Original Article

Survival Analysis among Patients Receiving Antiretroviral Therapy in Urban and Rural Settings of the Centre Region of Cameroon

Déterminants de la survie des patients sous ARV en zone urbaine et rurale de la région du Centre du Cameroun

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ABSTRACT

Objectives: With increasing antiretroviral therapy (ART) coverage in Cameroon (from 28,000 patients in 2008 to 122,000 by end 2012) following the World health organisation (WHO) criteria of CD4≤350 cells/mm^3, there are increasing risks of poor programmatic outcomes and HIV drug resistance (HIVDR) emergence. We aimed to determine survival rates and associated factors among patients enrolled on ART following the national guidelines in Cameroon. **Methods**: A longitudinal study was conducted in 2013 among patients initiating ART in rural (Mfou District Hospital) and urban (Yaoundé Central Hospital) settings of the Centre region of Cameroon. Socio-demographic, clinical, laboratory and mortality data were analysed with EPI INFO v.3.5.3 and SPSS v.20, using Cox model and Wilcoxon test for survival analysis. **Results**: A total of 350 patients initiating ART (median age 37 years; 71% female) were enrolled, with an overall delayed ART initiation (median CD4: 171 cells/mm^3 and 59.9% at WHO-clinical stages 3 and 4). Survival rates at 6 and 12 months were 93.9% and 91.3% respectively, without significant disparity between the rural and urban setting (p=0.21). Retention in care at 6 and 12 months after ART initiation was 78.6% and 69.1% respectively, suggesting increasing lost to follow-up. Mortality was predominantly associated with initial events of anaemia (p=0.00001), opportunistic infections (p=0.002), CD4 count<200 cells/mm^3 (p=0.004).
Conclusions: There are decreasing rates of survivals within 12 months of ART initiation, while retention in care drops below minimal target of 70%. An improved life expectancy on ART requires close monitoring for anaemia, preventing clinical events while ensuring earlier initiation on ART in both rural and urban resource-limited settings.

Keywords: HIV, survival , ART, Cameroon, center region

RÉSUMÉ

Introduction : Le nombre de malades sous Traitement Anti Rétroviral (TARV) au Cameroun est passé de 28000 à 122 000 de 2008 en 2012, laissant présager uneaugmentation des résistances au virus. L'objectif de notre étude était de déterminer le taux de survie des PVVIH mis sous ARV dans deux hôpitaux de la région du centre au Cameroun. **Matériel-Méthodes** Une cohorte de patients mis sous ARV en 2012 à l'Hôpital Central de Yaoundé et l'Hôpital de District de Mfou a été suivie. Le recueil des données s'est fait à partir des dossiers patients et du logiciel ESOPE. Les données ont été analysées à l'aide d'EPI INFO version 3.5.3 et SPSS 20. **Résultats :** L'âge médian des patients était de 37 ans (71% de femmes). Ces derniers avaient un taux médian de CD4 à l'initiation de 171/ mm^3 ainsi qu'un stade clinique OMS avancé. Les taux de survie à 6 mois et 12 mois étaient respectivement de 93,9% et 91,3%. Les taux de rétention des patients aux ARV de notre cohorte étaient de 78,6 % et 69,1% respectivement à 6 et 12 mois. La survie des patients était associée de façon significative avec la présence d'anémie et d'Infections Opportunistes à l'admission, ainsi que des niveaux de CD4 bas et un stade clinique OMS avancé. **Conclusion :** La survie des PVVIH a 12 mois dans ces structures est dans les limites définies par l'OMS. Elle est influencée par la présence d'anémie à l'initiation, ainsi que le fait pour le patient de se présenter tardivement pour la prise de traitement.

Mots clés: VIH, survie, Traitement antirétroviral, Cameroun, région du Centre

INTRODUCTION

The AIDS pandemic remains a major threat worldwide with the highest burden (69% global HIV infections), as well associated mortality (70% global HIV-related deaths) are reported from sub-Saharan Africa (SSA) [1].

