2015, 10.4 million new TB cases were estimated worldwide. Of these, 11.0% were co-infected with HIV and 22.2% of all TB deaths were attributed to TB–HIV co-infections. Furthermore, an estimated 22.0% of TB–HIV co-infected patients were solely in Southeast Asia and the Western Pacific regions (WHO, 2015).

Myanmar has been listed as one of the 30 TB–HIV high-burden countries in the world (WHO, 2015). In 2016, there were 212 000 PLHIV in Myanmar, with 9000 of these being newly infected patients (National AIDS Programme, 2016). In 2015, the incidence rate of all TB cases was 365 per 100 000 population and the associated mortality rate was 49 per 100 000 population (WHO,

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2015). Myanmar is also considered as having one of the highest HIV prevalence rates among high-risk populations in Southeast Asia. In 2014, the HIV prevalence rate was 6.3% among female sex workers, 6.6% among men who have sex with men, and 23.1% among people who inject drugs (WHO, 2016a). The HIV prevalence rate in the general population was 0.6% in 2016 (National AIDS Programme, 2016), while it was 8.5% among new TB patients in 2014 (National AIDS Programme, 2016).

Since 2005, Myanmar has actively applied the World Health Organization (WHO) TB–HIV collaborative activities policy (WHO, 2012), and these activities were implemented in all of its townships in 2016. All ART centers and decentralized sites provide free HIV treatment and care. Mingalardon Specialist Hospital (MSH) is one of the public ART centers located in Yangon Region. PLHIV can access HIV and TB services in the outpatient department during office hours on weekdays and inpatient HIV care at any time. In 2016, MSH covered 17.2% of the total patients on ART through provision from the public sector in Myanmar.

The early initiation of ART has been reported to reduce mortality among PLHIV (Thida et al., 2014; Sabapathy et al., 2012; Edessa and Likisa, 2015; Kumarasamy et al., 2010) and TB–HIV co-infected patients (WHO, 2010; Blanc et al., 2011). Accordingly, it is recommended that ART is started promptly during the intensive phase of anti-TB treatment (WHO, 2010). According to a private sector study in Myanmar, active TB disease is common in PLHIV (39.0%) (Sabapathy et al., 2012). However, very few studies on the survival rate and risk factors for mortality among TB–HIV co-infected patients have been reported in the literature (Thida et al., 2014; Thi et al., 2016). The aim of this study was to assess these factors among TB–HIV co-infected patients enrolled at MSH in Yangon Region, Myanmar, from July 1, 2005 to December 31, 2016.

Methods

Study subjects

The study subjects were TB–HIV co-infected patients on ART at MSH from July 1, 2005 to December 31, 2016. A total of 11 189 PLHIV aged 15 years and older were recruited. Of these, 4250 (38.0%) were co-infected with TB. Among them, 652 were excluded from this study as they had made only one initial hospital visit (602 patients) and/or had two or more missing data categories for TB (519 patients). A total of 3598 (84.7%) TB–HIV co-infected patients were considered as the total sample size (Figure 1).

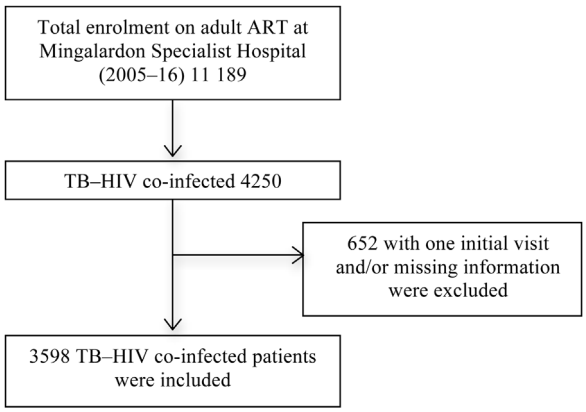


Figure 1. Selection procedure for the study subjects of adult TB–HIV co-infected patients enrolled on antiretroviral therapy at Mingalardon Specialist Hospital during July 1, 2005 to December 31, 2016.

