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Evaluating the Impact of the Universal Test and Treat Strategy on the Survival of Patients in the Northwest Region of Cameroon

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Abstract

Introduction: The main outcome of efficiently implemented universal test and treat (UTT) program is improved survival. UTT implementation has been ongoing in Cameroon since 2016 but evaluation data are scarce. This study aims to assess the survival of antiretroviral therapy (ART) patients initiated under UTT in Northwest region of Cameroon. **Methods**: This retrospective cohort study included HIV-positive patients initiated in 2016 at 27 purposefully selected sites and followed until 2021. Data was anonymously abstracted from ART registers and patients' charts. Kaplan-Meier survival estimates and Cox model were used to compare the survival of patients initiated under UTT with those initiated otherwise, using stata version 14.0. **Results**: In total, 2490 HIV-positive patients (median age 42.7 years, 94.7% adults, and 69.0% female) participated in the study. Of 1389 patients with viral load (VL) test results, 55% were initiated on ART late. The VL suppression rate of patients initiated late and those initiated early were similar. During follow-up, 1020 (40.9%) participants censored. The survival curves of patients initiated early on ART and those initiated late were similar during the first 2.5 years of follow-up but significantly ($p < 0.01$) differed in the subsequent 3.5 years, with patients initiated early having improved survival. Significant predictors of poor survival were initiating treatment late and being a male (AHR: 1.84 (95% CI: 1.13 - 2.99) and 2.12 (95% CI: 1.37 - 3.28)). **Conclusions**: This study confirms the expected impact of UTT. Programs only need to close existing implementation gaps along the critical pathways (diagnosis and treatment) of UTT, focusing more on males.

Keywords

Universal Test and Treat, Viral Load, Survival, Northwest, Cameroon

1. Introduction

A lot of global efforts have been made to control the HIV/AIDS epidemic, yet there were still 1.5 million new HIV infections worldwide in 2022 [1]. Despite an overall 32% decline in new HIV infections since 2010, Africa continue to bear the overwhelming brunt of the infection. An estimated 860,000 new infections (about 57% of the global cases) were recorded in sub-Saharan Africa in 2021 [1]. Even with the declining trends in the number of new infections globally, the number of people living with HIV/AIDS continues to rise. By the end of 2021, there were 38.4 million PLWHA; sub-Saharan Africa bore the majority of this global burden with 25.5 million (67%) cases [1]. Globally, the number of AIDS-related deaths has steadily declined since the peak (1.84 million) in 2004 to an estimated 650,000 in 2021. HIV prevalence in Cameroon has consistently declined from about 5.5% in 2004 to 3.4% in 2018 [2] [3]. The prevalence of HIV among adults age 15 - 49 is 4.3%, with the highest rates seen in the South (7.2%), East (6.3%), and Northwest (6.3%) regions, and the lowest in the Extreme North region (1.2%) [3]. The prevalence among females is nearly twice that for men (5.6% vs. 2.9%) due to high biological susceptibility to HIV infection, socio-economic determinants, and the country's almost (94%) universal circumcision rate [4]. The number of new HIV infections was estimated at 15,000 in 2021, and all people living with HIV were 500,000 [95% CI: 452,860 - 546,866], 78% of whom were receiving antiretroviral therapy (ART) [5]. The aforementioned figures indicate continuous reductions in incidence trends and improvements in the survival of people living with HIV, which are explained by the increasing availability of more effective antiretroviral therapy (ART) and the implementation of efficient HIV care and support services, especially in low and middle income countries [6]. The goal of the universal testing intervention in the test and treat strategy (UTT) studies was to ensure that all persons living with HIV knew their HIV status and were offered ART [7]. Critical pathways to the UTT are accurate diagnosis and early antiretroviral therapy (ART) treatment initiation which based on the several associated benefits were recommended from 2015.

HIV testing is an invaluable entry point to prevention, care, and treatment services for people living with HIV and AIDS [8]. Poor adherence to recommended protocols and guidelines reduces the performance of rapid diagnostic tests, leading to misdiagnosis and poor estimation of HIV seroprevalence [8].

