Treatment Outcomes From the Largest Antiretroviral Treatment Program in Myanmar (Burma): A Cohort Analysis of Retention After Scale-Up

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Background: Antiretroviral treatment (ART) coverage in Myanmar is well below average. This study describes retention and baseline predictors of prognosis from the largest ART program in the country.

Methods: A cohort analysis of adult patients who initiated ART during 2003–2007 was conducted, with follow-up until the end of 2009. The primary outcome was attrition [death plus losses to follow-up (LTF)]. Baseline variables were assessed as potential risk factors. The cumulative probabilities of death, LTF, and attrition up to 5 years were described using Kaplan–Meier estimates. Cox regression was used to calculate hazard ratios of attrition, overall and separately for 2 time periods on ART: 1–6 and 7–36 months.

Results: A total of 5963 adults enrolled in the program, providing 17,581 person-years of follow-up. Median age at baseline was 33 years [interquartile range (IQR): 28–38], 61% were men, 45% were in World Health Organization stage IV, and the median CD4 count was 71 cells per cubic millimeter (IQR: 29–164). There were 821 (13.8%) deaths and 389 (6.5%) LTF over the study period, with a 72% probability of being retained in care in the 5-year cohort. Double the rate of loss was contributed by death compared with LTF, and attrition was almost 4 times higher in the period 1–6 months compared with 7–36 months. In the multivariable analyses of the program overall, older age [adjusted hazard ratio (aHR): 1.56, 95% confidence interval (CI): 1.25 to 1.94], being male (aHR: 1.52, 95% CI: 1.25 to 1.85), World Health Organization stage IV (aHR: 1.44, 95% CI: 1.19 to 1.74), and body mass index <16 kg/m^2 (aHR: 2.13, 95% CI: 1.71 to 2.66) were independently predictive of attrition.

Conclusions: The excellent retention over >6 years in this large cohort demonstrates that ART delivery at the primary care level in Myanmar is feasible and should encourage support for further ART expansion in the country.

Key Words: antiretroviral treatment, HIV, predictors, risk factors, prognosis, attrition, retention, mortality, primary care, resource limited, Asia, Myanmar, Burma, cohort

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INTRODUCTION

The Union of Myanmar is ranked 132 of 169 countries on the Human Development Index and is the least developed country in Southeast Asia.[1] Government expenditure on health is 0.2% of total gross domestic product compared with 1.7% in neighboring Cambodia,[1] which receives 10 times more official development assistance ($US 46 per capita vs $US 4).[2] Formerly known as Burma, the country was renamed Myanmar in 1989. It has an estimated population of 50 million and adult HIV prevalence of 0.6%.[3] HIV prevalence estimates in "most-at-risk" groups in the capital city are the highest in the South and Southeast Asia region (18% for female sex workers and 29% for men who have sex with men). Over a third (38%) of injection drug users are HIV positive.[3] There were an estimated 17,000 new infections in 2009, second only to India in the South/Southeast Asia region, and 18,000 AIDS-related deaths.[3] Of the 120,000 people estimated to need antiretroviral therapy (ART), 24% (29,825) received it in Myanmar compared with 47% ART coverage overall for low-income and middle-income countries (based on ART eligibility at CD4 count <350 cells/mm^3).[4] In 2010, 55% (n = 16,519) of all reported ART provided in the country was supported by the program in this study.

The benefits of ART in resource-poor settings have long been demonstrated,[5] and Médecins Sans Frontières (MSF) began the first ART program in Myanmar in 2003. As an independent nongovernmental organization, MSF was

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K. Sabapathy and S. Floyd designed the study, and K. Sabapathy did the analysis with support from S. Floyd; F. Smithuis designed and headed the program during the study period; M.K. Kyaw was responsible for data management; K. Sabapathy, N. Ford, and S. Floyd wrote the initial draft, and all listed authors contributed to the intellectual content and writing of the article; and K. Sabapathy and S. Floyd vouch for the data, analysis, interpretation, and manuscript submission.

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not authorized to have unscheduled access to patients in hospital, and from the outset all care has been provided at the primary care level. In this article, we report outcomes from the MSF program where antiretroviral treatment was provided on a large scale from a primary care level over a period of >6 years in Myanmar—an Asian severely resource-limited setting where access to treatment is considerably outweighed by the need[4] and resources for health are limited.[1,2]

METHODS

Program Design and Care Provision

Patients accessed the clinics from all over the country but were principally from Yangon, Kachin, Shan, and Rakhine states (see **Map, Supplemental Digital Content 1**, http://links.lww.com/QAI/A279). These were the 4 locations where MSF worked based on unmet needs and government permission to operate. All care was provided free of charge across 10 main primary care and satellite sites. Clinical consultations were performed by medical doctors, as is the case in most Asian HIV treatment programs. In general, a multidisciplinary team composed of a specific doctor, nurse, counselor, and outreach support worker managed a given patient, providing continuity of care. The counselors and outreach support workers were lay people trained to perform their roles and were often people living with HIV/AIDS themselves. Adherence support was provided by these counselors in the clinic, and in the community by the outreach support workers. The latter had both defaulter tracing and defaulter prevention functions, and helped patients resolve social problems and address adherence issues with the clinic-based team. If patients had died in the community, this was ascertained and reported when possible. In exceptional cases (eg, those with disabilities or debilitating factors), patients were given financial support for transport to attend follow-up visits at the discretion of the multidisciplinary team. Local food support was provided for the first 6 months on ART.