Study setting

MSH is the largest public ART center in Myanmar and is located in the city of Yangon. Patients diagnosed with HIV are referred to this hospital for baseline clinical assessments and laboratory investigations, such as CD4 cell counts, hemoglobin levels, and liver function tests. The CD4 count criterion for receiving ART in TB–HIV co-infected patients was $\leq$350 cells/mm^3 from 2005 to 2010 (WHO, 2004) and $\leq$500 cells/mm^3 from 2011 to 2013 (National AIDS Programme, 2011). Since 2014, all TB–HIV co-infected patients have been eligible to receive ART regardless of their CD4 count (National AIDS Programme, 2014).

Data collection

Data were collected from standardized patient ART record cards and registers from July 1, 2005 to December 31, 2016. The data collected included patient socio-demographic characteristics and clinical and immunological information. Data were cleaned in Microsoft Excel 2013. After the data cleaning process, missing variables were re-collected and confirmed using paper-based patient ART records and registers.

ART regimens

ART is provided free of charge to PLHIV in Myanmar. Patients are scheduled to revisit the facility 1 to 2 months after the initial ART visit, and thereafter, every 3 months. Clinical assessments are conducted at every visit and laboratory investigations at least once every 6 months, depending on the patient's condition. First-line ART included stavudine- (d4T), tenofovir- (TDF), zidovudine- (AZT), and abacavir-based (ABC) regimens. The d4T regimen was phased out during 2012 to 2015 (National AIDS Programme, 2014) and replaced by the WHO recommended first-line regimens. Since then, TDF plus lamivudine (or emtricitabine) plus efavirenz (TDF + 3TC (or FTC) +EFV) have been used as the recommended first-line regimens in Myanmar (WHO, 2016b).

Outcome variable

The death outcome was recorded based on reports from family members or peer volunteers, as well as observation at MSH. All other cases were censored at the date of their last visit. The beginning of the follow-up was the date of ART initiation.

Exposure variable

Socio-demographic and clinical characteristics were considered as the independent variables. Socio-demographic characteristics included age, sex, literacy, occupation, point of entry (referral from other programs such as prevention of mother-to-child transmission), and the transmission risks (heterosexual, men who have sex with men, sex workers, people who inject drugs, blood transfusion, and mother-to-child transmission). Clinical information included performance activities (bedridden or normal), WHO clinical stage as revised in 2007 (WHO, 2007), baseline CD4 count (cells/mm^3), type of TB (extrapulmonary TB (EPTB) or pulmonary TB (PTB)), and anti-TB treatment regimen. WHO clinical staging of HIV consists of laboratory diagnosis of HIV infection and clinical diagnosis, such as PTB or EPTB or other relevant clinical symptoms. In this study, TB–HIV co-infected patients were included as part of the WHO clinical stages 3 and 4 (WHO, 2007).

Statistical analysis

The Excel dataset was imported into IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Socio-demographic and clinical

characteristics were described using the frequency and proportion for categorical variables, and the mean (standard deviation (SD)) or the median (interquartile range (IQR)) for continuous variables. Survival rates were calculated by Kaplan–Meier method. The survival curves were tested by log rank test. Unadjusted hazard ratios (HR) and adjusted hazard ratios (aHR) were calculated using the Cox proportional hazards model. Statistical significance was set at 0.05 and 95% confidence intervals (CI) were estimated for the HRs.

Ethical considerations

This study was approved by the National AIDS Program (NAP), Disease Control Division, Department of Public Health (Ref. PaKaYa/AKaTha-YaNa/2017 (485)), Department of Medical Services (Ref. Medical Services/Research/2017/1479), the Institutional Technical and Ethics Review Board, University of Public Health (Ref. ITERB 2017/Research/5), and the Ministry of Health and Sports, Myanmar. Patient identifiers used in this study were de-identified before the data analysis. Confidentiality was maintained at all stages of the data handling processes and the electronic data files were kept in a password-protected computer.

Results

Socio-demographic and clinical characteristics

A total of 3598 patients were enrolled, and the mean age at enrolment was 36.4 years (SD 8.7 years); 68% were male ($n = 2452$). The majority (85.9%) of the patients were literate; however 31.4% had an unknown HIV transmission route. At enrolment, 23.8% were bedridden, while 63.1% were in WHO clinical stage 3. The only WHO clinical stages included in this study were stages 3 and 4, because the study participants were already co-infected with TB. The median CD4 count at enrolment was 94.0 cells/mm^3 (IQR 36.0–120.3 cells/mm^3). The proportion of sputum smear-positive PTB was low at 8.7%. Most patients (89.9%) were treated with the initial anti-TB regimens (Table 1).

