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Five-year experience with scaling-up access to antiretroviral treatment in an HIV care programme in Cambodia

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Summary

OBJECTIVES To evaluate a 5-year HIV care programme (2003–2007) in the Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia.

METHODS Analysis of routine programme indicators per year: number of new patients, active patients, antiretroviral therapy (ART) coverage in the cohort, mortality and loss to follow-up. Comparison of mortality before and after the start of ART using Kaplan–Meier survival curves. Analysis of risk factors using Cox regression for the combined endpoint of mortality and loss to follow-up in patients on ART.

RESULTS 3844 patients were registered in the hospital between March 2003 and December 2007. The mortality and loss to follow-up rate fell and paralleled the rise of ART coverage from 23% in 2003 to 90% in 2007. The mortality and the loss to follow-up rate was significantly higher in patients not on ART but eligible (Log rank $P < 0.001$). The combined endpoint of mortality and loss to follow-up was 48.7% after one year in patients who were waiting for ART. 1667 patients were started on ART. The combined endpoint (mortality and loss to follow-up) in this group was 11.5% at 12 months and 14.2% at 24 months. Risk factors for mortality in the ART group were male sex, CD4 count <50 cells/μl, BMI <18 and haemoglobin levels <10 g/dl.

CONCLUSION Better access to ART is associated with lower mortality and fewer losses to follow-up. Pre-ART attrition remains significant. Strategies are needed to enable an earlier start of ART and to promote retention in care.

keywords ART, ART coverage scale-up, survival, loss to follow-up, programme indicators, Cambodia

Introduction

The estimated HIV prevalence in Cambodia among adults aged 15–49 years declined from 2.0% in 1998 to 0.9% in 2006 (Ministry of Health Cambodia 2008). The number of people living with HIV/AIDS at the end of 2006 was a 61 400 (Ministry of Health Cambodia, NCHADS Surveillance Unit 2008; National AIDS Authority 2008). Since 2001, nongovernmental organizations (NGOs) have started pilot projects to deliver antiretroviral therapy (ART) and Cambodia has successfully applied for consecutive rounds of the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM). In the third quarter of 2007, more than 25 000 patients were receiving ART at 48 treatment sites, approaching 80% ART coverage (National AIDS Authority 2008).

Most of the cohort studies published from low-resource settings focus on outcomes in patients on ART. However, the quality of an HIV care programme is also reflected by the absence of waiting lists for patients in need of ART, and the pre-ART care provided. Studies from South Africa have highlighted that mortality rates can be as high as 30% per year in patients eligible and waiting for ART (Lawn *et al.* 2005, 2006; Fairall *et al.* 2008). Moreover pre-ART loss to follow-up (LTFU) is high in resource-limited settings (RLSs) and underreported (Bassett *et al.* 2009). A significant amount of HIV-associated morbidity and mortality occurs even prior to eligibility (Badri *et al.* 2006; Lawn & Wood 2007). In this paper we want to highlight the importance of a comprehensive approach to programme monitoring, including as well patients who are not yet on ART.

Methods

Setting

The Sihanouk Hospital Center of HOPE (SHCH) is a private-not-for-profit hospital in Phnom Penh, Cambodia. Between 1 March 2003 and 31 December 2007, 3844 HIV positive patients were registered at the SHCH, of these 1667 were started on ART. The programme is funded by the GFATM and technical assistance is provided by the Institute of Tropical Medicine, Antwerp, Belgium. First-line ART consists of a non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen. According to the national guidelines in Cambodia, a patient is eligible for ART when he/she is in WHO stage 4 (WHO 2003) or has a CD4 count <250 cells/μl. At the SHCH, patients in WHO stage 3 with a CD4 count <350 cells/μl are also eligible.

Patients who are medically eligible must attend three ART counselling sessions. Due to limited access to ART in the beginning, additional (non-medical) criteria such as length of time in follow-up and regularity of clinic attendance, were employed and a selection committee consisting of counsellors and representatives of patients and community decided who could start ART (Khaim *et al.* 2004a,b).

Data collection

A data collection system was set up in 2003. A database program (Microsoft Access 2003) with corresponding data collection tools and guidelines that allows for automatic monthly reporting (ARTJournalV3) was developed (Thai *et al.* 2006). Doctors, clerks, and data managers were trained in the use of the tools. Data-entry was monitored every 6 months (Sok *et al.* 2008). At enrolment patients gave informed consent.