Routine follow-up after ART initiation was done at 2 weeks, 1 month, 2 months, 3 months, and 3 monthly thereafter. Initially, access to CD4 count testing was limited and ART was initiated based on World Health Organization (WHO) clinical staging criteria alone (WHO stage III or IV) as there was no access to reliable CD4 count testing. This became available in 2005 but was still not routinely accessible at the end of the study period at all sites. There was no access to routine viral load monitoring in the country throughout the study period.

All medications (antiretrovirals, treatment for opportunistic infections, and cotrimoxazole prophylaxis) were prescribed according to contemporaneous WHO guidelines[6–8] (national guidelines followed WHO guidelines). First-line ART comprised nevirapine, stavudine (with efavirenz and zidovudine, respectively, as alternatives when indicated), and lamivudine; and second-line ART comprised a ritonavir boosted protease inhibitor (lopinavir or saquinavir)–based regimen. Opportunistic infection [including tuberculosis (TB)] management was fully integrated with HIV care as a one-stop service at all clinics. When indicated, intravenous infusions were administered on site. Patients requiring hospitalization were referred to the nearest Ministry of Health hospital. During hospitalization, MSF clinicians were no longer involved in the clinical management of patients but ART supplies continued to be dispatched.

Data Management and Analysis

All adult patients (≥15 years) who initiated combination ART between March 2003 (when the program started) and July 2007 were included in the analysis and followed-up until the end of 2009. Baseline characteristics were collected by attending clinicians and entered into an Access database (Fuchia version 1.4; Epicentre, Paris, France). The primary outcome of interest was attrition, defined as known deaths plus losses to follow-up (LTF). This definition was used to include patients who would have a poor prognosis, whether due to death or not receiving further care. Rates for death and LTF were also examined separately. We defined LTF as an absence of >60 days from last appointment, consistent with empirically derived definitions.[9] Patients who transferred to another site were censored. Retention refers to all patients remaining in care (ie, after accounting for deaths, loss to follow-up, and transfers).

The following baseline variables, determined by history and clinical assessment by clinicians, were assessed as potential risk factors for attrition: age group, sex, WHO stage, body mass index (BMI), CD4 count, TB in the previous 5 years or at ART initiation, oral candidiasis and oral hairy leukoplakia (WHO stage III–defining conditions), prior ART exposure (mainly prescribed by private practitioners or bought in pharmacies), employment status, and year of ART initiation. TB diagnosis was based on clinical screening, microscopy (available at clinics), and chest x-ray (referred to radiography centers). CD4 count was expected to be missing in the majority of patients due to limited access to testing up to the end of the study period. Some sites had routine access after 2005, and others used it when in doubt of eligibility for ART or in exceptional cases. This variable was examined as a risk factor, acknowledging the limitations in terms of the generalizability of any associations found. Multiple imputation of missing CD4 counts and BMI values was considered, but there were concerns that inaccurate results could be obtained because it was not plausible to assume that data were missing at random. For example, in all but 5 patients, missing BMI values were due to lack of data for height. One reason for missing height data was that moribund patients did not have their heights measured and therefore patients with missing BMI data could be different to those with available data in important ways that could affect the outcome of interest. However, this was not the only reason, and omission by clinical staff also occurred in this operational setting. Thus, analyses that included BMI and CD4 count as explanatory variables were restricted to individuals with data on these variables.

The cumulative probability of death, LTF, and attrition over time were described using Kaplan–Meier estimates. Baseline characteristics were described using medians and

interquartile ranges (IQRs) for continuous variables, and counts and percentages for categorical variables. Univariable Cox regression was used to assess rates of attrition, and of death and LTF (data not shown). Multivariable Cox proportional hazards models for attrition were built for each explanatory variable, assessing the other variables as potential confounding factors, in a forward stepwise approach. The final multivariable models were limited to individuals with available values for all explanatory variables and included all variables except for CD4 count (n = 3879), with WHO stage preferred as a measure of immune suppression because data on it were available for almost all patients. The proportional hazards assumption was assessed by examining hazard ratios (HRs) over time using Nelson–Aalen plots and formally with likelihood ratio tests. Changing rates over time were examined with Lexis expansion of the data, and proportionality assessed for the several time periods. Finally, further analysis was done separately for the time intervals 1–6 and 7–36 months (still examining the association with baseline characteristics) on the basis of observed period-specific HRs and statistical tests for interaction, which showed evidence of variation in rate ratios between, but not within, these 2 time periods. The period beyond 3 years was not examined for risk factors due to smaller numbers in the cohort beyond this time.

All analyses were performed using Stata version 11.0 for Windows (Stata Corp, College Station, TX). The study was approved by the Ethics Committee of the London School of Hygiene and Tropical Medicine. All patient information was entered into the database using coded identification numbers, and no information that could reveal patient identity was entered into the database.

RESULTS

Between 2003 and mid-2007, 5963 adults enrolled for combination ART in the program (see **Figure, Supplemental Digital Content 2**, http://links.lww.com/QAI/A280), with a total of 17,581 person-years of follow-up over a period of 6.8 years and a median follow-up of 3 years (IQR: 2.4–3.8) in the study. Seventy-six percent of patients were retained alive at the end of the observation period, with 821 (13.8%) deaths, 389 (6.5%) LTF, and 210 (3.5%) transferred to other providers.

Median age at baseline was 33 years (IQR: 28–38) and 61% of patients were men. Forty-nine percent of patients were classified as WHO stage III and 45% as WHO stage IV at baseline. The proportion of patients with missing CD4 count values was the same whether individuals were in WHO stage IV or not (56%). Among patients for whom CD4 count was available (n = 2608), the median CD4 count was 71 cells per cubic millimeter (IQR: 29–164) and 42% had a CD4 count ≤50 cells per cubic millimeter. Of 4078 (68%) patients with BMI measurements, 54% (n = 2199) were underweight and 18% (n = 748) were severely underweight (defined as <18.5 and <16 kg/m^2, respectively, according to the WHO cutoffs[10]). Sixty-two percent of patients (n = 3721) had a history of TB at baseline (39% had active TB when initiating ART). A third of the cohort was unemployed when initiated on ART (Table 2).