Table 1
Socio-demographic and clinical characteristics of adult TB–HIV co-infected patients enrolled at Mingalardon Specialist Hospital in Myanmar, July 1, 2005 to December 31, 2016.

Characteristics	Total ($N = 3598$)	
	n	%
Age (years)		
15–29	669	18.6
30–39	1571	43.7
40–49	746	20.7
≥50	612	17.0
Sex		
Male	2452	68.1
Female	1146	31.9
Literacy		
Literate	3089	85.9
Illiterate	509	14.1
Occupation		
Employed	2541	70.6
Unemployed	1057	29.4
Transmission risk for HIV		
Risks assessed[a]	2468	68.6
Unknown	1130	31.4
Point of entry		
Public	944	26.2
Private	2654	73.8
WHO clinical stage		
Stage 3	2270	63.1
Stage 4	1328	36.9
Physical performance		
Normal	2742	76.2
Bedridden	856	23.8
Baseline CD4 cell count (cells/mm^3)[b]		
≤94.0	1805	50.2
>94.0	1793	49.8
Type of TB		
PTB	2029	56.4
EPTB	1569	43.6
ART regimen		
d4T-based	599	16.6
AZT-based	666	18.5
TDF-based	2126	59.1
ABC-based	196	5.4
Second-line	11	0.3
Anti-TB regimen		
Initial	3233	89.9
Retreatment	365	10.1
Outcomes of ART		
Under care	2416	67.1
Death	494	13.7
LTFU	536	14.9
Transferred out	152	4.2

TB, tuberculosis; WHO, World Health Organization; PTB, pulmonary TB; EPTB, extrapulmonary TB; ART, antiretroviral therapy; d4T, stavudine; AZT, zidovudine; TDF, tenofovir; ABC, abacavir; 3TC, lamivudine; FTC, emtricitabine; EFV, efavirenz; NVP, nevirapine; LTFU, lost to follow-up.

[a] Heterosexual, men who have sex with men, sex workers, people who inject drugs, blood transfusion, mother-to-child transmission.

[b] The median of the subjects.

Survival rate and mortality risk factors

Among the 3598 TB–HIV patients, 494 (13.7%) died and 536 (14.9%) were lost during the study follow-up period. The survival rate for all patients was 82.0% at 5 years and 58.1% at 10 years. The survival curves according to the types of TB and ART regimens are illustrated in Figures 2 and 3. Patients on the second-line ART regimen had significantly lower survival rates compared to the others ($p < 0.001$).

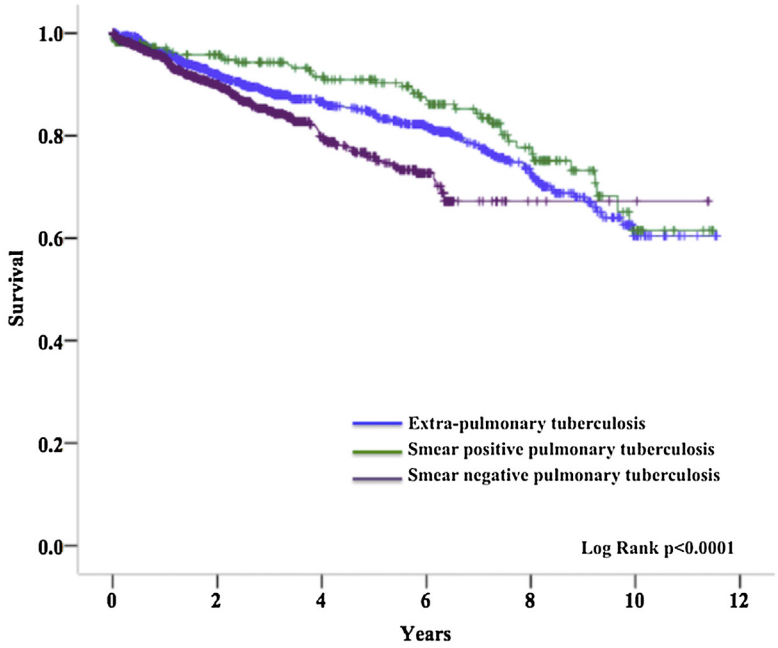
The unadjusted HR was significant for patients who were 40 years or older, illiterate, bedridden, whose point of entry was from the public sector, who had a low baseline CD4 count, who were on the second-line ART regimen, and who were diagnosed with PTB. Multivariate analysis revealed that the independent predictors of death were being 40 years or older (aHR 1.25, 95% CI 1.04–1.51), illiterate (aHR 1.35, 95% CI 1.05–1.74), bedridden (aHR 2.70, 95% CI 2.13–3.42), with a low baseline CD4 count (aHR 1.53, 95% CI 1.25–1.87), and on the second line ART regimen (aHR 8.12, 95% CI 3.56–18.54) (Table 2).

