

I AM MORE THAN...

...MY HIV+
STATUS

I am more than
my viral load

I am more than
my ART regimen

I am more than
a number

I AM MORE THAN...

...A
WOMAN

I am a mother,
a lover
and a colleague

I AM MORE THAN...

...MY
ANXIETY

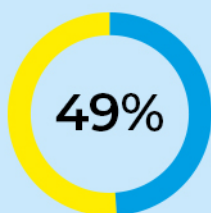
I can reach
a place where
I can just be me

I can be U=U

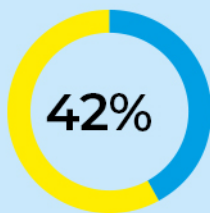
I can be me

NOW THAT
YOU KNOW ME
WHAT NEXT?

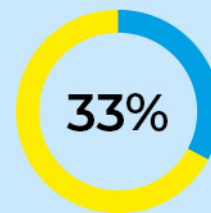
Fictional patient



Anxiety affects up to
49% of PLHIV¹



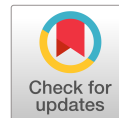
42% of women have had
a mental health diagnosis since
being diagnosed with HIV²



33% of women living with HIV
believe they have an undiagnosed
mental health issue²

1. Chaponda M, et al. European AIDS Clinical Society 2015, 21–25 October; Barcelona, Spain. PE15/50.

2. Terrance Higgins Trust. The Sophia Forum. Women and HIV: invisible no longer. A national study of women's experiences of HIV. 2018.



ORIGINAL RESEARCH

Integration of HIV services with primary care in Yangon, Myanmar: a retrospective cohort analysis

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Objectives

Integration of HIV care with general healthcare may improve patient engagement. We assessed patient outcomes in four clinics offering HIV care integrated into primary care clinics in Yangon, Myanmar.

Methods

We carried out a retrospective cohort analysis of 4551 patients who started antiretroviral therapy between 2009 and 2017. Mortality and disengagement from care were assessed using Cox regression.

Results

People living with HIV presented late with low CD4 counts [median (25th, 75th percentile) = 178 (65, 308) from 4216 patients] and advanced HIV (69% with stage 3 or 4). Survival was 0.95 at 1 year and 0.90 at 5 years. Males were at a higher risk of mortality than females [unadjusted hazard ratio (uHR) = 1.6 (95% CI: 1.3–2.0)]. Patients linked to HIV care via antenatal care or partner/parent notification were at reduced risk of mortality [uHR = 0.4 (95% CI: 0.1–1.0) and uHR = 0.5 (95% CI: 0.3–0.7)] relative to patients who presented for HIV testing. The cumulative incidence of disengagement was 0.06 at 1 year and 0.15 at 5 years. Young adults had a higher risk of disengagement than did children and older patients. Women linked to HIV care via antenatal care services were at increased risk of disengagement relative to patients who came for HIV testing (uHR = 2.4; 95% CI: 1.7–3.4). Mortality and disengagement remained steady over calendar time as the programme scaled up.

Conclusions

HIV care within a primary care model is effective to attain early linkage to care, with high survival. However, close attention should be given to disengagement from care, in particular for pregnant women.

Keywords: disengagement, HIV, integrated care, mortality, Myanmar

Accepted 14 May 2020

Introduction

Current HIV treatment guidelines recommend initiation of antiretroviral therapy (ART) on all people infected with HIV. However, as services expand, the quality may decline, with numerous reports of increased rates of loss to follow up [1–8]. In Myanmar, the HIV prevalence among people aged 15–49 years was 0.7% in 2017 which was the second highest in Asia [9]. Prevalence is high among people who inject drugs (35%), sex workers (5%)

and men who have sex with men (6%) [9]. Médecins Sans Frontières started to provide ART at scale in 2003 [10] and the public sector followed in 2005 [11]. The proportion of patients on treatment increased from 10% of people living with HIV (PLHIV) in 2010 to 66% in 2017. AIDS-related deaths have declined since 2007 (estimated 14 000 deaths in 2007 and 6700 in 2017) and the number of new infections decreased from 29 000 in 2000 to 11 000 in 2017 [9]. However, the rate of decline is slowing and additional strategies should be identified to decrease transmission.

Antiretroviral therapy in Myanmar was initially provided at HIV/AIDS specialist clinics. However, concerns were raised that stigma associated with HIV-only clinics

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could lead to delays in patients accessing treatment and increased disengagement from care. Medical Action Myanmar (MAM), a medical non-governmental organization (NGO), therefore started to offer ART in four primary care clinics in Yangon. To better understand the performance of HIV treatment integrated into a primary care clinic, we conducted a retrospective analysis of patients who started ART between June 2009 and October 2017. We report mortality and disengagement and assess patient level factors associated with these outcomes.

Methods

Study site and methods

Medical Action Myanmar is operating four free-of-charge clinics located in three suburban townships in Yangon with a population of 1.3 million. This population is at the lowest end of the socio-economic spectrum with a high burden of HIV infection. The clinics provide a broad package of services, including general medicine, reproductive health, antenatal care, and tuberculosis and HIV care. Consultations are led by general practitioners who receive additional training in the management of HIV. Adherence teams made up of a nurse, a counsellor and an outreach supporter provide counselling and trace patients (including ascertainment of death) if they miss appointments. The clinics have basic laboratories with CD4 cell count testing. All services are free of charge. Complicated patients are referred to government hospitals after initial clinic assessment. Patients who need in-patient care are referred to government hospitals after initial clinic assessment.