Before the 2015 release of the WHO recommendation for retesting for verification for all people newly and previously diagnosed with HIV before initiating ART, misdiagnosis and inappropriate treatment were reported at various levels

in countries across the world. False-positive diagnoses of HIV among clients already on ART were established to range from 2.6% in Burundi to 10.5% in the Democratic Republic of Congo [9]. It was reported at 0.4% and 0.6% in studies conducted in South Africa and Swaziland [10]. The performance of the HIV testing algorithm was established at 100% sensitivity and 98.3% specificity in a study conducted in Douala, Cameroon. In Cameroon, misdiagnosis was found to be 1.7% in a study carried out in Douala [11] and 0.5% in a study conducted in the Northwest and Southwest regions [12]. The testing algorithm evolved from single to double event testing, under which all newly diagnosed cases are retested for verification by a second tester prior to initiation of antiretroviral therapy (ART) to avoid treating HIV-negative persons unnecessarily [13]. In a study conducted in the Northwest region of Cameroon, it was established that there is over 92% adherence to the double event testing algorithm [14]. When the guidelines are implemented with fidelity and other factors controlled, it is expected that misdiagnosis and inappropriate ART treatment will almost be completely eliminated.

The WHO 2016 second edition guidelines for the use of antiretroviral drugs for treatment and prevention of HIV, recommended that clients who tested HIV positive should be placed on treatment irrespective of disease stage and the CD4 count value [15]. Cameroon adopted this guideline, and the Minister of Public Health issued a circular and held press conferences to promote its implementation [16]. Over the years of implementation of this guideline, early ART initiation has steadily improved from under 50% to over 80%.

The UTT has proven to have a lot of benefits for clients. A multicenter prospective randomized controlled trial conducted in nine countries revealed that early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy [17]. Also, a systematic review and meta-analysis to assess the effect of early initiation of ART among HIV/TB co-infected patients provided conclusive evidence on the reduction of the mortality rate as a result of early initiation of ART [18]. Additionally, other benefits of earlier ART initiation include fewer events of severe HIV morbidity and disease progression, improved uptake and initial linkage to care, better immune recovery, and decreased HIV transmission [19]. The implementation of the UTT has been hindered by individual level factors such as poor understanding of HIV, treatment in an asymptomatic state, and the difficulty of managing the practical demands of ART; interpersonal factors such as living conditions, disclosure to spouses, and spousal involvement, as well as the fear of negative consequences; community-level factors such as stigma; and structural factors such as an inefficient health system, a lack of funding, and a shortage of well-trained healthcare workers [20] [21]. Even when the uptake of UTT is good, other factors such as experiencing side effects to therapy (p-value 0.047, odds ratio = 0.412); understanding reason for taking combination antiretroviral therapy (p-value 0.006, odds ratio = 5.978) and being

reminded to take drugs (p-value 0.006, odds ratio = 0.505) have been found to hinder adherence to ART [22].

The target of the test and treat strategy are improvement of HIV outcomes: increased coverage, improved adherence, decreased the lost to follow up, improved viral suppression, reduced HIV transmission, increased quality of life, and ultimately improved survival [23]. Generally, in the late ART era, the survival of clients has continued to improve, which is an indication of effective implementation of the test and treat strategy. Although the gains among PLWHIV that are associated with the UTT are known, data on this is scarce in Cameroon, despite the technical assistance and institutional support provided by bilateral and multilateral international partners.

This study aims at evaluating the impact of the implementation of the Test and Treat strategy in the Northwest region of Cameroon by comparing the viral suppression rates and survival experiences of ART clients under the UTT and those who received treatment otherwise. Clients under UTT will be PLHIV on ART who were initiated within seven days of HIV diagnosis (early), while those treated otherwise will be ART clients who were initiated on treatment over days of their HIV diagnosis.

2. Methods

2.1. The Study Setting

The Northwest is one of the 10 regions in Cameroon, with an estimated land area of 17,812 km^2 and a population of about two million inhabitants that are predominantly Anglophones. The regions comprise of seven divisions: Bui, Boyo, Donga-Mantung, Menchum, Mezam, Momo, and Ngo-Ketunjia. Bamenda, and 34 sub-divisions [24]. The capital of the region is Bamenda with an urban population of over 550,000 inhabitants. The inhabitants of the region comprise both natives and immigrants from other regions and neighboring Nigeria, with the majority residing in the rural areas. The main economic activities are largely small-scale farming, and livestock, which, together with the public services serve as sources of employment.