Discussion

This study appears to be the first to report the survival rate and risk factors for mortality among TB–HIV co-infected patients at the largest public ART center in Myanmar. The survival probability of TB–HIV co-infected patients was 82.0% at 5 years and 58.1% at 10 years. The study revealed that important predictors of death were age 40 years or older, being illiterate, bedridden, with a low baseline CD4 count, and on the second-line ART regimen.

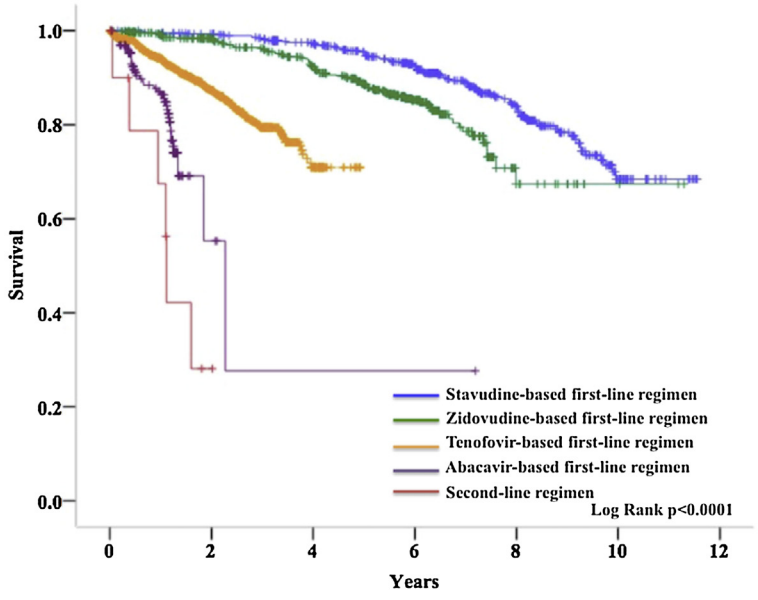
More than half of the patients had a low CD4 count (≤94.0 cells/mm^3) at the baseline assessment. Delayed access to HIV services for patients with low CD4 counts led to a higher death rate. Patients with advanced stages or complicated cases were referred to MSH for terminal care, as it is an HIV-specialist hospital. A 7-year retrospective cohort study from India also reported a high mortality rate for such patients (Bajpai et al., 2016).

Moreover, being on the second-line ART regimen was a strong predictor of mortality among TB–HIV co-infected patients. This finding is in line with those of multi-cohort studies in the Asian and African regions (Pujades-Rodrìguez et al., 2010). A possible reason might be the low CD4 counts at the baseline assessment. In addition, bedridden patients were more likely to die in this study.



Number at risk							
Extra-pulmonary tuberculosis	1569	998	615	400	154	25	0
Smear positive pulmonary tuberculosis	314	200	158	120	60	14	0
Smear negative pulmonary tuberculosis	1714	844	280	75	5	2	0

Figure 2. Kaplan–Meier estimate of survival regarding types of tuberculosis among adult TB–HIV co-infected patients enrolled on antiretroviral therapy at Mingalardon Specialist Hospital during July 1, 2005 to December 31, 2016.