Data were entered for every patient visit, though initially due to a backlog of patients, priority was given to patients who started ART. The data collected comprised age, sex, WHO clinical stage at inclusion, previous exposure to ART, previous and current opportunistic infections, any WHO stage 2, 3, or 4 condition during follow-up, prophylactic medications, body weight when healthy, current body weight and body mass index [BMI (weight in kg)/(height in m^2)], laboratory data (total lymphocyte count, CD4 count, haemoglobin, renal function, and liver function tests), ART regimen, side effects, reasons for substitution or stopping medication, and adherence measures. Adherence was measured with an adapted 'Simple Medication Adherence Questionnaire' (Knobel *et al.* 2002).

Follow-up

Patients were seen monthly and monitored according to WHO guidelines (WHO 2003). Haemoglobin and total lymphocyte counts were measured every 3 months using a Sysmex KX-21 (Sysmex Corp., Kobe, Japan). Every 6 months, a CD4 count was performed at the National Institute of Public Health, by FACSCount (Becton Dickinson, Franklin Lakes, NJ, USA). Viral load testing was not routinely available. All care was free of charge. Patients with a CD4 count <200 cells/μl received cotrimoxazole, and patients with a CD4 count <100 cells/μl or WHO stage 4 disease received fluconazole primary prophylaxis. Patients who missed an appointment were telephoned. If they did not have a phone, the home care team visited patients at home if they lived in the home care area.

Analysis

The analysis consists of two parts. First, we considered the HIV cohort as a whole, from the point of view of a programme manager looking at routinely collected data. Then, we assessed mortality before and after ART initiation using a survival analysis.

Programme analysis

Based on the periodical reports generated by the ART-JournalV3 we described the evolution of the programme indicators since the start of the data collection: new patients entering the HIV cohort; active patients at the end of the year, defined as having had at least 1 visit in the last 6 months; ART coverage within our HIV cohort, defined as number of patients on ART over the number of patients eligible for ART; number of patients on second-line ART; deaths, LTFU and transfer out (TO) to another facility during the year. Mortality and LTFU rate was calculated on the total number of patients who had at least one visit during the year. A patient was considered dead when the data managers received information from the physician or home care team that the patient had died. A patient who failed to visit the facility during 6 consecutive months was considered LTFU.

Cohort analysis

We described the mortality before and after ART initiation for patients eligible for ART between 1 March 2003 (start of the ART program) and 31 December 2007 (date of data extraction) using Kaplan–Meier survival curves. Patients who had at least 1 visit since March 2003 were included.

The survival analysis was limited to patients who started ART in SHCH (group 1) or were eligible for ART following SHCH guidelines but had not started ART yet due to limited access to ART (group 2). For group 1 the time origin was the date of starting ART. Patients were censored at their last visit date if LTFU or TO and on 31 December 2007 if still alive. The time origin for group 2 was the date of the first visit that the patient was eligible for ART according to SHCH guidelines. Patients were censored at time of ART initiation, at their last visit date if LTFU or TO and on 31 December 2007 if still alive and not started on ART. Patients of group 1 contributed person-time to group 2 between the date of eligibility and the start of ART.

For both groups the endpoint was time to death. In addition, a sensitivity analysis was performed using a combined endpoint of time to death or LTFU (i.e. assuming those that were LTFU had died). We compared survival curves using the log-rank test. For patients on ART, predictors of the combined endpoint of mortality and LTFU were assessed using Cox proportional hazards regression. Predictor variables evaluated were baseline CD4 count, haemoglobin level, BMI, WHO clinical stage at start of ART, sex, age, waiting time for ART and year of ART initiation. Waiting time for ART was calculated by subtracting date of eligibility for ART from date of ART initiation. The most frequent opportunistic infections (tuberculosis, cryptococcal meningitis and cytomegalovirus infection) occurring prior to ART initiation were examined as individual risk factors, as was any WHO stage 4 event prior to ART initiation. Adherence was systematically (over)reported as 100% and therefore not considered. Risk factors with P-value<0.10 during univariate analysis were considered for inclusion in the multivariate model. The model was reduced using backward elimination of non-significant variables, and the final model included those variables with P-values of less than 0.05. Single imputation was used for missing values. The most common missing data point was BMI (4.9%), due to missing height. In these cases, BMI was imputed based on the patient's weight and the average height for the patient's gender. In a few (≤2.2%) patients on ART, data for other predictors were missing; in these cases we imputed missing data as medians or most common category by WHO stage. The final model was confirmed using multiple imputation techniques (Royston 2004).

Predictor analysis of mortality while waiting for ART was not considered due to the amount of missing data. We examined as well the mortality and the LTFU in the group of patients prior to eligibility for different CD4 cell count strata; between 250 and 500 cells/μl and above 500 cells/μl.

Data were analysed using STATA version 9.2 (Stata Corp., College Station, TX, USA) and Excel 2003 (Microsoft Corporation, Redmond, WA, USA).

The data collection and informed consent procedure were approved by the institutional review board of the SHCH and Institute of Tropical Medicine, Antwerp, Belgium.