There are 20 health districts in the region with 415 health facilities, including one regional hospital, 19 district hospitals, and 395 health centers, comprising a mix of public sector, private not-for-profit (belonging to faith-based organizations), and private for-profit (belonging to individuals) health facilities that operate at various levels. Both the public and private sector health facilities deliver HIV services according to the national guidelines. By mid-2020, there were 296 facilities providing ART treatment in the region, with 153 providing comprehensive HIV services and 143 treating only HIV-infected pregnant women [25].

2.2. Rationale for the Selection of Study Facilities

A total of 27 of the 296 health facilities providing comprehensive HIV to over 90% of the 35,302 ART clients in the region were purposefully included in this

study. The site selection was based on patient load, desired minimum sample size, functional level, diversity of ownership, and location (rural or urban). This ensured the inclusion of a good mix of facilities because of perceived differences that could exist amongst them with regards to staffing, availability of commodities, monitoring and evaluation tools, and compliance with standard operating procedures.

2.3. Study Population

The study population was people living with HIV who were diagnosed and placed on antiretroviral therapy at the selected sites in 2016.

2.4. Sampling Technique

All HIV positive persons who were initiated in 2016 and whose date of HIV diagnosis was documented were included in the study, followed up until 2021, and their outcomes determined.

2.5. Data Collection and Management

The data used to compare the viral load suppression rates of ART clients and to evaluate the impact of the test and treat strategy was abstracted from ART registers and files into designed forms. The data was entered into a customized Excel database, where cleaning was done.

2.6. Data Analysis

The viral load suppression rates of cohorts of clients initiated late on ART (more than seven days after HIV diagnosis) were compared with those initiated early (within seven days of HIV diagnosis) after six years on treatment. The impact of the test and treat strategy was determined by performing survival analysis using the Kaplan-Meier survival estimates to compare the survival of cohorts of clients initiated late on ART with those initiated early over a six-year period and the Cox model to determine factors predicting survival.

2.7. Ethical Considerations

The study received ethical clearance from the Cameroon Baptist Convention Health Services Institutional Review Board (IRB study number: IRB2021-74) and the administrative approval of the Regional Delegation of Public Health for the Northwest Region (Appendices 1 and 2). All data abstracted from registers and patient charts were treated with strict confidentiality. Data entered in software excluded participants' names, dates of birth, and any other personal information to ensure anonymity, and the data was password-protected.

3. Results

The implementation of the test and treat strategy commenced in 2016, and between January and December 2016, a total of 2490 HIV-positive patients (medi-

an age 42.7 years and 69% female), predominantly (94.7%) adults, were enrolled in the study. Most (69.3%) of the participants were either formally or self-employed. The distribution of the study participants by WHO clinical stage declined from 32.5% at stage I down to 3.1% at stage IV. There were 43.2% of the participants who were initiated on ART within seven days of diagnosis (early) and 56.8% who were initiated after seven days of diagnosis (late). Table 1 presents the distribution of the study participants on some key variables by their survival status at the end of the follow up period.

Table 1. Key characteristics of patients enrolled in the study by their survival status.

Characteristic/Level	Alive		Died		Total	
	N = 2379	% = 95.5	N = 111	% = 4.5	N = 2490	%
Sex						
Male	737	93.3%	53	6.7%	790	31.7%
Female	1642	96.6%	58	3.4%	1700	68.3%
Age Group (years)						
<15	123	93.2%	9	6.8%	132	5.3%
15+	2256	95.7%	102	4.3%	2358	94.7%
Employment status						
Employed	1644	95.3%	81	,047	1725	69.3%
Unemployed	735	96.1%	30	3.9%	765	30.7%
WHO clinical stage						
I	785	96.9%	25	3.1%	810	32.5%
II	524	93.9%	34	6.1%	558	22.4%
III	449	94.9%	24	5.1%	473	19.0%
IV	71	95.5%	5	6.5%	76	3.1%
Missing	550	96.0%	23	4.0%	573	23.0%
Time to ART initiation						
Early (within 7 days of diagnosis)	1043	96.9%	33	3.1%	1076	43.2%
Late (beyond 7 days of diagnosis)	1336	94.5%	78	5.5%	1414	56.8%

Of the study participants, 1389 had current viral load test results, most (55%) of whom were initiated on ART late. There was no significant difference in the viral load suppression rate between clients initiated early on ART and those initiated late. Table 2 presents the details of viral suppression rates, comparing clients initiated early with those initiated late.

Table 2. Viral suppression rate by time of ART initiation.