Number at risk							
Stavudine-based first-line regimen	599	574	501	382	203	40	0
Zidovudine-based first-line regimen	666	563	483	213	17	2	0
Tenofovir-based first-line regimen	2126	900	68	0	--	--	--
Abacavir-based first-line regimen	196	3	1	0	--	--	--
Second-line regimen	11	0	--	--	--	--	--

Figure 3. Kaplan–Meier estimate of survival regarding antiretroviral therapy regimens among adult TB–HIV co-infected patients enrolled on antiretroviral therapy at Mingalardon Specialist Hospital during July 1, 2005 to December 31, 2016.

Table 2
Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for adult TB–HIV co-infected patients enrolled at Mingalardon Specialist Hospital in Myanmar during the period July 1, 2005 to December 31, 2016.

Characteristics	Unadjusted		Adjusted[a]	
	HR	(95% CI)	HR	(95% CI)
Age (years)				
15–39	1	Reference	1	Reference
≥40	1.31	(1.09–1.58)**	1.25	(1.04–1.51)*
Sex				
Female	1	Reference	1	Reference
Male	0.92	(0.76–1.11)	0.98	(0.80–1.19)
Literacy				
Literate	1	Reference	1	Reference
Illiterate	1.57	(1.23–2.02)***	1.35	(1.05–1.74)*
Occupation				
Employed	1	Reference	1	Reference
Unemployed	0.95	(0.79–1.15)	0.93	(0.76–1.14)
Point of entry				
Private	1	Reference	1	Reference
Public	2.08	(1.73–2.49)***	1.15	(0.92–1.45)
Transmission risk for HIV				
Risks assessed[b]	1	Reference	1	Reference
Unknown	1.14	(0.94–1.39)	1.17	(0.96–1.42)
Performance				
Normal	1	Reference	1	Reference
Bedridden	3.38	(2.82–4.06)***	2.70	(2.13–3.42)***
WHO staging				
Stage 3	1	Reference	1	Reference
Stage 4	1.08	(0.90–1.29)	0.90	(0.72–1.13)
Baseline CD4 cell count (cells/mm^3)[c]				
≤94.0	1.90	(1.59–2.28)***	1.53	(1.25–1.87)***
>94.0	1	Reference	1	
ART regimen				
First-line	1	Reference	1	Reference
Second-line	12.58	(5.59–28.31)***	8.12	(3.56–18.54)***
Type of TB				
EPTB	1	Reference	1	Reference
PTB	1.27	(1.06–1.52)**	1.19	(0.96–1.48)
Anti-TB regimen				
Initial	1	Reference	1	Reference
Retreatment	1.14	(0.86–1.51)	1.02	(0.76–1.36)

TB, tuberculosis; WHO, World Health Organization; ART, antiretroviral therapy; EPTB, extrapulmonary TB; PTB, pulmonary TB; *$p < 0.050$, **$p < 0.010$, *** $p < 0.001$.
[a] Adjusted for age, sex, literacy, occupation, point of entry, transmission risk for HIV, performance, WHO staging, baseline CD4 counts, ART regimens, types of TB, and anti-TB regimens.
[b] Heterosexual, men who have sex with men, sex workers, people who inject drugs, blood transfusion, mother-to-child transmission.
[c] The median of the subjects.

This is consistent with the results of systematic reviews from Ethiopia (Ayalew, 2017; Gesesew et al., 2017), and may be because the bedridden patients had low CD4 counts at enrolment, leading to increased mortality (Ayalew, 2017; Sieleunou et al., 2009). A low CD4 count has been reported as a predictor of mortality in several studies (Ayalew, 2017; Sieleunou et al., 2009; Gupta et al., 2011). High attention in care should be provided for bedridden patients as they need more psychosocial and nutritional support.

In this study, patients aged 40 years and above were at higher risk of death. This finding is consistent with those of prospective observational studies in Taiwan (Feng et al., 2011) and South Africa (Heunis et al., 2017). Being illiterate was also a risk factor for mortality among TB–HIV co-infected patients. This is consistent with the results of a previous study in Myanmar (Sabapathy et al., 2012). A possible explanation might be the associated poor awareness and knowledge of HIV infection, as well as inadequate practices in health-seeking behaviors (Deblonde et al., 2010; Ekstrand et al., 2013). HIV education and health promotion programs targeting illiterate patients are recommended.