The cumulative probabilities of retention after losses due to mortality, LTF, and attrition in the program over time after starting ART are shown in Table 1 and Figure 1; Figure 2 displays these outcomes by year of ART initiation. Attrition in the first year on ART was 11%, and among those eligible for 5 years of follow-up, 72% were still retained alive at this time. During the first 6 months, 499 attritions occurred over 2811 person-years at risk and the rate of attrition was 17.8/100 person-years [95% confidence interval (CI): 16.3 to 19.4]. This is almost 4 times higher than in the period 7–36 months, with 562 attritions over 12,043 person-years at risk (4.7/100 person-years, 95% CI: 4.3 to 5.1). Double the rate of attrition was contributed by death compared with LTF (4.7 compared with 2.2/100 person-years) overall.

Risk factors for attrition in the program over 6.8 years of follow-up included BMI <16 kg/m^2 (HR: 2.04, 95% CI: 1.66 to 2.51), WHO stage IV (HR: 1.62, 95% CI: 1.44 to 1.81), age ≥40 years (HR: 1.58, 95% CI: 1.36 to 1.83), and being male (HR: 1.22, 95% CI: 1.08 to 1.37) (Table 2). After adjusting for confounding factors, these associations persisted (Table 2), but individuals with current or previous TB had a lower rate of attrition [adjusted HR (aHR): 0.75, 95% CI: 0.62 to 0.92]. Multivariable analyses of attrition, and death and LTF separately, show a very similar pattern of associations between the baseline characteristics and each of attrition and death (data not shown). Most estimates for associations with LTF did not reach statistical significance, although being unemployed was associated with lower LTF rates and age ≥15–29.9 years was associated with 68% higher LTF (aHR: 1.68, 95% CI: 1.17 to 2.42).

Examining the associations by time period on ART, the strongest predictor of attrition (among those with complete

TABLE 1. Cumulative Probabilities of Retention Over Time on ART

Duration on ART	Losses Due to Deaths and LTF* (95% CI)	Losses Due to Deaths Only† (95% CI)	Losses Due to LTF Only‡ (95% CI)
3 mo	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.95)	1.00 (0.99 to 1.00)
6 mo	0.92 (0.91 to 0.92)	0.93 (0.92 to 0.93)	0.99 (0.99 to 0.99)
1 yr	0.89 (0.88 to 0.90)	0.91 (0.90 to 0.91)	0.98 (0.98 to 0.99)
3 yr	0.82 (0.81 to 0.83)	0.87 (0.86 to 0.87)	0.94 (0.93 to 0.95)
5 yr	0.72 (0.70 to 0.74)	0.83 (0.82 to 0.85)	0.86 (0.84 to 0.88)

The lower/upper 95% CI may be the same as some point estimates due to rounding to 2 decimal places.
*Transfers censored from analysis.
†LTF and transfers censored.
‡Deaths and transfers censored.

TABLE 2. Baseline Characteristics, Rates, and Hazard Ratios of Attrition in the Program Overall