The increasing access to antiretroviral therapy (ART) has significantly improved the life expectancy of PLHIV worldwide, including in SSA were first-line ART regimens are commonly available in routine care [1]. Of note, combination ART is known to control viral replication, which in turns allows for immune recovery, lower transmission chain in the community and reduced mortality (especially when diagnosed earlier) [2-4]. Furthermore, the number of life-saving years has recently increased by four-fold within SSA, thus highlighting a changing paradigm in the history of HIV/AIDS even in these RLS [1,4].

With poor adherence, defaulters, lost to follow-up, limited therapeutic regimens and the rapid scale-up of ART, the risk of HIV drug resistance (HIVDR) is a threat to ART effectiveness in SSA health programs, including Cameroon [5-7].

Cameroon is a central-African country facing a generalized HIV epidemiology in Cameroon (from 5.5% in 2004 to 4.3% by end 2011) in the populations aged 15-49 [8,9]. About half (49.5%) of the 267,069 PLHIV eligible for ART were under ART by end 2012 [10], due to national efforts in scaling up ART (from 28,000 by end 2008 to more than 122,000 by end 2012) [11]. This exponential increase in ART coverage certainly indicates an increasing risk of HIVDR emergence [12]. Of note, a national survey conducted in 40-health facilities in 2010 revealed 55% of retention in care 12 months after ART initiation, and 33% of lost to follow-up among Cameroonian adults [13], a suboptimal performance likely underscoring probable unreported mortality during the first year of ART in the community [13,14]. As earlier reported (in 2006), 77% of patients survived after 12 months of ART in North-Cameroon, with the World Health Organization (WHO) advanced clinical stage, lower CD4 count and anaemia as leading predictors of mortality [15]. We sought to ascertain survival rates and related determinants among ART initiators, in order to provide informed measures for policy-making. Specifically, we aimed to: (a) assess retention rates at six and 12 months following ART initiation; (b) determine survival rates at six and 12 months following ART initiation; (c) and identify local factors associated with early mortality on ART in the Cameroonian rural and urban context.

MATERIALS AND METHODS

Study design

A longitudinal and retrospective study was conducted in 2013 among patients initiating ART during the first-six months of the year in two health facilities of the Centre region of Cameroon: the Yaoundé Central Hospital (YCH) representing the urban setting, and the Mfou District Hospital (MDH) representing the rural setting. These two facilities were conveniently selected based on their geographical locations (urban vs. rural), availability of first-line ART, experience in providing ART (above 3years for each), use of standard ART registers and patient monitoring software (ESOPE), and the presence of community relay agents (CRA).

Patients were enrolled in the study if they initiated ART within six months time; aged 15 years and above; and registered in the study sites.

Data abstraction process

Using a standard reporting sheet, data were abstracted from patient medical records, ART registers and the ESOPE monitoring software [16]. Briefly, medical records from the therapeutic committees were used to identify patients initiating ART during the study enrolment period for follow-up at six and 12 months after ART initiation. Missing data were systematically retrieved from other sources (ART registers, pharmacy registers, or ESOPE software) [16]. Throughout the study, patients who defaulted from clinic appointment were subjects for an active search by CRAs (either by phone calls and/or home visits) and either returned to care, identified as dead, or confirmed as lost to follow-up after several unsuccessful attempts of searching strategies.

Data analysis

Data were entered into EPI INFO version 3.5.3, and analysed using both EPI INFO v.3.5.3 and SPSS v.20. At endpoint, "***retention in care***" was defined as a patient who is known to be alive and on ART at the end of the study period; "***survival***" was defined as a patient alive who is still in care or lost to follow-up without further notice, excluding reported transfer-out and deaths; "***death***" was defined as a patient reported dead at the clinic or a lost to follow-up that was found dead after search in the community by CRAs. For dead cases, life expectancy on ART was calculated based on date of ART initiation and date of death.