About one third of TB–HIV co-infected patients reported an unknown HIV transmission route. Many patients in this study were diagnosed with HIV while they were accessing anti-TB treatments. Poor awareness of the HIV infection may be one of the possible reasons for late testing (Deblonde et al., 2010). A second possible explanation is related to the disclosure of HIV transmission routes (Ekstrand et al., 2013). The patients' spouses or partners may have belonged to high-risk groups such as people who inject drugs, homosexual or bisexual men, or the clients of female sex workers, or may have been sex workers themselves. They may not have wanted to disclose their partners' status if they were infected. Another reason might be the limited disclosure by the patients to the healthcare providers, due to the fear of discrimination (Ekstrand et al., 2013). Stigma and discrimination are barriers to accessing HIV services (Zarei et al., 2015). Educational programs are urgently needed to reduce the stigma and discrimination of PLHIV and consequently improve awareness of HIV infection and early testing in Myanmar.

The first and major strength of this study is that it was conducted at the largest public HIV-specialist hospital in the country. Second, the data may reflect the ART centers throughout Myanmar because the same system and support are provided under the NAP. Lastly, robust methods of data cleaning and analysis using a multivariate logistic method were applied in the evaluation of the factors predicting mortality. Furthermore, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in the reporting of this study (von Elm et al., 2007).

This study has several limitations. First, the population characteristics of the cohort changed over the 12-year study period. During the follow-up period, the national eligibility guidelines CD4 criterion for the initiation of ART was updated, which resulted in patients with a poor prognosis being enrolled in the later years of the cohort compared to the earlier years. In addition, the availability of the new ART regimens, improvements in investigations, and better clinical management over time may have impacted the mortality seen in the study. Second, a majority of the study subjects were from urban areas where the ART centers are located. Therefore, the subjects may not be representative of all PLHIV in Myanmar; however, Yangon is the most populated region and is included in the high priority rank in the National Strategic Plan for HIV/AIDS (2016–2020) (National AIDS Programme, 2017). This increases the possibility for the generalization of the findings. Third, as the study was a registry-based retrospective cohort study, missing data on important variables such as body mass index, alcohol use, hemoglobin, and liver function tests could not be assessed. Last, under-reporting of death might have occurred. However, the NAP has trained and recruited peer volunteers as part of a case management care system and support for PLHIV. Their responsibilities include the reporting of patient deaths for those treated at the ART center and contacting patients via phone or home visits if they have missed an ART appointment at the center.

The findings of this study are timely and relevant for NAP and National Tuberculosis Program planning for better outcomes of TB–HIV management. As it was not possible to assess the time interval between anti-TB treatment initiation and ART initiation, it is recommended that future studies explore this important area. To explore and tackle the challenges of the long-term follow-up period, a master patient index should be considered for individual tracking systems and qualitative studies. We also encourage future qualitative studies on TB–HIV to fill the gaps of referral and patient tracking systems between these programs.

In conclusion, this study revealed that 5- and 10-year survival rates for TB–HIV co-infected patients were 82.0% and 58.1%, respectively. The risk factors for mortality included being aged 40 years and above, illiterate, bedridden, with a low baseline CD4 count, and on the second-line ART regimen. Current HIV prevention and treatment programs should give more attention to TB–HIV co-infected patients with these mortality risk factors.

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None.

Ethical approval

This study was approved by the National AIDS Program (NAP), Disease Control Division, Department of Public Health (Ref. PaKaYa/AKaTha-YaNa/2017 (485)), Department of Medical Services (Ref. Medical Services/Research/2017/1479), the Institutional Technical and Ethics Review Board, University of Public Health (Ref. ITERB 2017/Research/5), and the Ministry of Health and Sports, Myanmar. Patient identifiers used in this study were de-identified before the data analysis. Confidentiality was maintained at all stages of the data handling processes and the electronic data files were kept in a password-protected computer.

Conflict of interest

The authors declare no conflicts of interest for this study.

Author contributions

ZZA, STN, NO, HNNA, and SA coordinated, collected, and cleaned the data. ZZA and SYM conducted the analysis. ZZA, SYM, HNO, SMC, ST, MK, TK, EY, and NH were involved in the analysis plan and interpretation. ZZA, STN, and SYM drafted the manuscript; SYM and NH edited the manuscript. All authors contributed to the interpretation of the data and approved the manuscript.

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