Results

HIV care programme analysis, including all patients with HIV infection, also those not on ART

At the end of 2003, 462 active patients were enrolled in the HIV cohort. That year 30 patients died and 248 were LTFU. The number of new patients per year varied between 475 and 981. In 2005 we set up a system of actively calling patients who did not return for their appointment. The mortality rate and the LTFU fell over the next two years (Table 1 and Figure 1). The percentage of ART patients on second-line treatment remained rather low (3–7%). The number of patients referred from Voluntary Counseling and Testing (VCT) services rose from 8% in 2003 to 77% in 2007. Although access to ART was 90% in 2007, 68 patients died, 42 of them before accessing ART. Figure 1 shows the association between increased ART coverage and mortality and LTFU rates.

Table 1 Evolution of programme indicators in SHCH HIV cohort, 2003–2007

Year	New patients admitted during the year	% Diagnosed in VCT	% ART coverage at the end of the year	% on second line ART	Deaths during the year	LTFU during the year	Transfer out during the year	In active FU at the end of the year
2003*	475	8	23	3.6	30	248	9	462
2004	981	38	43	3.3	111	423	24	885
2005	773	58	76	2.5	146	302	34	1176
2006	699	71	90	4.3	81	210	23	1561
2007	644	77	90	6.7	68	204	18	1915

*Before the start of the ART programme in March 2003, 274 patients were in FU.

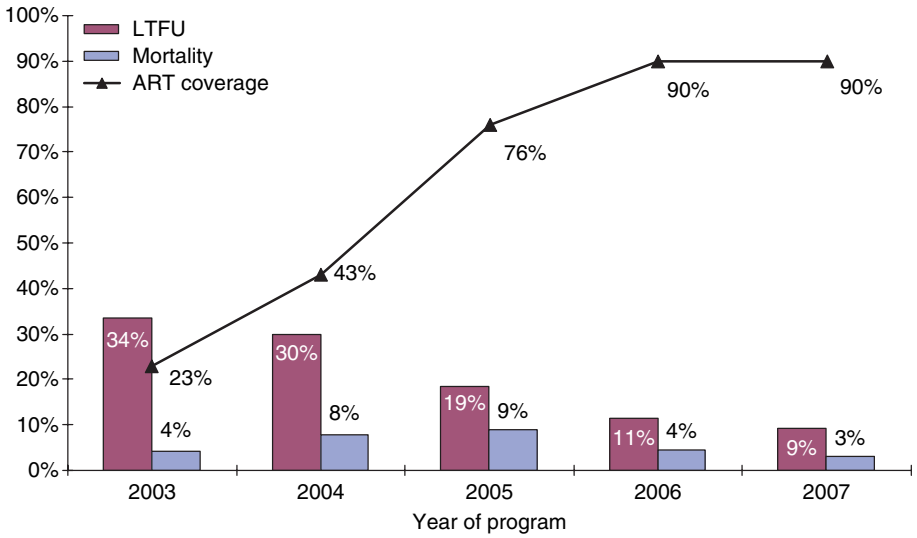

Figure 1 Evolution of ART coverage, mortality and LTFU rates in the HIV cohort in SHCH, 2003–2007.

In 2007 only 9% of patients were LTFU compared to 34% in 2003, when access to ART was only 23% among those eligible.

Survival analysis

Figure 2 shows the flow diagram of the SHCH HIV cohort, for the 3844 patients who had at least one visit after 1 March 2003.

Patients initiated on ART (group 1)

Between March 2003 and December 2007, 3291 adult patients were eligible for ART and 1667 initiated ART in the programme (Figure 2). The baseline characteristics of patients on ART are given in Table 2.

All except four patients were started on an NNRTI-based regimen, and almost half of them were in WHO stage 4. In Table 3 the yearly enrolment rate of patients in the ART program, the median CD4 count and the WHO stage at the start of ART are given. Due to limited access to ART in the beginning, enrolment was slow and patients were initiated at a very advanced stage. The waiting time for eligible patients to ART fell from a median 11.9 months (IQR 4.9–24.7) in 2003 to 1.3 months (IQR 0.6–2.3) in 2007 (Table 3).

The median CD4 cell count at start of ART rose over the years (from 22 in 2003 to 105 in 2007), and the proportion of patients in WHO stage 4 fell (from 77.9% in 2003 to 31.6% in 2007; Table 3).

137 (8.2%) patients on ART died and 73 (4.4%) were LTFU between 1 March 2003 and 31 December 2007. The average cumulative mortality was 7.6% (95% CI: 6.4–9.1%) after 1 year of ART and 10.2% (95% CI: 8.5–12.1%) after 4 years. More than half of the deaths occurred in the first 6 months after ART initiation (Figure 3a). Similar trends were observed when the endpoint was mortality and LTFU combined. The overall rate of this composite endpoint was 11.5% (95% CI: 10.0–13.3%) at 1 year (Figure 3b), 14.2% (95% CI: 12.4–16.2%) at 2 years and 15.9% (95% CI: 13.8–18.3%) after 4 years.