Five Years Outcome	Time to ART Initiation				p-value
	Early		Late		
	N	%	N	%	
Viral load test results available	623	44.9%	766	55.1%	0.315
Virally suppressed	579	44.5%	722	55.5%	
Suppression rate (%)	92.9%		94.3%		

Over the six years follow up period, 111 (4.5%) died while 1020 (40.9%) were censored by either stopping medication for various reasons including lost to follow up and transfer out of the study site to another treatment center. Thirty-three (3%) died amongst the participants who were initiated early on ART, while 78 (6%) of those initiated late died. Only 1359 (54.6%) patients were on treatment by the end of the study. Table 3 presents more details of this information.

Table 3. Outcomes of study participants by the sixth year and by time of ART initiation.

Data Element	Early		Late		All	
	N	%	N	%	N	%
On treatment	615	57%	744	53%	1359	55%
Censored	430	40%	590	42%	1020	41%
Died	33	3%	78	6%	111	5%
Total	1078	100%	1412	100%	2490	100.0%

Kaplan-Meier survival estimates comparing groups of patients over six-year period

The 2490 HIV positive patients who entered the study were followed up until December 2021. Eighty-nine were lost immediately after entry. The median follow-up time for patients who survived was 5.0 years (interquartile range: 2.5 to 5.4 years) and was 2.7 years (interquartile range: 1.6 to 3.6 years) for those that were censored. The follow-up time for patients who initiated ART early was like that of patients who started late: 5.0 years (interquartile range: 2.5 to 5.4 years) versus 4.9 years (interquartile range: 2.3 to 5.4 years) respectively. There seems to have been no difference in the survival curves between patients who were initiated early on ART and those initiated late during the first 2.5 years of follow-up. During the second half (about 3.5 years) of the follow-up period, the survival experience of the patients who were initiated early on ART was significantly better than that of patients initiating treatment late. This was confirmed by the Logrank test, which showed that the two curves were significantly differ-

ent ($p < 0.01$). Figure 1 presents the Kaplan-Meier survival curves that compare clients who were initiated early on ART with those initiated late.

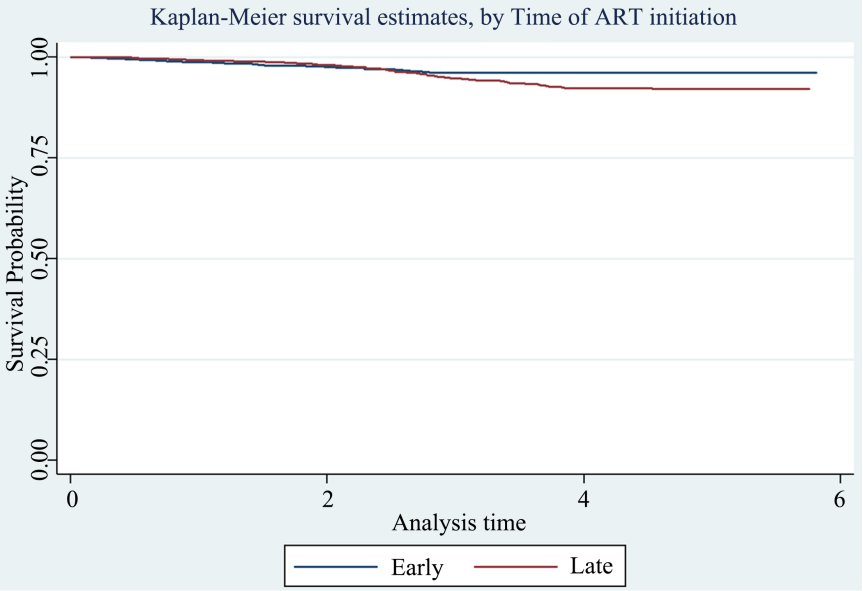

Figure 1. Kaplan-Meier (K-M) survival curves on time from treatment initiation for the groups categorized by early or late start.

As seen in Figure 2, there was no significant difference between the survival experiences of children and adults.