HIV counselling and testing were initially offered to patients who wanted to get tested, or patients who attended the clinics with symptoms or risk factors of HIV ('opt-in' testing). In 2016 the policy changed to 'opt-out' testing for all adult patients. Patients who started ART were classified depending on the mode of entry in the clinics: (a) HIV testing and counselling services (HIV-TC); (b) antenatal care services (ANC); (c) patients referred because of HIV-positive partners or parents (partner-parent); (d) patients referred by private general practitioners (GP); (e) patients referred by other NGOs (NGO); and (f) patients entered for other reasons ('other').

The policy to start ART changed over time: in 2009 and 2010 a CD4 cell count threshold of 200 cells/ μ L was used; from 2011 till July 2013 this increased to a CD4 count of 350 cells/ μ L; from August 2013 to October 2017 it increased to 500 cells/ μ L and after that all HIV patients were offered treatment. ART was prescribed according to national guidelines at the time of enrolment.

Patient characteristics were collected at baseline and at follow-up visits. Data were entered into a database (FUCHIA; Epicentre). A quality check of the data was conducted in 2017 by re-entering paper records of a random subset of 1% of the patients into a new database; error rates across key variables were < 1%.

Outcomes and study definitions

Our primary endpoint was all-cause mortality, defined as a patient who initiated ART and died during the observation period whether or not on ART at the time of event. Our secondary endpoint was disengagement, defined as a patient who missed their clinic appointment and subsequently did not attend for a further 91 days.

Statistical analysis

Patient variables at ART initiation (baseline) were summarized with proportions and medians (with 25th and 75th percentiles). Kaplan–Meier curves, graphs of the cumulative incidence function and graphs of the Nelson–Aalen cumulative hazard function were created to visually assess differences between patient groups. We used Cox proportional hazards models (using the 'stcox' function in Stata) to estimate associations between patient risk factors and time to death and time to disengagement. Cause-specific hazard ratios (HRs) are presented for the analysis of disengagement; these are ratios of the hazard rates of disengagement as a single time t among individuals still alive at time t . The cause-specific HR attempts to quantify the effect of each covariate on the rate of occurrence of the specific named event (in this case, disengagement from care) among subjects who are currently free of the competing event (in this case, death). Covariates for inclusion in the adjusted model were specified *a priori* [12] and included baseline factors (sex, mode of entry to programme, ART initiation date, ART initiation age) and time-updated factors [CD4 count, HIV staging (cumulative) and opportunistic infections]. We stratified our models by clinic, assuming each clinic cohort has their own unique baseline hazard function, but assuming covariates had the same effect across clinics. We report HRs for unadjusted and adjusted models, each with a 95% confidence interval. Subjects were considered at risk from the date they initiated ART and exited the risk set at the first of: date of death, date of transfer, date of last visit or 31 October 2017. For the disengagement from care analysis, patients who experienced death were right censored at the date of death and future visit dates until 30 April 2018 were used to determine if a patient had disengaged from care; the event date was considered to

be the day after the last clinic visit. Analyses were carried out with Stata 14.2 (Stata Corp, College Station, TX, USA). Further details of the statistical analysis are provided in Methods S1.

Results

Between June 2009 and October 2017, 1 356 287 patient consultations were conducted by the four MAM-NAP supported clinics, including 549 920 HIV/TB consultations; 274 215 for testing and counselling and 275 705 other medical consultations. A total of 4551 HIV patients started ART during the study period. Patient baseline characteristics are given in Table 1. Most patients were referred through the HIV-TC programme ($n = 2515$, 55%). Other patients were referred by ANC services ($n = 129$, 3%); because of HIV-positive partners-parents ($n = 494$, 11%); by private GPs ($n = 240$, 5%); by other NGOs ($n = 694$, 15%); or through other routes ($n = 479$, 11%). Among 4216 patients with an available CD4 count at baseline, the median CD4 count at ART initiation was 178 cells/ μL (25th–75th percentile: 65–307) and 54% of the patients initiated ART with a CD4 count less < 200 cells/ μL . Median CD4 counts were higher in females (214 cells/ μL) relative to males (147 cells/ μL , $P < 0.001$) and among women attending ANC (271 cells/ μL), partner/parent (286 cells/ μL) and NGO-referred patients (235 cells/ μL) relative to other modes of entry (GP, 112 cells/ μL ; HIV-TC, 131 cells/ μL ; other, 139 cells/ μL , $P < 0.001$) (Table S1). The CD4 count of patients initiating ART increased with calendar year (Fig. S1), from 73 cells/ μL (25th–75th percentile: 32–190) in 2009 to 214 (69–390) cells/ μL in 2017. The median age of female patients was 32 years (25th–75th percentile: 26–39) and the median age of male patients was 34 (29–40) years. The majority (69%) of patients initiating ART had advanced HIV staging (41% stage 3 and 28% stage 4). The proportion of patients with advanced HIV stage was lower in females than in males (58% *vs.* 78%). At initiation of ART, many patients had concurrent tuberculosis: 471 (22%) of females and 865 (35%) males had pulmonary tuberculosis, while 230 (11%) females and 429 (18%) males had extrapulmonary tuberculosis.