Predictors for death and LTFU combined in the ART cohort

CD4 cell count (<50 cells/μl), haemoglobin (<10 g/dl), BMI (<18), WHO stage at baseline, male sex and year of ART initiation were predictors for the combined endpoint of mortality and LTFU in univariate survival analysis (crude hazard ratio, Table 4). Tuberculosis, cryptococcal meningitis, cytomegalovirus infection, and any WHO stage 4 event before ART initiation were predictive of mortality during univariate analysis, but were not withheld as independent risk factors during multivariate analysis. Multivariate analysis indicated that male sex or a CD4 count <50 cells/μl or a BMI <18 or haemoglobin <10 g/dl at ART initiation were significant risk factors for the combined endpoint of death and LTFU (Table 4).

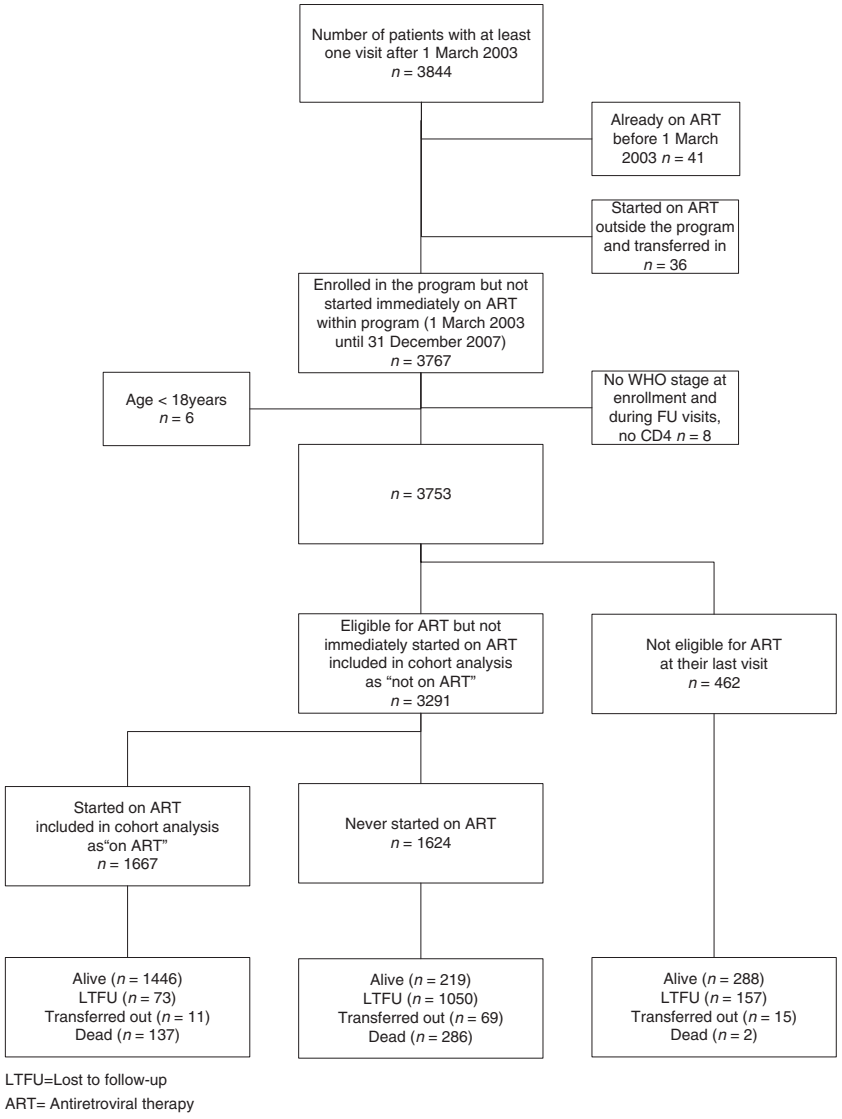

Figure 2 Flow diagram of patients in the SHCH HIV cohort. LTFU: lost to follow-up; ART: antiretroviral therapy.

Patients starting ART in 2005 had a higher mortality using the 2003–2004 cohort as a reference (Adjusted Hazard Ratio: 1.47, *P*-value: 0.040; Table 4).