	n (%*)	Rate of Attrition† Per 100 Person-Yr (95% CI)	Univariable HR of Attrition† (95% CI)	P‡	Multivariable HR of Attrition† (95% CI)	P‡
Overall	5963 (100)	6.9 (6.5 to 7.3)				
Sex						
Female	3656 (61.3)	6.1 (5.5 to 6.7)	1	0.001	1	<0.001
Male	2307 (38.7)	7.39 (6.9 to 7.9)	1.22 (1.08 to 1.37)		1.52 (1.25 to 1.85)	
Age at ART initiation (yr)						
≥15–29.9	1786 (34.9)	6.7 (6.1 to 7.4)	0.94 (0.81 to 1.08)	<0.001	1.04 (0.85 to 1.27)	
≥30–39.9	2370 (46.4)	6.3 (5.7 to 7.0)	1	<0.001§	1	<0.001
≥40–79.9	957 (18.7)	10.6 (9.5 to 12.0)	1.58 (1.36 to 1.83)		1.56 (1.25 to 1.94)	
Missing	*850 (14.3)*	*4.7 (3.9 to 5.6)*	*0.64 (0.53 to 0.78)*			
WHO stage IV						
No	3198 (54.0)	5.4 (4.9 to 5.8)	1	<0.001	1	<0.001
Yes	2740 (46.0)	8.7 (8.0 to 9.4)	1.62 (1.44 to 1.81)		1.44 (1.19 to 1.74)	
Missing	*25 (0.4)*	*18.8 (10.4 to 33.9)*	*2.17 (1.19 to 3.93)*	*0.02*§		
CD4 count (cells/mm^3)						
≤50	1082 (41.5)	9.4 (8.4 to 10.6)	1	<0.001	1	<0.001
>51–100	540 (20.7)	5.3 (4.3 to 6.6)	0.57 (0.44 to 0.72)		0.65 (0.47 to 0.91)	
>101–200	597 (22.9)	3.9 (3.0 to 4.9)	0.41 (0.31 to 0.53)		0.58 (0.41 to 0.82)	
>201	389 (14.9)	3.8 (2.8 to 5.1)	0.40 (0.29 to 0.55)		0.55 (0.36 to 0.85)	
Missing	*3355 (56.3)*	*7.3 (6.8 to 7.8)*	*1.15 (1.03 to 1.29)*	*0.02*§		
BMI (kg/m^2)						
≥18.5	1879 (46.1)	3.5 (3.0 to 4.0)	1	<0.001	1	<0.001
≥16 to <18.5	1451 (35.6)	4.0 (3.4 to 4.6)	1.15 (0.94 to 1.40)		1.17 (0.95 to 1.45)	
<16	748 (18.3)	7.1 (6.0 to 8.2)	2.04 (1.66 to 2.51)		2.13 (1.71 to 2.66)	
Missing	*1885 (31.6)*	*14.1 (13.1 to 15.3)*	*3.31 (2.95 to 3.71)*	*<0.001*§		
Ever had TB						
No	2242 (37.6)	6.4 (5.8 to 7.0)	1	0.05	1	0.005
Yes	3721 (62.4)	7.2 (6.7 to 7.7)	1.13 (1.00 to 1.27)		0.75 (0.62 to 0.92)	
Oral candidiasis						
No	3583 (60.1)	6.6 (6.1 to 7.1)	1	0.09	1	0.19
Yes	2380 (39.9)	7.3 (6.7 to 7.9)	1.10 (0.98 to 1.24)		1.13 (0.94 to 1.37)	
Oral hairy leukoplakia						
No	2921 (49.0)	7.2 (6.7 to 7.8)	1	0.09	1	0.18
Yes	3042 (51.0)	6.5 (6.0 to 7.1)	0.91 (0.81 to 1.02)		0.88 (0.73 to 1.06)	
Prior ART exposure						
No	5461 (91.6)	7.0 (6.6 to 7.4)	1	0.02	1	0.28
Yes	502 (8.4)	5.4 (4.4 to 6.8)	0.78 (0.62 to 0.97)		1.11 (0.92 to 1.35)	
Unemployed						
No	3849 (66.4)	6.2 (5.8 to 6.7)	1	<0.001	1	0.30
Yes	1944 (33.6)	7.7 (7.0 to 8.4)	1.23 (1.10 to 1.39)		0.84 (0.62 to 1.17)	
Missing	*170 (2.9)*	*14.4 (11.1 to 18.6)*	*2.14 (1.64 to 2.80)*	*<0.001*§		
Year of ART start						
2003	78 (1.3)	6.5 (4.4 to 9.7)	0.81 (0.53 to 1.23)		0.97 (0.57 to 1.65)	
2004	384 (6.4)	6.3 (5.1 to 7.6)	0.78 (0.62 to 0.98)		0.43 (0.29 to 0.65)	
2005	1380 (23.1)	7.0 (6.3 to 7.8)	0.87 (0.74 to 1.03)		0.62 (0.48 to 0.81)	
2006	2741 (46.0)	6.4 (5.9 to 7.0)	0.80 (0.69 to 0.93)		0.59 (0.47 to 0.73)	
2007 (up to July)	1380 (23.1)	8.1 (7.1 to 9.1)	1	0.06	1	<0.001

*Percentage shown for available values are after excluding missing values; for missing values, percentages are as proportion of total.

†Univariable HRs were derived from Cox regression and therefore adjusted for time since ART initiation. Multivariable HRs are adjusted for all the other variables except for CD4 count (n = 3879), and the multivariable model for CD4 count is adjusted for all the other variables except for WHO stage (n = 2085) (see Methods). The multivariable models are limited to individuals with available values for all explanatory variables. Limiting the univariable analyses to individuals with available values for all explanatory variables did not change the conclusions drawn. When separate multivariable analyses were done adjusting for clinic site, the conclusions were the same (data not shown).

‡Likelihood ratio test.

§*P* value for the HR of attrition, comparing individuals with missing data with those with data available on the explanatory variable.

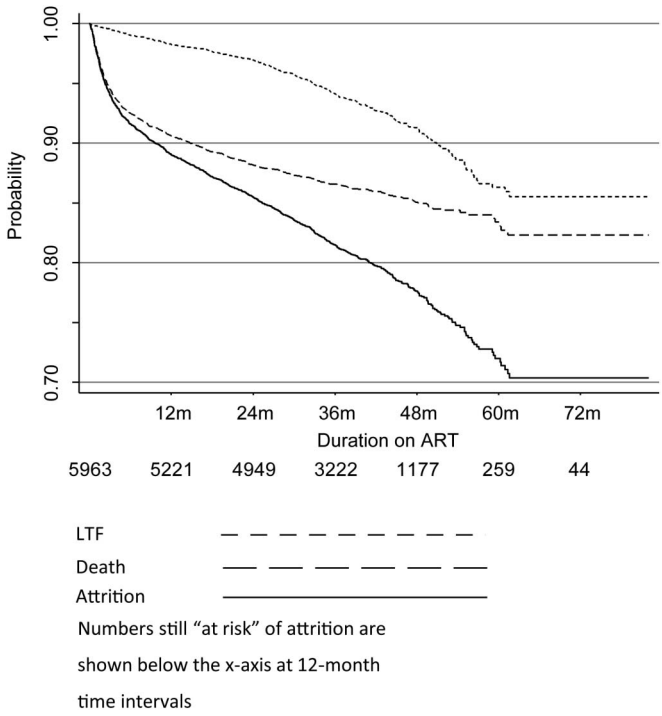

FIGURE 1. Cumulative probabilities of retention on ART in the program overall with LTF, death, and attrition (death + LTF) as failure outcomes.

data on all outcomes: n = 3879) in the first 6 months was BMI <16 kg/m^2, and the rate at which these individuals were lost from the program was 4 times higher than those with normal BMI (HR: 4.15, 95% CI: 2.93 to 5.91); and even those with BMI ≥ 16 to <18.5 kg/m^2 had a 62% higher rate of attrition (HR: 1.62, 95% CI: 1.11 to 2.34). After adjusting for confounding factors, the attrition rate associated with having BMI <16 kg/m^2 remained considerable (aHR: 3.80, 95% CI: 2.60 to 5.53) in this early period and was still predictive of attrition among individuals surviving into the period 7–36 months after starting ART (aHR: 1.48, 95% CI: 1.06 to 2.07).