The median number of clinic visits after initiating ART was 24 (25th–75th percentile: 14, 40) and the median years of follow-up was 2.9 (1.4–4.5). The total number of person-years of follow-up was 12 898. During follow-up, 1778 (39%) and 1039 (23%) patients were suspected of having pulmonary and extrapulmonary tuberculosis, respectively; 114 (2.5%) patients were diagnosed with cytomegalovirus retinitis; 133 (2.9%) with extrapulmonary cryptococcosis; and 1801 (40%) with oral

Table 1 Characteristics of 4551 HIV patients initiating antiretroviral therapy (ART) between 19 June 2009 and 31 October 2017 at baseline and during follow-up

	Female ($N = 2107$)	Male ($N = 2444$)	Total ($N = 4551$)
Baseline (at ART initiation)			
CD4 count (cells/ μL)*	214 (82–344)	147 (53–275)	178 (65–307)
Advanced HIV (CD4 count < 200 cells/ μL)*	911 (47%)	1386 (61%)	2297 (54%)
Age (years)	32 (26–39)	34 (29–40)	33 (28–40)
Haemoglobin (g/dL) [†]	10.4 (9.0–11.8)	11.4 (9.5–13.3)	10.9 (9.3–12.5)
Weight (kg) – adults [‡]	47 (41–54)	51 (46–57)	49 (44–56)
Weight (kg) – children [‡]	15 (10–23)	14 (11–19)	14 (10–21)
Cumulative WHO staging			
Stage 1	511 (24%)	253 (10%)	764 (17%)
Stage 2	364 (17%)	274 (11%)	638 (14%)
Stage 3	747 (35%)	1131 (46%)	1878 (41%)
Stage 4	485 (23%)	786 (32%)	1271 (28%)
Infections			
Pulmonary tuberculosis	471 (22%)	865 (35%)	1336 (29%)
Extrapulmonary tuberculosis	230 (11%)	429 (18%)	659 (14%)
Cytomegalovirus retinitis	25 (1.2%)	20 (0.8%)	45 (1.0%)
Extrapulmonary cryptococcosis	14 (0.7%)	32 (1.3%)	46 (1.0%)
Oral candidiasis	153 (7.3%)	193 (7.9%)	346 (7.6%)
Mode of entry			
Antenatal care (ANC)	129 (6%)	0 (0%)	129 (3%)
General practitioner (GP)	88 (4%)	152 (6%)	240 (5%)
HIV testing and counselling (HTC)	1099 (52%)	1416 (58%)	2515 (55%)
Other	201 (10%)	278 (11%)	479 (11%)
Partner/parent referral	276 (13%)	218 (9%)	494 (11%)
Transfer from other NGO	314 (15%)	380 (16%)	694 (15%)
Starting drug regimen			
Reverse transcriptase inhibitor	2087 (99%)	2424 (99%)	4511 (99%)
Boosted protease inhibitor	20 (1%)	20 (1%)	40 (1%)
Follow up			
Total clinic visits	24 (14–40)	24 (14–39)	24 (14–40)
Years of follow-up	2.8 (1.3–4.4)	3.0 (1.4–4.6)	2.9 (1.4–4.5)
Died [§]	113 (5.4%)	212 (8.7%)	325 (7.2%)
Disengaged from care [¶]	261 (12%)	258 (11%)	519 (11%)
Infections			
Pulmonary tuberculosis	645 (31%)	1133 (46%)	1778 (39%)
Extrapulmonary tuberculosis	369 (18%)	670 (27%)	1039 (23%)
Cytomegalovirus retinitis	52 (2.5%)	62 (2.5%)	114 (2.5%)
Extrapulmonary cryptococcosis	47 (2.2%)	86 (3.5%)	133 (2.9%)
Oral candidiasis	764 (36%)	1037 (42%)	1801 (40%)
Talaromycosis	11 (0.5%)	30 (1.2%)	41 (1.0%)
Hepatitis B**	116 (7.0%)	208 (11%)	324 (9.1%)
Hepatitis C**	31 (1.9%)	73 (3.8%)	104 (2.9%)

Data are presented as median (25th percentile–75th percentile) for continuous measures, and n (%) for categorical measures.

*165 females and 170 males did not have a CD4 count recorded prior to ART initiation.

[†]841 females and 1081 males did not have a haemoglobin measurement prior to ART initiation.

[‡]Six (four female adults, one male adult and one male child) patients did not have a recorded weight.

[§]Five females and seven males had no follow-up time to assess death.

[¶]Two females and four males had no follow-up time to assess disengagement.

**Hepatitis B testing commenced in 2013; 452 females and 520 males were never tested for hepatitis B.

^{††}Hepatitis C testing commenced in 2013; 452 females and 515 males were never tested for hepatitis C.

candidiasis. A total of 3579 patients were screened for hepatitis B coinfection and 3584 for hepatitis C during follow-up; 324 (9.1%) tested positive for hepatitis B surface antigen and 104 (2.9%) tested positive for hepatitis C antibodies. *Talaromyces marneffei* infection was diagnosed in 41 (0.9%) patients.