Patients eligible but not yet initiated on ART (group 2)

Of the 3291 patients eligible for ART, 1667 started ART, but not all were started immediately because of limited availability of drugs (contributing person-time to group 2). There were 1624 patients who never started ART (Figure 2). Using the best case scenario (mortality as endpoint and censoring patients who were LTFU) 19.9% (95% CI: 18.0–22.0%) of these patients had died after 1 year (Figure 3a). Using the worst case scenario (considering patients who were LTFU as dead) the mortality was 48.7% (95% CI: 46.6–51.0%) after one year (Figure 3b).

Patients not initiated on ART because they were not eligible

462 patients were not eligible for ART at their last visit (Figure 2). The mortality in this group was very low (2/462) but the LTFU rate was high (34%). CD4 counts at last visit were available for 294 patients (64%). Mortality

Table 2 Patient characteristics at ART initiation (*n*=1667) for patients on ART

Characteristic	*n* = 1667
Gender: *n* (%)	
Male	824 (49.4)
Female	843 (50.6)
Age (years): median (range)	35 (18–75)
Weight (kg): mean (SD)	48.4 (9.5)
Missing: *n* (%)	4 (0.2)
Height (cm): mean (SD)	160 (8)
Missing: *n* (%)	78 (4.7)
BMI (score): mean (SD)	19.0 (3.2)
Missing: *n* (%)	81 (4.9)
CD4 (cells/μl): median (IQR)	61 (18–173)
Missing: *n* (%)	37 (2.2)
Haemoglobin (g/dl): mean (SD)	11.1 (2.1)
Missing: *n* (%)	24 (1.4)
Prior ART experience: *n* (%)	87 (5.2)
Missing	1 (<0.1)
WHO stage at start	
WHO stage 1: *n* (%)	58 (3.5)
WHO stage 2: *n* (%)	190 (11.4)
WHO stage 3: *n* (%)	647 (38.8)
WHO stage 4: *n* (%)	771 (46.3)
Missing: *n* (%)	1 (<0.1)
Regimen at initiation	
NNRTI based regimen	
NVP based: *n* (%)	1267 (76.0)
EFV based: *n* (%)	396 (23.8)
PI based regimen: *n* (%)	4 (0.2)

and LTFU were similar between patients with CD4 cell count between 250 and 500 cells/μl (0% and 22.4% respectively) and CD4 cell count above 500 cells/μl (0.8% and 25.0% respectively) (data not shown).

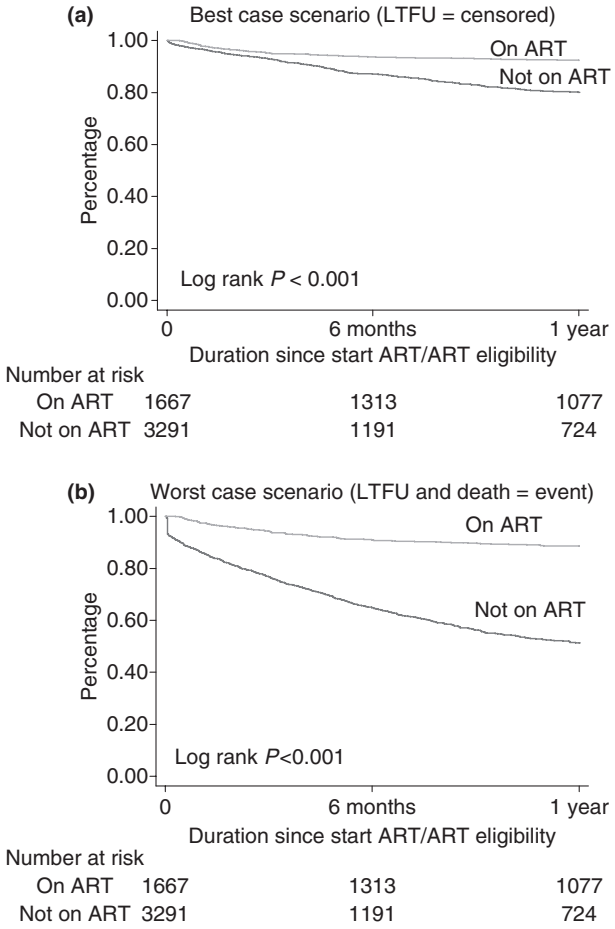

Figure 3 (a) Kaplan–Meier estimates of 1 year mortality ('best case scenario') before and after starting ART. (b) Kaplan–Meier estimates of combined endpoint of one year mortality and LTFU ('worst case scenario') before and after starting ART.