Men had a higher rate of attrition in both the time periods (aHR: 1.29, 95% CI: 0.94 to 1.78 for 1–6 months; aHR: 1.63, 95% CI: 1.23 to 2.15 for 7–36 months), and individuals aged ≥ 40 years had a higher attrition rate compared with those aged ≥ 30–39.9 years in both time periods even after adjusting for confounding factors (aHR: 1.54, 95% CI: 1.07 to 2.21 for 1–6 months; aHR: 1.76, 95% CI: 1.28 to 2.43 for 7–36 months). Being in WHO stage IV was also associated with worse outcomes for both time periods and remained a significant risk factor for attrition in the multivariable analysis in the first 6 months (aHR: 1.88, 95% CI: 1.35 to 2.61) but was less predictive after this period (aHR: 1.26, 95% CI: 0.95 to 1.66). Similarly, for patients with available CD4 counts, this variable was strongly predictive of loss from the program in the early period on ART but was not associated with worse prognosis after this (Table 3).

WHO stage and BMI were the most important confounding factors in the multivariable analyses. Patients with missing values had worse attrition than those with available values for all relevant explanatory variables except for missing age category (Table 2).

DISCUSSION

This study describes outcomes on ART from a large cohort (almost 6000 patients) over a substantial period of time (6.8 years) and demonstrates the feasibility of obtaining excellent outcomes (probability of retention 5 years after starting ART was 72%) from a primary care setting in Myanmar. Published data on simplified ART provision come mainly from sub-Saharan Africa,[11–13] and Asian studies are mainly from programs in middle-income countries and/or providing hospital-linked care.[14–17] In contrast, little robust independent data from Myanmar have been published to date.

A recent systematic review estimated retention in sub-Saharan African programs of 72% at 3 years, and a network of South African cohorts demonstrated retention of 56% at 5 years,[13,16] whereas in our study these probabilities were 82% and 72%, at 3 and 5 years, respectively (Table 1). The outcomes here are commendable even compared with other established ART programs with international support.[12,18,19] The free provision of integrated "one-stop" care for HIV, TB, and other opportunistic infections and also nutrition support could be a key reason for the good outcomes seen in this study. Additionally, this program had relatively highly trained local clinical staff and a patient-centered approach to clinic and community adherence support. The disproportionately high rate of mortality-associated attrition in the early months on treatment are well documented,[11,15,16,20,21] along with the association with advanced disease by the time of presentation for treatment,[12,19] which was also seen in our study. ART scale-up was not associated with increases in attrition overall in this program, unlike what has been seen elsewhere,[16,22] and attrition rates differed little according to the calendar year in which ART was initiated (Table 2). Over calendar time, we did find that death rates declined as clinical experience grew, whereas LTF worsened (Fig. 1) possibly due to the increasing cohort size, as has been reported by other studies.[22,23] Death was the major contributor to attrition, with rates of LTF accounting for less than a third of the overall attrition rate. This is similar to what was seen in a study from Cambodia[15] but is in contrast to what is reported in ART programs in sub-Saharan Africa, where LTF was the dominant contributor to attrition.[13,16] This program had an intensive community adherence, defaulter prevention, and tracing component, which could have minimized LTF and supported the accurate ascertainment of deaths and transfers.

The proportion of patients with low BMI (18% <16 kg/m^2 or 54% <18.5 kg/m^2) and WHO stage IV (46%) indicates the advanced condition of the patients presenting for HIV and ART care. The median value for those with access to CD4 count was 71 cells per cubic millimeter, which is much lower than the median count reported for Asian Antiretroviral Therapy in Lower Income Countries cohorts (123 cells/mm^3).[24]

Most risk factors were strongly predictive of attrition in the first 6 months, but this waned over time. Older patients (≥ 40–79.9 years), comprising almost a fifth of the cohort overall (19%), were identified to be at higher risk of poor