Survival analyses were performed using Cox model to determine periodic survival estimates within equal time intervals. Wilcoxon test (Gehan) was used to compare survivals between the two groups (urban vs. rural) of patients, with p-value <0.05 considered statistically significant. Significant variables from the Cox model univariate analysis were further processed for multivariate analysis.

Ethical considerations

As an activity conducted under the national monitoring and evaluation of ART program for the Ministry of Public Health in Cameroon, the hospital directorate provided

research authorization (N°588L/MINSANTE/SG/DHCY/STAGES; HDMFOU/ACCORD29/11/2013), and ethical clearance was requested from the Ethics Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I, followed by approval through the academic research defence. With respect to the study design, ART initiators were retrieved from the site files, and information were provided to each potential participant on the study programmatic relevance. Following verbal agreement, baseline data were abstracted from the site files while follow-up data at months 6 and 12. Parental attention was considered for the participant of 17 years old. At each point, data were processed anonymously, for confidentiality and privacy, using unique identifiers for each participant. To prevent a performance due to further interventions not reflecting the routine programmatic context, active search of ART defaulters was conducted as per national guidelines, without altering standards of care (See supplementary digital content).

RESULTS

Characteristics of the study population

350 patients initiating ART were enrolled during the study period. The median age at ART enrolment was 37 [interquartile range (IQR): 24-48] years, min-max: 17-70 years; and women were predominant (71%). Up to 336 (96%) had a CD4<350 cells/mm^3, with a similar median value (171 cells/mm^3) in both health facilities (IQR: 90-251 urban vs. 5-269 rural). Interestingly, 174 (50.9%) initiated ART with a WHO clinical stage 3 with a higher proportion for patients living in the rural setting (65.9% vs. 40.9%), as shown in table 1.

Table 1: Patient outcomes after six and 12 months of ART initiation

Patient outcomes	Month-6 of ART		Month-12 of ART	
	N	**(%)**	**N**	**(%)**
Lost to follow-up	43	(12.3)	61	(17.4)
On ART	275	(78.6)	242	(69.1)
ART interruption	11	(3.1)	17	(4.9)
Dead	21	(6.0)	30	(8.6)
Total	350	(100.0)	350	(100.0)

Retention on ART at six and 12 months

Of the 350 patients initiating ART, overall retention in care dropped from 78.6% (275) at six months to 69.1% (242) at 12 months, while lost to follow-up increased 12.3% to 17.4% respectively (table 2).

Table 2: Determinants of survivals

	Univariate Analysis		Multivariate Analysis	
Characteristics	**Hazard ratio (95% CI)**	**P**	**Hazard ratio (95% CI)**	**P**
Gender				
Male	1.00	-	-	-
Female	0.81 (0.36-1.81)	0.61	-	
WHO Staging				
Stage I	1			
Stage II	-		-	0.000
Stage III	-	0.000		0.000
Stage IV		0.000	- -	
CD4 cells count				
<200	1	-	-	-
200-349	0.24 (0.083-0.7)	0.009	0.29 (0.08-0.98)	0.047
350-499		1.000		1.00
≥500	-	1.00	-	1.00
	-		-	
Opportunistic Infection	1.00		1.00	
Presence	0.28 (0.12-0.64)	0.003	0.54 (0.2-1.5)	0.237
Absence				
Anaemia				
Presence	1.00	-	1.00	-
Absence	0.17 (0.06-0.5)	0.001	0.25 (0.2-1.5)	0.01

Overall survival rates

Out of the 350 patients enrolled in the study, 21 and 30 cumulative deaths were reported respectively at six and 12 months following ART initiation. These represented overall survival rates of 93.9% and 91.3% respectively at six and 12 months following ART initiation (Fig.1).