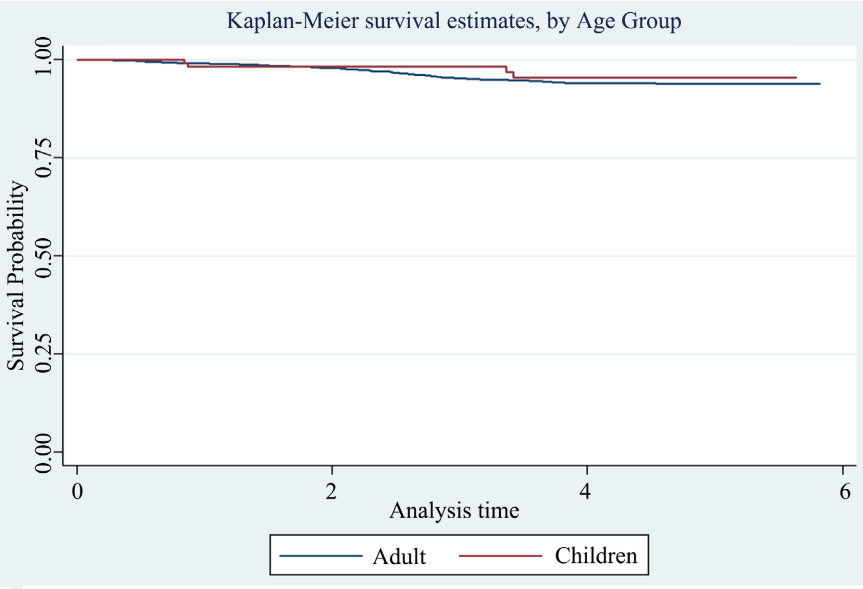

Figure 2. K-M survival curves comparing the survival of children on ART with adults.

Also, comparing the survival experience among children who started treatment early with those that started late (Figure 3), it was observed that there was no significant difference ($p = 0.45$).

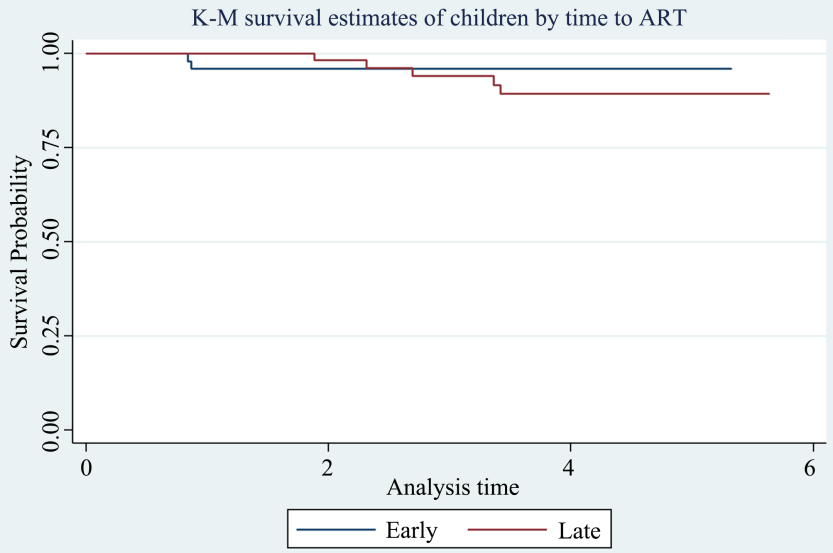

Figure 3. K-M survival estimates comparing the survival of children by time to ART initiation.

Using the Logrank test, there was strong statistical evidence ($p < 0.01$) of a difference in the survival curves of adults comparing those that started ART early with those that started it late. Adult patients starting treatment late were less likely to survive in the second half of the follow up period than patients starting early. **Figure 4** presents the survival estimates comparing adults by the time from diagnosis to ART initiation.