Discussion

Overall programme evaluation

The LTFU rate and mortality diminished over the years (Figure 1). Especially in the beginning LTFU was high. Many patients were shopping around between the ART clinics in Phnom Penh in order to increase their chance of getting access to ART. However, all sites had waiting lists and stringent selection criteria. Because of the limited ART

Table 3 Evolution of WHO stage and CD4 count at initiation of ART, 2003–2007

Year of ART initiation	Number of patients initiated on ART	CD4 cells/μl: median (IQR)	WHO stage 1–2: *n* (%)	WHO stage 3: *n* (%)	WHO stage 4: *n* (%)	Waiting time: months (IQR)
2003	68	22 (4–132)	1 (1.5)	14 (20.6)	53 (77.9)	11.9 (4.9–24.7)
2004	199	36 (10–101)	18 (9.1)	52 (26.1)	129 (64.8)	6.7 (4.2–11.4)
2005	480	53 (14–137)	33 (6.9)	182 (37.9)	265 (55.2)	5.2 (2.8–9.0)
2006	493	66 (26–178)	83 (16.9)	220 (44.7)	189 (38.4)	2.2 (1.2–4.2)
2007	427	105 (29–222)	113 (26.5)	179 (41.9)	135 (31.6)	1.3 (0.6–2.3)
Total	1667	61 (18–173)	248 (14.9)	647 (38.8)	771 (46.3)	3.0 (1.2–6.8)

One patient with missing WHO stage at start.

Table 4 Predictors/risk factors for the combined endpoint (mortality and LTFU) after ART initiation, 2003–2007

Risk factor	Number of patients 1667	Patients with the event (death or LTFU): *n* (%) 210 (12.6)	Crude HR (95% CI)	*P*-value univariate analysis*	Adjusted HR (95% CI)	*P*-value
Year of ART initiation						
2003 and 2004	267	42 (15.7)	1	<0.001	1	0.009
2005	480	95 (19.8)	1.40 (0.97–2.02)		1.47 (1.02–2.13)	0.040
2006	493	55 (11.2)	0.83 (0.55–1.25)		1.06 (0.70–1.60)	0.799
2007	427	18 (4.2)	0.48 (0.28–0.85)		0.69 (0.39–1.23)	0.207
Waiting time						
<3 months	834	79 (9.5)	1	0.038		
≥3 months	833	131 (15.7)	1.35 (1.02–1.79)		/	/
Gender						
Male	824	126 (15.3)	1.55 (1.18–2.05)	0.002	1.73 (1.29–2.32)	<0.001
Female	843	84 (10.0)	1			
Age						
<35 years	829	113 (13.6)	1.14 (0.87–1.50)	0.338	/	/
≥35 years	838	97 (11.6)	1			
ART exposure						
Yes	87	4 (4.6)	0.35 (0.13–0.95)	0.040	/	/
No	1579	205 (13.0)	1			
Missing	1	1 (100.0)				
WHO stage at initiation						
Stages 1 and 2	248	13 (5.2)	1	<0.001		
Stage 3	647	62 (9.6)	1.66 (0.92–3.04)		/	/
Stage 4	771	135 (17.5)	3.00 (1.69–5.30)		/	/
Missing	1	0 (0.0)				
BMI at initiation (kg/m^2)						
BMI < 18	485	97 (20.0)	3.25 (2.40–4.40)	<0.001	2.87 (2.15–3.83)	<0.001
BMI ≥ 18	1101	73 (6.6)	1		1	
Missing	81	40 (49.4)				
CD4 cell count (cells/μl) at initiation						
CD4 < 50	725	142 (19.6)	3.82 (2.28–6.40)	<0.001	2.00 (1.16–3.44)	<0.001
CD4 ≥ 50 <200	583	44 (7.6)	1.39 (0.78–2.46)		1.12 (0.63–1.98)	0.012
CD4 > 200	322	16 (5.0)	1		1	0.707
Missing	37	8 (21.6)				
Haemoglobin (g/dl) at initiation						
Hb < 10	456	99 (21.7)	2.64 (2.00–3.48)	<0.001	2.00 (1.49–2.66)	<0.001
Hb ≥ 10	1187	104 (8.8)	1		1	
Missing	24	7 (29.2)				
TB before ART initiation						
Yes	693	111 (16.0)	1.53 (1.16 – 2.0)	0.002	/	/
No	974	99 (10.2)	1			
Cryptococcal meningitis before ART initiation						
Yes	86	23 (26.7)	2.56 (1.66–3.95)	<0.001	/	/
No	1581	187 (11.8)	1			
CMV infection before ART initiation						
Yes	32	11 (34.4)	3.10 (1.66–5.61)	<0.001	/	/
No	1635	199 (12.2)	1			
Any WHO stage 4 event before ART initiation						
Yes	792	144 (18.2)	2.33 (1.74–3.12)	<0.001	/	/
No	875	66 (7.5)	1			

ART, antiretroviral therapy; BMI, body mass index; CI, confidence intervals; HR, hazard ratio; LTFU, lost to follow-up; TB, tuberculosis; CMV, cytomegalovirus.