Mortality

There were 325 (7.2%) known deaths. Survival curves stratified by baseline characteristics are displayed in Fig. 1. Patients commencing treatment with a lower CD4 count and advanced HIV staging were at greater risk of death, and males were at increased risk of death relative to females (Fig. 1a–c). PLHIV who came through the ANC pathway, partner/parent contacts and those transferred by other NGOs were less likely to die than PLHIV who entered treatment via HIV-TC and those referred from GPs (Fig. 1d). PLHIV who initiated ART as children

(<15 years) were at reduced risk of death relative to older age groups (Fig. 1e); there were 12 deaths among the 250 children who initiated ART. Mortality was similar across calendar years of ART initiation (Fig. 1f). Among all PLHIV, the cumulative probability of survival was 0.95 at 1 year and 0.90 at 5 years (Fig. S2).

The relative hazards of mortality, both crude and adjusted, are displayed in Table 2. The reduced crude rate of mortality seen in PLHIV entering the programme via ANC [unadjusted hazard ratio (uHR) *vs.* HTC = 0.4 (95% CI: 0.1–1.0)], partner/parent [uHR *vs.* HTC = 0.5 (95% CI: 0.3–0.7)] and NGO transfer [uHR *vs.* HTC = 0.6 (95% CI: 0.5–0.9)] was not observed after adjustment for other patient characteristics. Similarly, the increased mortality of males relative to females [uHR = 1.6 (95% CI: 1.3–2.0)] was not observed after adjustment for other factors. Lower CD4 count (adjusted hazard ratio (aHR) = 3.4 (95% CI: 2.6–4.5) for 50 *vs.* 200 cells/ μ L) and advanced WHO staging [aHR = 5.3 (95% CI: 2.0–13.1) for WHO stage 4

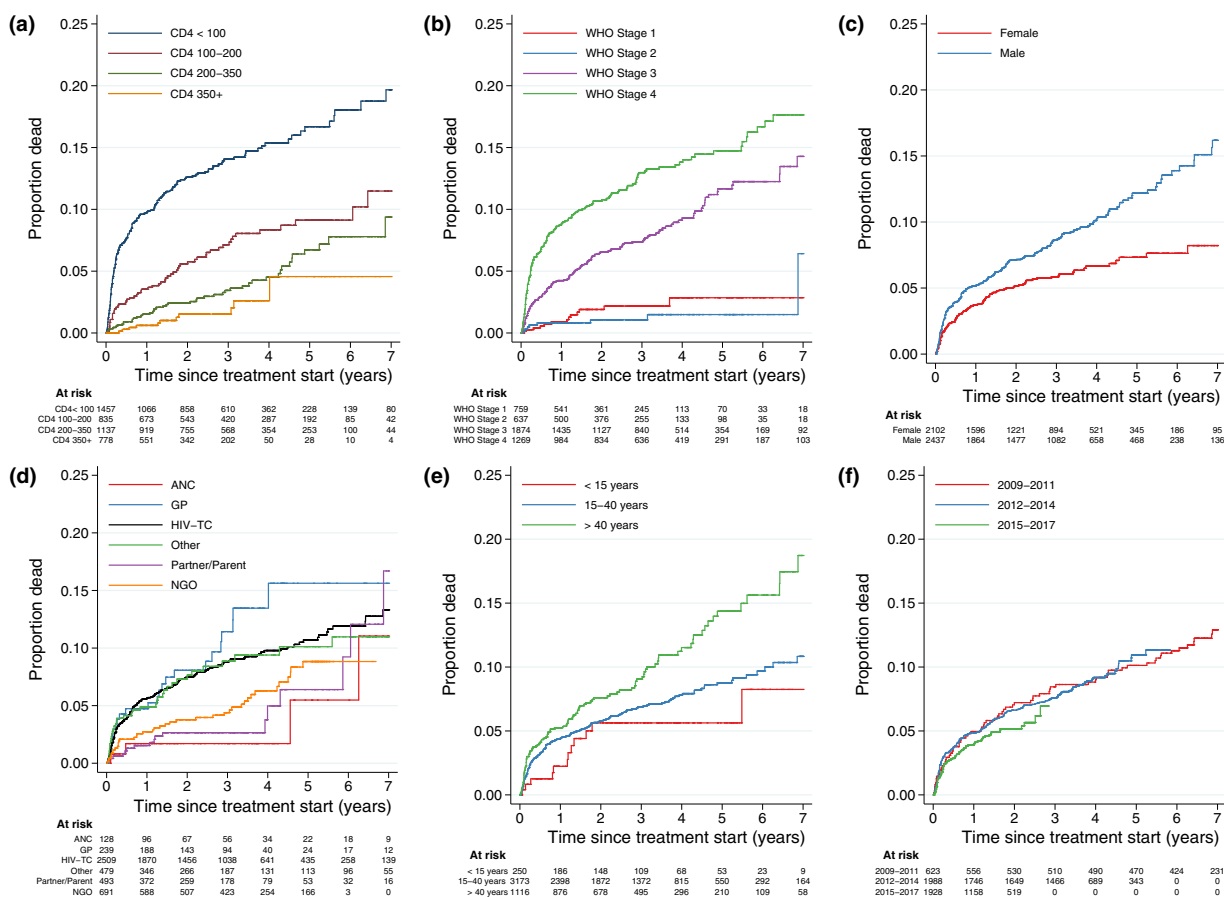


Fig. 1 Probability of mortality in HIV patients initiating antiretroviral therapy (ART) during 2009–2017 as assessed by the Kaplan–Meier estimator. Estimates stratified by baseline: (a) CD4 count (cells/ μ L); (b) WHO stage; (c) gender; (d) mode of entry; (e) age; and (f) calendar year.