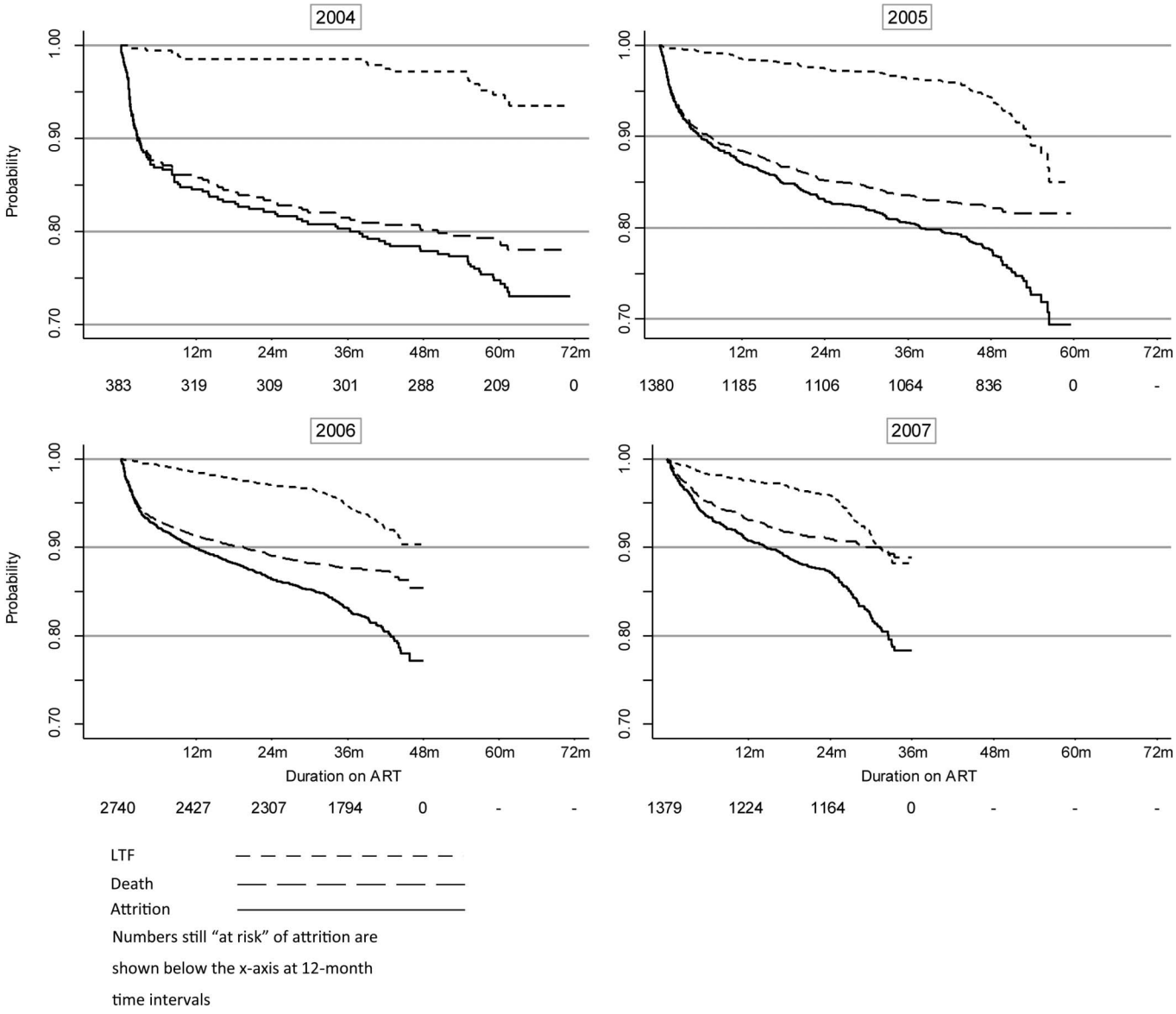

FIGURE 2. Cumulative probabilities of retention on ART with LTF, death, and attrition (death + LTF) as failure outcomes, by year of ART initiation.

prognosis in both time periods. It is noteworthy that this was not explained by markers of disease severity and alludes to the complex interplay of HIV and aging.[25] We also identified men as being at higher risk of attrition; given that the majority of HIV-infected adults in Myanmar are male[26] (and comprise 61% in this cohort), they are an important target group for earlier diagnosis and recruitment into HIV treatment programs.

Sixty-two percent of patients had a history of TB diagnosis at the time of ART initiation (either diagnosed and treated before presenting for ART care or concurrent with ART initiation), and this highlights the fact that HIV–TB coinfection is common in this setting, which is a recognized high TB prevalence country.[27] The worse attrition associated with having TB was explained by WHO staging and BMI, and after adjusting for these factors, it was associated with reduced attrition. The reason for this is probably complex. For example, the majority of patients who had a history of TB were on TB treatment when starting ART and had lower LTF (data not shown) and their lower attrition rate may be due to enhanced adherence while on TB treatment, whereas patients with previous TB had already survived this before starting ART and thus may have had other survival advantages (eg, better prepared for adhering to treatment).

BMI category in this cohort turned out to be the strongest independent predictor of attrition from the ART program. This is an ominous finding, given that almost a fifth (18%) of those with BMI measurements had a BMI of <16 kg/m^2 in this cohort and is relevant for countries where both food insecurity and HIV are important public health

TABLE 3. Hazard Ratios of Attrition (Death + LTF) After 1–6 and 7–36 Months on ART