*Risk factors with *P*-value <0.10 during univariate analysis were considered for inclusion in the multivariate model.

coverage (23%) in our cohort in 2003, we assume that the high initial LTFU rate was largely explained by mortality, although some patients self-referred to other sites.

A weakness of the study is that we have no information on the real outcome in patients LTFU. Despite doubling the ART coverage in 2005 (Figure 1), the mortality in our cohort had increased. Several explanations were given by the clinical staff. Rapid scaling-up may have compromised quality of care. During that period many hospitals and NGOs outside Phnom Penh were starting up ART programs. Stable patients from the SHCH cohort from rural areas were asked to return to their own provinces, while more complex patients stayed for follow-up at the SHCH. The active defaulter tracing system set up in 2005 may have caused a relative increase in the number of ascertained deaths and a corresponding decrease in patients LTFU. Due to the increase in access to ART, and probably because physicians were more experienced, the mortality rate and LTFU decreased over the next two years (Table 1 and Figure 1). Whilst ART coverage was 90% in 2007, 42 patients died before accessing ART, because they presented in an advanced stage of disease. Hence to reduce pre-ART mortality and LTFU it is important to diagnose HIV in an earlier stage. Fortunately we have observed a positive trend in earlier access to care. From 2003 to 2005, more than 85% of patients diagnosed with HIV in the SHCH were in WHO clinical stages 3 and 4 at presentation. This number declined to 45% in 2007 (Activity report 2007 SHCH). Increasingly patients were diagnosed through VCT services, and not because of an opportunistic infection. The number of patients on second-line treatment is low (Table 1). This may be an underestimation of the real need for second-line treatment, as treatment failure is mainly based on clinical and immunological criteria. Even so, delays in switching to second-line have been recognized by other projects in RLSs, even when virological failure is diagnosed (Ive *et al.* 2009; Keiser 2009). The decrease in mortality and LTFU rates paralleled the increase in access to ART (Figure 1), and resulted in a growing number of patients in active follow-up every year. With the current stable admission of new patients, we can expect an annual increase of some 400 patients per year. This raises the question of how big a single HIV clinic can become without compromising quality of care. HIV is a chronic problem, and HIV cohort sizes will increase for many years to come. Decentralization of ART delivery to more peripheral health facilities is needed. Furthermore, providing ART closer to patients' homes is likely to improve long-term adherence and retention. There are indications too that clinics with smaller numbers of patients have better ART outcomes, including higher retention rates (Brinkhof *et al.* 2008).

By collecting a few indicators (number of new patients, active patients, eligible patients on ART, number of patients on second-line ART, deaths, LTFU, TO) on a monthly or quarterly basis, we were able to monitor the performance of the programme over time, estimate treatment gaps and predict future treatment needs. These indicators are available with minimal effort.

Cohort analysis

The advantage of a survival analysis is that cohorts can be compared. In this ART cohort from Cambodia Kaplan–Meier survival estimates are similar to other published ART cohort data from RLSs (Coetzee *et al.* 2004; Calmy *et al.* 2006; Etard *et al.* 2006; Ferradini *et al.* 2006, 2007; Stringer *et al.* 2006; Madec *et al.* 2007; Bussmann *et al.* 2008). The reliability of mortality data of a cohort depends strongly on the way LTFUs are dealt with (Lawn *et al.* 2008). The ART-LINC collaboration demonstrated that sites with an active defaulter tracing system reported higher mortality than sites without. By looking for defaulters, one will ascertain deaths more frequently (Braitstein *et al.* 2006). A few cohort studies from RLSs have shown that more than 50% of patients LTFU have, in fact, died (Yu *et al.* 2007; Bisson *et al.* 2008). Therefore, if we calculate survival using the endpoint of death, and censor patients at the last follow-up date in the LTFU group, mortality will be underestimated due to misclassification of unascertained deaths as LTFU.

In our cohort, mortality was highest in the first months on ART. This high early mortality was also demonstrated by others (Coetzee *et al.* 2004; Calmy *et al.* 2006; Etard *et al.* 2006; Ferradini *et al.* 2006; Stringer *et al.* 2006). Ferradini ascribed the high initial mortality in Malawi to the late presentation of patients, with overwhelming opportunistic infections and immune reconstitution inflammatory syndrome (Ferradini *et al.* 2006). The ART-LINC collaboration has shown that early mortality rates are sevenfold higher in cohorts from low-income than from high-income countries (Braitstein *et al.* 2006).