Table 2 Unadjusted and adjusted Cox regression analyses of associations between patient factors and mortality among patients initiating antiretroviral therapy (ART)

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age (per 10 years)	1.20 (1.08–1.32)	1.11 (0.99–1.24)
Date ART start (per year)	0.97 (0.91–1.04)	1.04 (0.97–1.12)
Sex		
Female (ref.)	1.00	1.00
Male	1.58 (1.26–1.98)	1.06 (0.84–1.34)
Mode of entry		
ANC	0.39 (0.14–1.04)	1.13 (0.41–3.10)
GP	1.26 (0.83–1.94)	1.04 (0.67–1.61)
HIV-TC (ref.)	1.00	1.00
Other	0.94 (0.66–1.34)	0.98 (0.68–1.40)
Partner/parent	0.45 (0.28–0.74)	1.09 (0.66–1.82)
NGO	0.65 (0.46–0.91)	1.20 (0.84–1.73)
CD4 count (cells/ μ L)*		
50	5.92 (4.61–7.62)	3.71 (2.84–4.85)
100	2.86 (2.46–3.32)	2.14 (1.83–2.51)
200 (ref.)	1.00	1.00
350	0.55 (0.39–0.77)	0.70 (0.49–0.98)
500	0.39 (0.26–0.58)	0.55 (0.36–0.84)
WHO staging		
WHO Stage 1 (Ref)	1.00	1.00
WHO Stage 2	1.17 (0.39–3.49)	1.00 (0.32–3.17)
WHO Stage 3	5.32 (2.33–12.2)	3.04 (1.21–7.63)
WHO Stage 4	13.9 (6.14–31.2)	5.03 (2.00–12.7)
Infection		
Oral candidiasis	3.12 (1.79–5.45)	1.44 (0.82–2.53)
Pulmonary TB (< 1 year) [†]	1.84 (1.33–2.55)	0.92 (0.66–1.30)
Pulmonary TB (\geq 1 year) [†]	32.0 (21.2–48.2)	8.97 (5.71–14.1)
Extrapulmonary TB	4.96 (3.67–6.71)	1.85 (1.34–2.55)
Cytomegalovirus infection	6.99 (3.88–12.6)	2.43 (1.30–4.52)
Cryptococcosis	4.07 (2.01–8.28)	1.62 (0.79–3.33)

ANC, antenatal care; GP, general practitioner; HR, hazard ratio; NGO, non-governmental organization; ref., reference group; TB, tuberculosis; TC, testing and counselling.

*Estimates of HRs of specific CD4 cell counts relative to a CD4 cell count of 200 cells/ μ L are derived from a restricted cubic spline relationship (see Fig. S3 for graphs of the continuous relationship between last CD4 count and HR).

[†]Pulmonary TB reported separately for events in the first year and events thereafter due to lack of proportionality of hazards.

vs. WHO stage 1] were associated with higher hazards of mortality after adjustment for other patient factors. PLHIV experiencing other infections were at increased risk of death: pulmonary TB [aHR = 9.8 (95% CI: 6.3–15.5) in the year after ART start]; extrapulmonary TB [aHR = 1.8 (95% CI: 1.3–2.5)]; cytomegalovirus retinitis [aHR = 2.5 (95% CI: 1.3–4.6)]; and cryptococcosis [aHR = 1.6 (95% CI: 0.8–3.4)]. An increase in the last recorded CD4 count was associated with reduced mortality, and the magnitude of association between a unit increase in CD4 count and mortality was more pronounced at low CD4 counts (Fig. S3). Estimates of unadjusted and adjusted HRs were similar in planned

sensitivity analyses that excluded 272 children (Table S2) and excluded 392 pregnant women (Table S3).

Disengagement from care

There were 519 (11%) patients who disengaged from care. The cumulative incidence of disengagement was 0.06 at 1 year and 0.15 at 5 years (Figs S4, S5). Cumulative hazard curves stratified by baseline characteristics are presented in Fig. 2. The cumulative hazard of disengagement was similar for patients initiating ART with early and advanced disease (as indicated by CD4 counts and HIV staging; Fig. 2a,b). Females had an elevated cumulative hazard of disengagement relative to males after 2 years of ART. Women who entered the HIV programme after accessing antenatal care services were at much greater risk of disengagement than other patients (Fig. 2d). Young adults (15–40 years) were at increased risk of disengagement relative to children (< 15 years) and older adults (> 40 years) (Fig. 2e). Similar rates of disengagement were seen across calendar years of ART initiation (Fig. 2f).