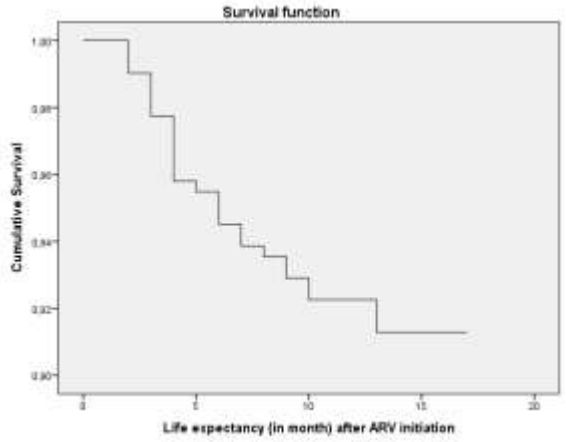

Figure 1: Overall survival rate

Survival rates according to geographical settings

According to settings, survival rates from the urban health facility (YHC) were 92.0% (209) and 89.3% (203) respectively at six and 12 months following ART initiation vs. 97.7% (120) and 94.3% (116) from the rural health facility (MDH); p=0.21.

Survival rates according to WHO clinical staging

According to the WHO clinical staging assessed at ART initiation, survivals at six and 12 months were respectively 100% (86) throughout for patients at clinical stage I; 95.9% (53) and 93.9% (52) for patients at clinical stage II (55); 93.0% (161) and 89.2% (154) for patients at clinical stage III (173); 83.3% (29) and 80.0% (28) for patients at clinical stage IV (35); with a slight difference (p=0.057) observed between clinical stages II and IV (Fig.2).

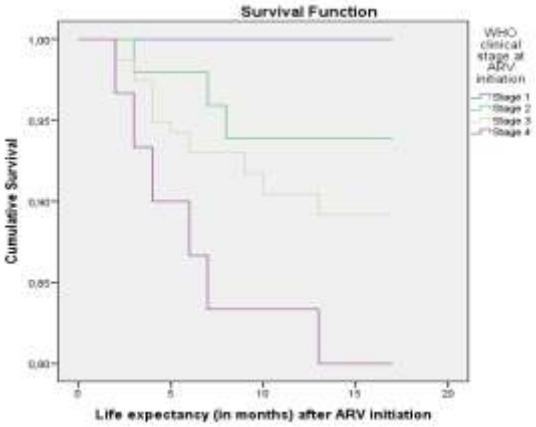

Fig 2 : Survival Rates according to WHO clinical stage

Survival rates according to CD4 cells count

At the moment of ART initiation, 171, 121 and 9 patients were respectively severely (<200 CD4 cel/mm^3), moderately (200-350 CD4 cel/mm^3) and mildly immunocompromised (350-500 CD4 cel/mm^3). Only two had a normal immune status (≥500 CD4 cel/mm^3); and 47 had missing data on CD4 cells count. Survival rates at six and 12 months were respectively 90.1% (154) and 87.1% (149) for patients with <200 CD4 cel/mm^3, vs. 99.2% (120) and 96.7% (117) for patients with 200-350 CD4 cel/mm^3; p=0.004. For patients with >350 CD4 cells/mm^3, no case of death was reported up to 12 months (Fig.3).

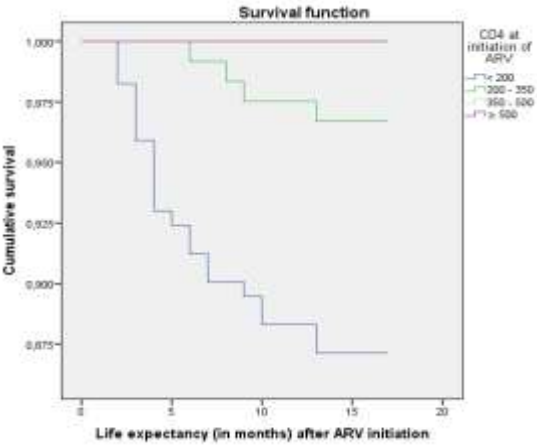

Fig 3 : Survival rates according to CD4 at ART initiation

Survival rates according to events of an opportunistic infection

At ART initiation, 42 patients were reported with an opportunistic infection, and survival rates were 83.3% (35) at six and 78.6% (33) at 12 months after ART initiation, with a statistically significant difference compared to asymptomatic patients (Fig. 4), p=0.002. From the reported opportunistic infections, tuberculosis had the lowest survival rates: 85.0% (18) and 81.0% (17) respectively at six and 12 months, as compared to other opportunistic infections: toxoplasmosis with 88.9% (8/9) at both six and 12 months, cryptococcal encephalitis with 91.6% (11/13) at 6 months and 83.3% (10/12) at 12 months; p=0.67.