	7–36 Months				
Baseline Characteristics (excluding missing values)	**Rate of Attrition* (per 100 py) (95% CI)**	**Univariable HR* (95% CI)**	***P*†**	**Multivariable HR (95% CI)***	***P*†**
Overall	17.8 (16.3 to 19.4)				
Sex					
Female	14.9 (12.8 to 17.3)	1	0.004	1	1
Male	19.6 (17.6 to 21.8)	1.31 (1.09 to 1.59)		1.29 (0.94 to 1.78)	0.1
Age at ART start (yr)					
≥15–29.9	18.2 (15.6 to 21.4)	0.94 (0.77 to 1.16)		0.91 (0.65 to 1.28)	
≥30–39.9	19.4 (16.9 to 22.1)	1	0.02	1	0.06
≥40–79.9	25.6 (21.3 to 30.8)	1.32 (1.05 to 1.66)		1.54 (1.07 to 2.21)	
Missing	*4.3 (2.7 to 6.8)*	*0.22 (0.14 to 0.35)*	*0.001*‡		
WHO stage IV					
No	10.3 (8.8 to 12.0)	1	0.001	1	<0.001
Yes	26.7 (24.0 to 29.7)	2.57 (2.13 to 3.11)		1.88 (1.35 to 2.61)	
Missing	*46.4 (19.3 to 111.6)*	*1.72 (0.71 to 4.15)*	*0.27*‡		
CD4 count (cells/mm^3)					
≤50	35.6 (30.6 to 41.3)	1	<0.001	1	<0.001
>51–100	14.7 (10.7 to 20.2)	0.42 (0.29 to 0.59)		0.51 (0.31 to 0.84)	
>101–200	5.8 (3.6 to 9.3)	0.17 (0.10 to 0.27)		0.26 (0.13 to 0.51)	
>201	4.7 (2.5 to 9.1)	0.14 (0.07 to 0.26)		0.29 (0.13 to 0.64)	
Missing	*16.6 (14.7 to 18.7)*	*0.86 (0.72 to 1.03)*	*0.10*‡		
BMI (kg/m^2)					
≥18.5	5.5 (4.2 to 7.3)	1	0.001	1	<0.001
≥16 to <18.5	8.9 (7.0 to 11.5)	1.62 (1.11 to 2.34)		1.55 (1.05 to 2.28)	
<16	23.1 (18.6 to 28.8)	4.15 (2.93 to 5.91)		3.80 (2.60 to 5.53)	
Missing	*36.4 (32.5 to 40.7)*	*3.64 (3.04 to 4.36)*	*0.001*‡		
Ever had TB			<0.001		0.13
No	13.9 (11.9 to 16.4)	1		1	
Yes	20.1 (18.1 to 22.3)	1.44 (1.19 to 1.74)		0.76 (0.53 to 1.09)	
Oral candidiasis					
No	13.8 (12.2 to 15.7)	1	<0.001	1	0.06
Yes	23.9 (21.1 to 26.9)	1.72 (1.44 to 2.05)		1.30 (0.95 to 1.78)	
Oral hairy leukoplakia					
No	18.2 (16.1 to 20.6)	1	0.60	1	0.63
Yes	17.3 (15.3 to 19.6)	0.95 (0.80 to 1.14)		0.87 (0.63 to 1.19)	
Prior ART exposure					
No	18.1 (16.5 to 19.8)	1	0.17	1	0.28
Yes	14.3 (10.2 to 19.9)	0.79 (0.56 to 1.12)		0.68 (0.38 to 1.23)	
Unemployed					
No	16.1 (14.4 to 18.1)	1	0.09	1	0.97
Yes	19.0 (16.4 to 22.1)	1.1 (0.98 to 1.42)		0.96 (0.69 to 1.32)	
Missing	*42.1 (29.6 to 59.9)*	*2.43 (1.69 to 3.50)*	*<0.001*‡		
Year of ART start					
2003	24.7 (12.8 to 47.4)	1.79 (0.90 to 3.56)		1.38 (0.57 to 3.33)	
2004	28.8 (21.8 to 38.0)	2.09 (1.48 to 2.96)		0.57 (0.29 to 1.11)	
2005	21.3 (18.0 to 25.2)	1.56 (1.19 to 2.03)		0.73 (0.47 to 1.11)	
2006	16.4 (14.4 to 18.8)	1.21 (0.94 to 1.54)		0.58 (0.40 to 0.83)	
2007 (up to July)	13.6 (11.1 to 16.8)	1	0.001	1	0.02

(continued on next page)

TABLE 3. *(Continued)* Hazard Ratios of Attrition (Death + LTF) After 1–6 and 7–36 Months on ART

	7–36 Months				
Baseline Characteristics (excluding missing values)	**Rate of Attrition* (per 100 py) (95% CI)**	**Univariable HR* (95% CI)**	***P*†**	**Multivariable HR (95% CI)***	***P*†**
Overall	4.7 (4.3 to 5.1)				
Sex					
Female	4.3 (3.7 to 4.9)	1	0.09	1	<0.001
Male	4.9 (4.4 to 5.5)	1.16 (0.97 to 1.38)		1.63 (1.23 to 2.15)	
Age at ART start (yr)					
≥15–29.9	4.2 (3.6 to 4.9)	0.95 (0.77 to 1.17)		1.08 (0.80 to 1.46)	
≥30–39.9	4.4 (3.8 to 5.0)	1	<0.001	1	0.007
≥40–79.9	7.9 (6.7 to 9.3)	1.78 (1.44 to 2.21)		1.76 (1.28 to 2.43)	
Missing	*3.21 (2.5 to 4.2)*	*0.65 (0.50 to 0.86)*	*0.001*‡		
WHO stage IV					
No	4.3 (3.8 to 4.8)	1	0.04	1	0.06
Yes	5.1 (4.5 to 5.8)	1.20 (1.01 to 1.41)		1.26 (0.95 to 1.66)	
Missing	*11.0 (4.1 to 29.3)*	*2.10 (0.78 to 5.65)*	*0.18*‡		
CD4 count (cells/mm^3)					
≤50	4.3 (3.5 to 5.3)	1	0.65	1	0.89
>51–100	3.6 (2.7 to 4.9)	0.84 (0.58 to 1.22)		0.86 (0.54 to 1.37)	
>101–200	3.5 (2.6 to 4.7)	0.82 (0.58 to 1.18)		0.95 (0.60 to 1.50)	
>201	3.6 (2.5 to 5.1)	0.84 (0.55 to 1.27)		0.84 (0.47 to 1.48)	
Missing	*5.3 (4.8 to 5.9)*	*1.38 (1.17 to 1.65)*	*<0.001*‡		
BMI (kg/m^2)					
≥18.5	2.9 (2.4 to 3.4)	1	0.10	1	0.05
≥16 to <18.5	3.0 (2.4 to 3.6)	1.02 (0.78 to 1.33)		0.99 (0.73 to 1.34)	
<16	4.0 (3.1 to 5.2)	1.39 (1.02 to 1.89)		1.48 (1.06 to 2.07)	
Missing	*9.1 (8.1 to 10.2)*	*2.94 (2.49 to 3.47)*	*<0.001*‡		
Ever had TB		1	0.94		
No	4.6 (4.1 to 5.3)	1		1	0.14
Yes	4.6 (4.2 to 5.2)	0.01 (0.85 to 1.19)		0.80 (0.60 to 1.08)	
Oral candidiasis					
No	4.9 (4.5 to 5.5)	1	0.07	1	0.65
Yes	4.2 (3.7 to 4.9)	0.86 (0.72 to 1.02)		1.10 (0.84 to 1.45)	
Oral hairy leukoplakia					
No	4.9 (4.4 to 5.5)	1	0.07	1	0.68
Yes	4.4 (3.9 to 5.0)	0.90 (0.76 to 1.06)		0.94 (0.72 to 1.25)	
Prior ART exposure					
No	4.8 (4.4 to 5.2)	1	0.08	1	0.44
Yes	3.6 (2.6 to 4.9)	0.75 (0.54 to 1.05)		0.81 (0.51 to 1.29)	
Unemployed					
No	4.3 (3.8 to 4.7)	1	0.02	1	0.11
Yes	5.3 (4.6 to 6.0)	1.23 (1.04 to 1.47)		1.34 (1.02 to 1.76)	
Missing	*7.9 (5.2 to 12.0)*	*1.72 (1.13 to 2.64)*	*0.02*‡		
Year of ART start					
2003	4.4 (2.1 to 9.2)	0.65 (0.31 to 1.38)		1.00 (0.43 to 2.39)	
2004	3.2 (2.2 to 4.7)	0.47 (0.31 to 0.73)		0.40 (0.20 to 0.79)	
2005	4.5 (3.8 to 5.4)	0.67 (0.53 to 0.85)		0.66 (0.45 to 0.97)	
2006	4.2 (3.7 to 4.7)	0.62 (0.51 to 0.75)		0.57 (0.42 to 0.79)	
2007 (up to July)	6.5 (5.6 to 7.6)	1	0.001	1	0.002