Poor adherence (Nachega *et al.* 2006; Lima *et al.* 2009) and treatment failure, combined with delayed switch, especially with NNRTI-based regimens, have been associated with increased mortality (Hogg *et al.* 2006; Petersen *et al.* 2008). In our cohort treatment adherence was measured by SMAQ and reportedly 100% for almost all patients. However, a study conducted in SHCH showed that SMAQ was not predictive of treatment failure while visual analogue score (VAS) was (Lynen *et al.* 2009), indicating that SMAQ is not a reliable tool in this setting.

Treatment failure too was not analysed as a predictor because viral loads were not available. However, as this is

a relatively young cohort with mortality occurring mainly in the first 6 months, treatment failure was unlikely to contribute significantly to the mortality in this study. Our study of predictors of death confirms the findings of other cohort studies from RLSs. Men were more likely to die than women (Calmy *et al.* 2006; Ferradini *et al.* 2007). The reasons for higher mortality in men are not clear, but programme managers have mentioned lower adherence rates in men, and higher mobility. Low CD4 counts (<50 cells/μl), low BMI (<18 kg/m^2) and low haemoglobin levels (<10 g/dl) are predictive of death (Table 4). Identifying patients with these risk factors at ART initiation and monitoring them more closely could possibly reduce mortality. One strategy could be to initiate ART in these patients in 'specialized' centres with more ART experience. Transferring these patients to less specialized centres can be done after 6 months when the risk of ART-associated mortality has declined. Initiation of ART in patients with lower risk of complications and death should not be delayed and can be organized immediately in less specialized centres. Indeed, in addition to the high early mortality in patients on ART, another concern is the significant number of patients that die before they can access ART. We observed a one-year mortality of 19.9% among patients who were eligible but did not receive ART because of limited availability of ART (Figure 3a). An even more disturbing figure of 48.7% mortality is obtained when patients LTFU were not censored (Figure 3b). Although we have to be careful to compare the mortality in patients on ART and not on ART, because of selection bias, the benefit of rapid ART scale-up is evident. Lawn *et al.* described a similar finding in a community-based ART programme in South Africa where 66% of the patients who died within 90 days of enrolment into the programme were not receiving ART, using this finding to argue that the pre-ART interval should be minimized (Lawn *et al.* 2005). In another study from South Africa the pre-ART attrition rate was very high (65%); 40% of the patients were LTFU, 34% had died while a minority had switched to another care provider (Bassett *et al.* 2009). The improved survival in recent years among patients on ART in our cohort is probably because patients started ART earlier (Table 3). Physician's experience plays a role as well in survival of patients on ART (Kitahata *et al.* 1996).

In our ART cohort retention rate was good. More than 85% of patients were alive and in care after 2 years. This compares favourably to some sub-Saharan African ART cohorts (Rosen *et al.* 2007), where retention rates at two years ranged between 50% and 90%. LTFU accounted for the majority of attrition. Also in the West retention in care has been identified as a problem (Giordano *et al.* 2007). Early loss to programme has been increasing over time in RLSs and was attributed to rapid scale-up (Brinkhof *et al.* 2008). This contrasts with our findings where mortality temporarily increased but LTFU rates and overall attrition rates decreased, favouring rapid scale-up. Researchers in South-Africa reached the same conclusion (Lawn *et al.* 2006; Walensky *et al.* 2008). We need to understand the reasons for attrition, both in the pre-ART and ART group. We should determine what assistance patients need to remain in follow-up and try to prevent patients from missing appointments. Defaulter tracing without delay is important to improve patient outcomes. This requires correct recording of the patient's address and contact details (Yu *et al.* 2007). Defaulter tracing is also important to have a clear idea on patient outcomes in a program, and to improve reporting on mortality.

The mortality in the group of patients prior to eligibility was negligible, suggesting that the starting criteria in this setting are appropriate as opposed to the South African setting (Lawn & Wood 2007), although we have to carefully interpret these data due to the relatively high number of LTFU. This high LTFU rate is food for thought. By promoting an opt-out strategy for HIV testing and earlier access to care, patients who are not yet eligible for ART will make up a larger part of the patient population hence the need for an appropriate care plan.

Not all HIV programs are capable of doing Kaplan–Meier survival analyses. The quarterly cohort analyses as proposed by WHO and practiced in Malawi are difficult to maintain as the number of analyses after several years becomes very large in established programs (Harries *et al.* 2004). With a few indicators programme managers can monitor and compare the performance of their programs over time. To have a clear idea about the bottlenecks and the gaps, it is important to monitor outcomes in both the ART and pre-ART group. Capacity strengthening of programme managers for these tasks is needed.

Conclusion

Universal access to ART has significantly improved the survival and retention of patients with HIV in our cohort in Cambodia. Nevertheless, the attrition rate remains high prior to the start of ART. Strategies are needed to enable earlier access to ART and to retain patients in care. A future challenge will be to set up decentralized ART sites to cope with the growing number of patients while maintaining high quality care and low attrition rates.

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