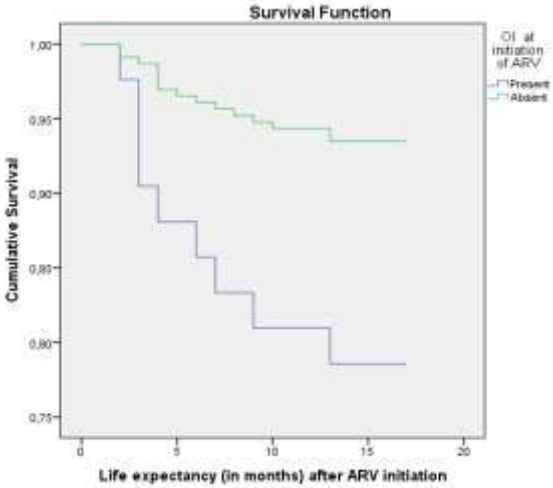

Figure 4 : Survival rates according to events of opportunistic infections

Survival rates according to events of anaemia

Out of 150 anaemic patients at ART initiation, survival rates at six and 12 months were respectively 88.7% (133) and 85.3% (128), vs. 99.3% (147) and 97.3% (144) among non-anaemic patients; p=0.00001 (Fig.5).

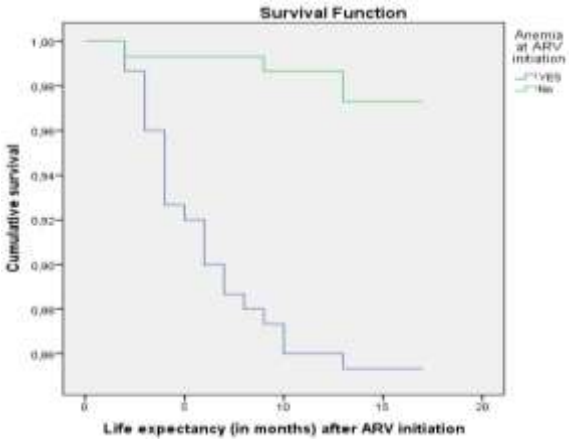

Fig 5 : Survival rates according to event of anemia

Determinants of survivals in the entire study population

Multivariate analysis, using significant factors in the univariate analysis, confirmed three of those factors as key predictors of mortality: (1) advanced WHO clinical stages ($p<0.0001$), (2) severely immunodeficiency ($p=0.047$), (3) anaemia ($p=0.01$), (4) opportunistic infection ($p=0.237$), as detailed in table 3.

DISCUSSION

In our cohort of 350 patients enrolled on ART both from rural (123) and urban (227) health facilities in Cameroon, we identified major factors associated with early mortality in the course of ART. The high number of patients from the urban facility simply reflects the role of the YCH as the most accessed HIV treatment centre in the country [17]. Also, the high rate of women in our study population is in line with the national gender distribution of HIV infection (5.6% in female and 2.9% in male) [8,9], thus indicating the potential representativeness of our data on these target populations in Cameroon, for informed policies.

The delayed enrolment on ART in our study, in the frame of poor clinical conditions (60.5% at the WHO clinical stages III and IV), is similar to findings from Alemu *et al.* (70%) [18], and Sielenou *et al.* (90%) [15]. These confirm that a considerable number of patients in RLS might be enrolled on ART following hospital consultation-based HIV diagnosis [10,19,20]. Strategies to promote volunteering HIV testing might uptake access to care and overcome such programmatic challenges, especially in rural settings [6,7,17,20]. Of note, ART enrolment at a WHO stage I was only observed in the urban facility (HCY), whereby monitoring is close to reference standards [10].