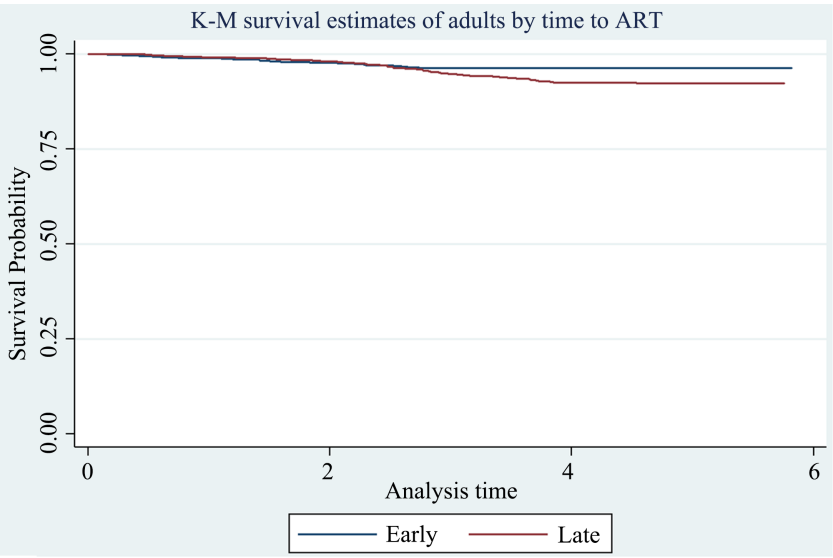

Figure 4. K-M survival estimates comparing the survival of adults by time to ART initiation.

There was strong evidence ($p < 0.01$) of a difference in the survival curves of the patients, when compared by sex, with females more likely to survive than males. **Figure 5** presents this survival comparison.

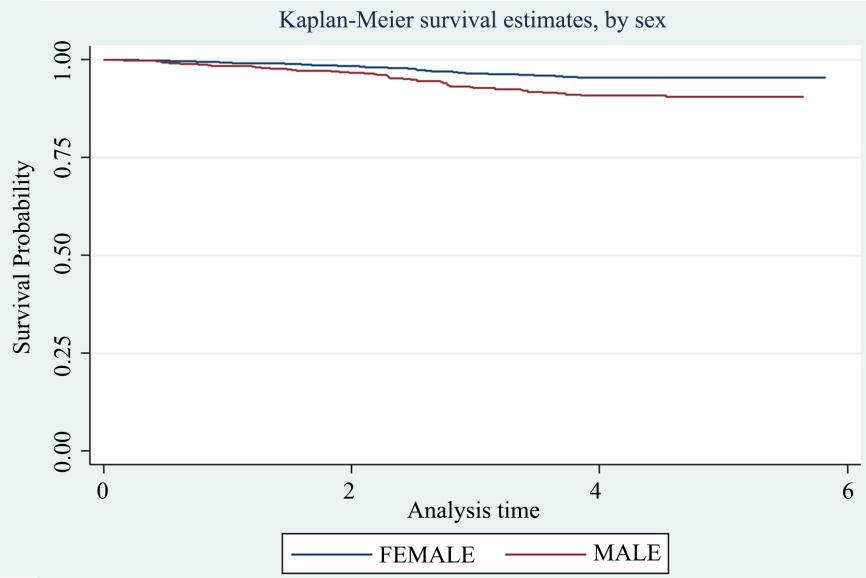

Figure 5. K-M survival estimates comparing survival between male and female.

Survival analysis using Cox regression models

After assessing and ascertaining the attainment of the Cox proportionality assumptions, including hazards for different subjects being constant throughout the entire follow-up time and the correct specification of the linear predictor and link function, univariate Cox regression models were fitted for each of the variables. Results of univariate analyses (**Table 4**) revealed that the explanatory variable sex was highly statistically significant ($p < 0.01$) at the 5% level of significance, while WHO clinical stage II was statistically significant ($p = 0.02$) and there was little departure from significance for stages II and IV. There was about a double fold [1.98 (1.23 - 3.20)] increase in the hazard ratio in patients initiated late on treatment compared with those who were placed on treatment early, meaning delay in treatment doubles the hazard if all other variables are kept constant. There was no evidence of a very small increase in hazard ratio (1.01; 95% CI: 0.99 - 1.02) for a one-year increase in age. Compared with patients who were placed on treatment at WHO clinical stage I, the hazard ratio was 1.89 (1.12 - 3.20) for patients who were initiated on treatment at WHO clinical stage II, 1.72 (0.97 - 3.06) for those who were at stage III, and 2.27 (0.87 - 5.93) for those at stage IV.