Results from Cox proportional hazards models of time to disengagement with death as a competing risk are presented in Table 3. Women who entered HIV care through the ANC pathway were at increased risk of disengagement after adjustment [aHR = 2.4 (95% CI: 1.7–3.3) for ANC entry relative to HIV-TC entry]. Patients with high CD4 counts were less likely to disengage than patients with low CD4 counts [aHR = 0.6 (95% CI: 0.5–0.8) for last CD4 count of 500 *vs.* last CD4 count of 200; Fig. S6]. Young adults were at increased risk of disengagement relative to older individuals [adjusted HR = 2.9 (95% CI: 2.2–3.7; Fig. S6) for patients who were 20 years old *vs.* 40 years old at ART initiation]. Most estimates of unadjusted and adjusted HRs were similar in planned sensitivity analyses that excluded 311 children (Table S4), excluded pregnant women (Table S5), defined disengagement as 30 days elapsed after missed appointment (Table S6) and defined disengagement as 180 days elapsed after missed appointment (Table S7). The exclusion of pregnant women from the analysis reduced the magnitude of difference between male and female hazards of disengagement (Table S5).

Discussion

In this cohort 4551 PLHIV were followed up for a median of 2.9 years (25th–75th percentile: 1.4–4.5 years), in clinics that provided decentralized HIV care integrated with a broad range of other health services. The results of this study suggest that survival rates of this patient cohort,

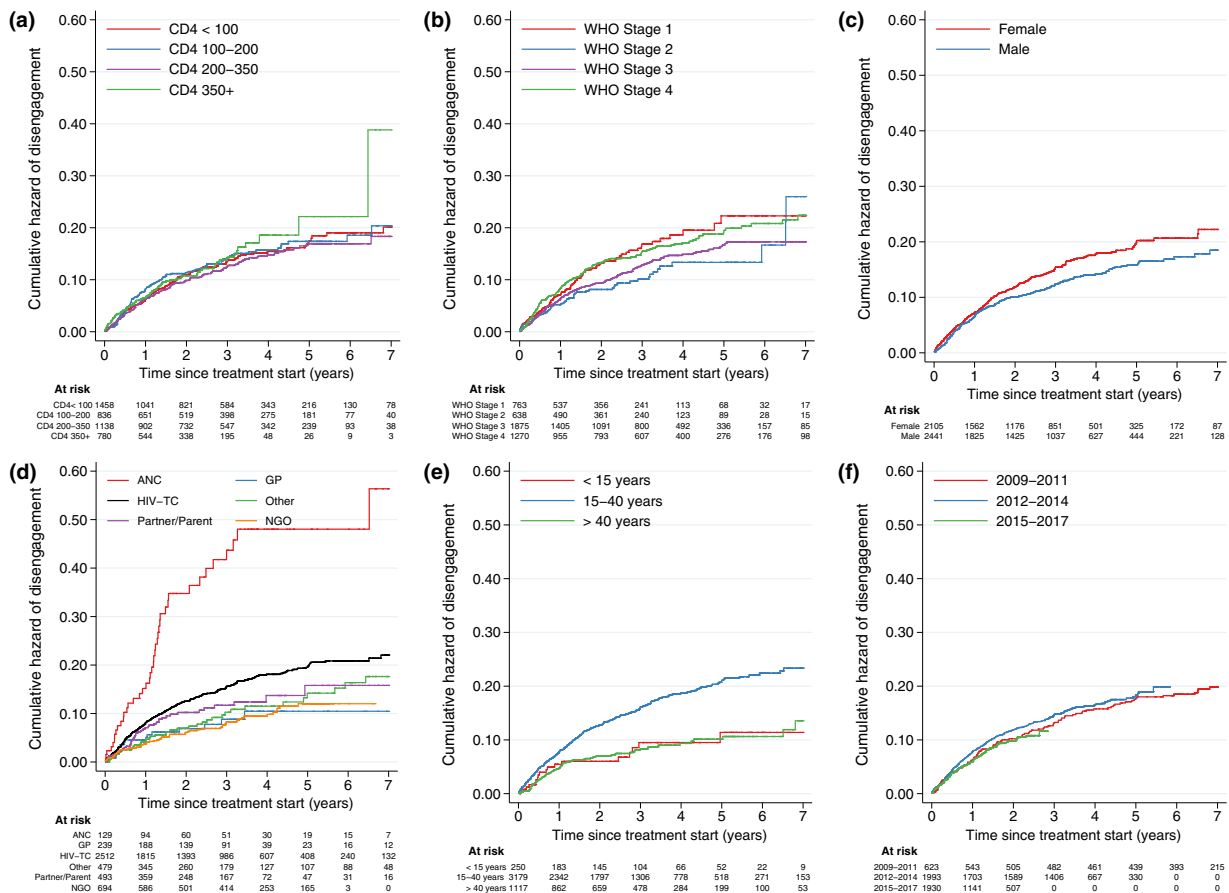


Fig. 2 Cumulative hazard of disengagement from care in HIV patients initiating antiretroviral therapy (ART) during 2009–2017. Estimates stratified by baseline: (a) CD4 count (cells/μL); (b) WHO stage; (c) gender; (d) mode of entry; (e) age; and (f) calendar year.

who were treated in decentralized integrated healthcare clinics were comparable to those reported from specialist hospitals in Yangon [13]. Mortality rates remained similar over time despite the policy change to adopt opt-out testing and start ART at any CD4 count. There were 335 deaths and the cumulative probabilities of survival were 0.97, 0.95 and 0.90 at 6 months, 1 year and 5 years, respectively, which compares favourably with survival rates reported previously from a cohort (2003–2007) that included patients from the same location (0.93, 0.91 and 0.83) [10]. There were 12 deaths among 250 children and children were at a reduced risk of death relative to adults, consistent with other studies [14].