The immune status of patients was severely compromised in general (171 median-CD4 cells), with 56% having <200 CD4 cells/mm^3, thereby underscoring potential risks of poor therapeutic outcomes. Previous findings are concordant from Ethiopia (103 median-CD4 cells and 85% with <200 CD4 cells/mm^3), Nigeria (152 median-CD4), Burkina-Faso (115-148 median-CD4), and other reports from Cameroon; altogether indicating that many patients in SSA context arrived late at the health facility [15,18,19,21,22]. Enrolments are expected to improve as countries transition towards higher thresholds for ART initiation [10,12].

Our findings indicated that, ~80% and ~70% of ART initiators remain in care respectively at six and 12 months after treatment initiation. Though our findings are closed to the WHO target for a fair performance (70%) at 12 month [23,24], the decreasing trend indicates risks of HIVDR subsequently, as long-term ART would be associated with increasing defaulters (considered possible HIVDR patients) [14,25]. Similar data were reported by Assefa *et al.* (80% and 74% retention in care at 6 and 12 months of ART) [19], Odafe *et al.* (85% retention at 12 months) [21], while poor performance was previously reported in-country Billong *et al.* in the same country (55% retention at 12 months of ART) [13]. The later difference is justifiable by the larger sampling in the later study, with widely varying site performances (17-90%) [13]. Active search for defaulters, launched by the national ART program during study period, could also account for the differences, and in turns stresses the necessity to support community engagement while scaling-up ART programs in SSA [13,23,26].

High rates of survivals in our study were similar to previous reports from Kouanda *et al.* (94.2% and 92.4% at six and 12 months) [22]. However, the difference observed in survival rates according to geographical settings, though non-significant, could be due to proximity of rural health facilities to local patients and an acceptable workload (staff/patient ratio) [13,19]. This in turns suggests creating or ART clinics in order to reduce the impact of distance on patient attendance/adherence to the program [13,23,24]. Similar performances (~90%) were also reported in Ethiopia and in South Africa [14,18,19], suggesting that lost to follow-up, and not mortality per say, represents a major programmatic challenge to a successful scale-up of ART [13,21-24]. Thus, supporting home visits, through CRAs, might gradually help in sustaining survivals while reducing lost to follow-up [13,24]. However, differences in performance, observed in other studies conducted within other SSA settings (77%-89% at 12 months), could be due to varying sampling and use of CRA for retrace defaulters [6].

Predictors of early mortality at ART initiation were advanced predominantly WHO clinical stages, poor CD4 cells count (<200/mm^3), and anaemia, confirming data from Sielenou *et al.*, and Alemu *et al.* [15,18]. Moreover, according to Odafe *et al.*, only two of these factors (advanced WHO clinical stages and poor CD4 cells count) predicted early mortality [21], underscoring that late clinic attendance by PLHIV is a considerable impediment to both patient and ART program performance in RLS [20].

Conclusively, the decreasing rates of survivals during the first year of ART suggest increasing defaulters from treatment. A closer follow-up, especially among symptomatic, immunocompromised and anaemic patients would improve adherence and life expectancy, while preventing HIVDR emergence in RLS.

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CONFLICT OF INTEREST

Dr David Anouar KOB YE SAME III benefited from this work to undertake his academic research in partial fulfilment of the requirements for the Master in Public Health at the University of Yaoundé I.

Authors have no other potential conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

Conceived the paper: DAK, ACZ, SCB, JF, JBE; Collected the data: DAK, FMN, NA; Analysed the data: SAM, DAK, YK; Interpreted the data: DAK, ACZ, SCB, JF, JBE; Wrote the manuscript: DAK, SCB, JF, ACZ; Reviewed the manuscript: SCB JBE MTP MNN EFL GEL GB RN JO; Approved the final version: All authors.

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