*Univariable HRs were derived from Cox regression and therefore adjusted for time since ART initiation. Multivariable HRs are adjusted for all the other variables except for CD4 count (n = 3879), and the multivariable model for CD4 count is adjusted for all the other variables except for WHO stage (n = 2085) (see Methods). The multivariable models are limited to individuals with available values for all explanatory variables. Limiting the univariable analyses to individuals with available values for all explanatory variables did not change the conclusions drawn. When separate multivariable analyses were done adjusting for clinic site, the conclusions were the same (data not shown).

†Likelihood ratio test.

‡*P* value for the HR of attrition, comparing individuals with missing data with those with data available on the explanatory variable.

py, person-years.

issues. An important "negative" finding in this study was that WHO stage IV at the time of starting ART was not predictive of attrition in the 7- to 36-month period. It is most likely explained by the fact that those with the worst condition died early. However, it is also encouraging that with immune reconstitution on ART, the extent of severity of baseline condition mattered less over time.

Strengths of this study include the large cohort size and long duration of follow-up, which allowed for precise estimates to be reported over a long time frame. The predictors of prognosis we identified add to the existing body of evidence from a setting from which few published data are available. As an observational study, this study had inherent unmeasured risk factors, and thus, confounding effects and the high proportion of missing data on baseline variables (such as BMI and CD4 count) are a common problem for operational cohorts.[24]

The potential for misclassification of mortality as loss to follow-up is an important consideration that has been highlighted by a recent systematic review that found that when tracing studies were done, 20%–60% of patients lost to follow-up have died.[28] In Myanmar, patients who are lost to follow-up are unlikely to receive further care, given that access to treatment in the country is relatively low and they will have a poor prognosis without continued treatment. LTF could also represent misclassification of deaths that have already occurred[22,29,30] and was regarded as a marker of poor prognosis to avoid overestimating success in the program. This study therefore examined attrition as the primary outcome of interest taking a worst-case scenario approach. When only known mortality was measured as an outcome instead, the baseline characteristics were found to have similar associations as seen with attrition (with the exception of year of ART initiation, as described previously). This affirmed the choice of attrition as the outcome of interest for this particular study and is backed by evidence suggesting an inverse relationship between proportion of LTF overall and the proportion of deaths among those classified as lost to follow-up.[28] There is also evidence to suggest that the relative contribution of death and LTF to overall attrition may diverge over time.[23] Methods that have been proposed to estimate true deaths out of those LTF were considered but were not applied in this study because they are not applicable for data beyond 12 months after starting ART.[31] Finally, the contribution of an external organization is likely to have been an important part of the program's success. However, it is important to note that the vast majority of clinical care is provided by local clinical staff and with sufficient government prioritization and donor support, the services supported by MSF could be more widely sustainable in the future.

Additional research on social and demographic factors that may explain the low rates of LTF seen in this setting would be illuminating. The routine clinical data used in this study did not include extensive information on lifestyle factors or on potential risk factors such as sex work, homosexuality, or injecting drug use to avoid potential stigmatization. It is known, however, that much of the cohort had a history of 1 or more of these risk factors. An examination of risk factors updated after periods of time on ART and their associations with subsequent outcome would also be valuable in guiding practice.

HIV prevalence in Myanmar is the second highest in South/Southeast Asia (after Thailand), and the plight of those who are HIV infected in Myanmar is dire, as evidenced by the high proportion of patients with advanced disease at baseline of treatment initiation and the low national ART coverage.[1] The need for greater investments to support HIV/AIDS service provision in Asia has been highlighted.[32–34] The findings from this study show that ART delivery in Myanmar is feasible and a key policy implication should be for increased support for ART expansion in one of the worst affected countries in the region. The favorable treatment outcomes also demonstrate that delivery of ART and integrated HIV management at primary care level is a means to expand access to treatment not only in Myanmar but also in other Asian resource-limited settings.

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