Most PLHIV presented late in the course of their disease. CD4 count at ART initiation increased over time; however, in 2017, 66% of patients initiating ART still had advanced HIV (WHO stage 3 or 4 or a CD4 count < 200 cells/μL) [15]. CD4 counts at ART initiation were lower in this cohort (median 178) than those observed in

comparable low and middle-income country (LMIC) settings (234 in 11 LMICs in 2015) [16] but were similar to those in PLHIV treated at a specialist hospital in Yangon [17]. Males on ART had an elevated risk of mortality [uHR = 1.6 (95% CI: 1.3–2.0)] relative to females, which is similar to a meta-analysis of 31 studies in LMIC settings which observed a pooled HR of 1.5 (95% CI: 1.4–1.6) and a pooled hazard ratio in Asia of 1.8 (95% CI: 1.4–2.2) [18]. After adjustment for clinical features, the association between male sex and mortality was small and consistent with no association, suggesting that the relationship is probably driven by lower CD4 count and more advanced WHO staging upon ART initiation. This is consistent with trends for males having more advanced disease when starting ART [19,20]. Tuberculosis was by far the most common other infection, with 471 (22%) females and 865 (35%) males diagnosed with pulmonary tuberculosis, and 230 (11%) females and 429 (18%) males diagnosed with extrapulmonary tuberculosis at ART

Table 3 Unadjusted and adjusted Cox regression analyses of associations between patient factors and disengagement from care among patients initiating antiretroviral (ART) therapy

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age*		
10 years	1.45 (1.01–2.07)	1.77 (1.21–2.59)
20 years	2.83 (2.22–3.61)	2.89 (2.23–3.73)
30 years	1.59 (1.25–2.01)	1.60 (1.26–2.04)
40 years (Ref)	1.00	1.00
50 years	0.85 (0.65–1.10)	0.88 (0.68–1.14)
Date ART start (per year)	0.96 (0.91–1.01)	0.99 (0.93–1.04)
Sex		
Female (ref.)	1.00	1.00
Male	0.81 (0.69–0.96)	0.92 (0.77–1.10)
Mode of entry		
ANC	2.95 (2.18–4.00)	2.36 (1.68–3.31)
GP	0.57 (0.36–0.92)	0.58 (0.36–0.94)
HTC (ref.)	1.00	1.00
Other	0.70 (0.51–0.95)	0.70 (0.51–0.96)
Partner/parent	0.79 (0.58–1.06)	0.99 (0.72–1.36)
NGO	0.55 (0.42–0.72)	0.64 (0.48–0.86)
CD4 count (cells/ μ L) [†]		
50	1.20 (0.92–1.56)	1.08 (0.82–1.42)
100	1.17 (1.03–1.34)	1.11 (0.97–1.29)
200 (ref.)	1.00	1.00
350	0.71 (0.57–0.90)	0.68 (0.53–0.86)
500	0.70 (0.56–0.89)	0.62 (0.48–0.79)
WHO staging		
WHO Stage 1 (ref.)	1.00	1.00
WHO Stage 2	0.63 (0.44–0.89)	0.67 (0.47–0.96)
WHO Stage 3	0.79 (0.61–1.02)	0.84 (0.62–1.13)
WHO Stage 4	1.01 (0.78–1.30)	0.99 (0.73–1.36)
Infection		
Oral candidiasis	1.48 (0.72–3.03)	1.49 (0.72–3.09)
Pulmonary TB	1.59 (1.18–2.16)	1.40 (1.01–1.94)
Extrapulmonary TB	1.37 (0.93–2.02)	1.09 (0.72–1.67)
Cytomegalovirus infection	1.77 (0.66–4.76)	1.10 (0.35–3.46)
Cryptococcosis	0.76 (0.19–3.05)	0.52 (0.13–2.10)

ANC, antenatal care; GP, general practitioner; HR, hazard ratio; NGO, non-governmental organization; ref., reference group; TB, tuberculosis; TC, testing and counselling.

*Estimates of HRs of specific ages relative to an age of 40 years are derived from a restricted cubic spline relationship (see Fig. S6 for graphs of the continuous relationship between age and HR).

[†]Estimates of HRs of specific CD4 cell counts relative to a CD4 cell count of 200 cells/ μ L are derived from a restricted cubic spline relationship (see Fig. S6 for graphs of the continuous relationship between last CD4 count and HR).

initiation. These rates are far above the national average among HIV patients of 11% [9]. This might be related to the low socio-economic status and poor living conditions of the people in these townships.

There were 519 patients who disengaged from care. The cumulative incidences of disengagement were 0.03, 0.06 and 0.15 at 6 months, 1 year and 5 years, respectively. We had no information about 'silent transfers' which could have led to an overestimation of disengagement [21]. Young adults and patients referred through

antenatal care were at higher risk of disengaging, which agrees with findings of prior research [22–27]. Women entering via antenatal care who started ART had a low probability of death, most likely due to the early stage of HIV they were in, but their probability of disengagement, mostly post-delivery, was very high. Due to the small size of this subgroup (129 women) there is considerable uncertainty around the estimates of association, but results are extremely worrying because it can lead to a higher mortality of the mothers and increased risk of the children, as the risk of mother-to-child transmission will increase. The reason for the high rate of disengagement is not clear. Anecdotal observations from counsellors point to a fear of negative consequences in the family after disclosure. Women are said to be afraid that the family will break up and that they will end up alone with the baby, without a home or income. This requires urgent further study as it is critical to improve treatment retention among pregnant women and young mothers. It is notable that we did not observe a worsening risk of disengagement with calendar time and programme scale-up, a finding in contrast to many studies in LMICs which observed alarming increases in loss to follow up [1–8]. This may possibly be explained by the use of a prospective definition of disengagement from care in this study, which avoids the bias of retrospective definitions of loss to follow-up where recently enrolled patients have less time to return from care after a transient disengagement from care event [28–30].

This study analysed routine HIV clinic data, which carries strengths and limitations. The analysis is representative of routine care as implemented in this setting; all patients initiating ART were included in the analysis and the data reflect the information clinicians are likely to have available to them in similar low-resource settings. Viral load counts were only captured on clinical grounds and we had no data on drug resistance genotypes. Our analysis of mortality assumed that censoring was non-informative, and any bias resulting from a departure from this assumption is likely to increase with time since ART start. We assumed all deaths were reported and captured in the dataset, as follow-up with home visits was intense, but the reported mortality could nevertheless be an underestimate.

This model of decentralized and integrated care had mortality and disengagement rates comparable to hospital-based care. In an integrated primary care setting, people with as yet undiagnosed HIV can be identified earlier. Patients who are identified with tuberculosis, or women who would not self-identify as high risk but are diagnosed with a sexually transmitted infection, will get tested for HIV and start treatment earlier, which can

contribute to decreased mortality and reduced transmission. However, many patients were still diagnosed late, which contributes to high mortality and HIV transmission, and hence more efforts are needed to promote earlier linkage to care, particularly in men. Earlier linkage does not necessarily guarantee retention, as shown by the high disengagement rates after delivery among women entering the programme via antenatal care. Younger adults were also more likely to disengage than older adults. These findings are similar to observations from other LMICs. Integrating HIV care into non-specialized primary care clinics is feasible in this low-income setting and has been shown to be an effective model in some high-income settings, such as Australia where approximately half of all HIV patients are managed by GPs [31]. The applicability and feasibility of this model to other contexts with higher staff workload and HIV prevalence would need further assessment. To further reduce the burden of disease, additional strategies to test and treat early and reduce transmission should be considered, for example introducing self-testing. More research is needed to understand the barriers to early testing and determinants of disengagement in Myanmar, in particular for pregnant women who enter the programme through ANC.

Acknowledgements

We thank all the patients, MAM staff, the Myanmar National AIDS Programme and donors who were essential to the success of the programme.

Financial disclosure: This work was supported by private donors of MAM. The Myanmar Oxford Clinical Research Unit is part of the MORU Tropical Health Network, funded by the Wellcome Trust of Great Britain.

Conflict of interest: There are no conflicts of interest.

Author contributions

NNT, AM, EW, EA and FS conceived the study. NNT, EW, MMMH, YYA, TL and FS carried out the investigations. AM, NNT, EA and FS analysed the data. NNT, AM and EA prepared the original draft. NNT, AM, EW, MMMH, YYA, TL, EA and FS reviewed and edited the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1 (a) Increasing CD4 counts at ART initiation over time. Median (black dots) and interquartile range (black capped bars) of patient CD4 counts (cells/ μ L) at time of ART initiation by calendar year. (b) Decreasing proportion of patients with CD4 count < 200 cells/ μ L at ART initiation over time.

Fig. S2 Cumulative probability of survival over time on ART.

Fig. S3 Restricted cubic spline showing association of time-updated CD4 count with mortality.

Fig. S4 Cumulative incidence of disengagement from care.

Fig. S5 Cumulative incidence of disengagement from care in HIV patients initiating ART in 2009–2017.

Fig. S6 Restricted cubic spline showing association of last available CD4 count and age at baseline with disengagement from care.

Table S1 CD4 counts of 4216 patients at ART initiation by mode of entry

Table S2 Sensitivity analysis excluding 272 children: unadjusted and adjusted Cox regression analyses of associations between patient factors and mortality among patients initiating ART

Table S3 Sensitivity analysis excluding 392 pregnant women (pregnant at any time): unadjusted and adjusted Cox regression analyses of associations between patient factors and mortality among patients initiating ART

Table S4 Sensitivity analysis excluding children: unadjusted and adjusted Cox regression analyses of associations between patient factors and disengagement from care among patients initiating ART

Table S5 Sensitivity analysis excluding pregnant women: unadjusted and adjusted Cox regression analyses of associations between patient factors and disengagement from care among patients initiating ART

Table S6 Sensitivity analysis – 30-day definition: unadjusted and adjusted Cox regression analyses of associations between patient factors and disengagement from care among patients initiating ART

Table S7 Sensitivity analysis – 180-day definition: unadjusted and adjusted Cox regression analyses of associations between patient factors and disengagement from care among patients initiating ART

Methods S1 Statistical analysis.