Variables that were statistically significant (Wald test) at 5% level in the univariable analysis were considered in the subsequent analysis. However, considering the high confounding potential of age, it was considered in the multivariable model, although it was not significant in the univariable analysis. A multivariate Cox regression model was fitted for all potential prognostic variables and verified for goodness of fit using the proportional hazards test. The final multivariate model included the following factors: time to ART initiation, age, sex, and WHO clinical stage. After mutually adjusting the factors in the multivariate model, the hazard ratios decreased for time to ART initiation, age, sex, and

WHO clinical stages. This suggests some mutually negative confounding effect on each of these variables. The adjusted hazard ratio was 1.84 (95% CI: 1.13 - 2.99; p = 0.01) for patients who were initiated late on treatment, 2.12 (95% CI: 1.37 - 3.28; p < 0.01) for males and 1.63 (95% CI: 0.96 - 2.76; p = 0.07) for patients at WHO clinical stage II, 1.31 (95% CI: 0.73 - 2.36, p = 0.36) for WHO clinical stage III patients, and 1.65 (95% CI: 0.63 - 4.37; p = 0.31) for patients at WHO clinical stage IV. Table 5 presents the results of the multivariable analysis.

Table 4. Hazard ratio estimates from univariate analysis.

Variable	Categories/units	CHR^	(95%CI)	p*
Time to ART initiation	Early	1		
	Late	1.98	(1.23 - 3.20)	0.05
Age	Years	1.01	(0.99 - 1.02)	0.29
Sex	Female	1		
	Male	2.27	(1.48 - 3.48)	<0.01
Employment status	Employed	1		
	Unemployed	0.76	(0.45 - 1.26)	0.28
WHO clinical stage	I	1		
	II	1.89	(1.12 - 3.20)	0.02
	III	1.72	(0.97 - 3.06)	0.06
	IV	2.27	(0.87 - 5.93)	0.09

CHR = Crude Hazard Ratio, *: Wald test.

Table 5. Multivariable and mutually adjusted hazard ratio estimates.

Variable	Units/Category	AHR	AHR (95% CI)	p*
Time to ART initiation	Early	1		
	Late	1.84	(1.13 - 2.99)	0.01
Age	Years	1.00	(0.98 - 1.02)	0.69
Sex	Female	1		
	Male	2.12	(1.37 - 3.28)	<0.01
WHO clinical stage	I	1		
	II	1.63	(0.96 - 2.76)	0.07
	III	1.31	(0.73 - 2.36)	0.36
	IV	1.65	(0.63 - 4.37)	0.31

AHR = Adjusted Hazard Ratio, *: Wald test.

4. Discussion

Our study found out that 5% of all patients died by the end of the sixth year which is much lower than the 13.1% and 10.3% death rates that were registered

after the fifth and fourth year respectively in a study that was conducted to estimate the survival of antiretroviral therapy patients at the outpatient treatment centre of the Community University Hospital of Bangui from 2015 to 2020 [26] and another study on mortality of HIV-infected patients on antiretroviral therapy in a Large public cohort in Burkina Faso [27]. In this study, we found out that there was no significant difference at sixth year viral suppression of patients who were initiated early on ART and those that were started late: 92.9% versus 94.3%. In another study carried out among children in Cameroon, viral suppression after five years of ART was estimated at 64.0% (54.0 - 74.0) with the only factor associated with it being the achievement of confirmed virological success within the first two years of ART (OR = 2.7 (1.1 - 6.8); p = 0.033) [28]. Most studies have investigated viral suppression in the short term but not at a long term and their findings are not consistent with those of this study. A study conducted in Thailand established that early ART initiation had a higher significant proportion of HIV viral load suppression at twelve months compared with late start (81.0% vs. 70.1%, p = 0.041) [29]. The findings of our study were similar to those obtained in a study carried out in South Africa that found no evidence of lower rates of viral suppression one year after starting ART between the arms [30] [31]. The lack of a difference in viral load suppression rates between early and late ART initiators could be because there are higher death and censoring rates among those initiating ART late and these are the individuals that are likely to have been unsuppressed and would have pulled down the suppression rate among those that initiated ART late.

Our study found that there seems to be no difference in the survival curves between patients who were initiated early on ART and those who started it late during the first 2.5 years of the follow-up but during the following 3.5 years of the follow-up period, the survival experience of the patients who were initiated early on ART was significantly (Logrank test: $p < 0.01$) better than that of patients initiating treatment late. The mutually adjusted hazard ratio was 1.84 (95% CI: 1.13 - 2.99; $p = 0.01$) for patients who were initiated late on treatment, 2.12 (95% CI: 1.37 - 3.28; $p < 0.01$) for males and 1.63 (95% CI: 0.96 - 2.76; $p = 0.07$) for patients at WHO clinical stage II, 1.31 (95% CI: 0.73 - 2.36, $p = 0.36$) for WHO clinical stage III patients and 1.65 (95% CI: 0.63 - 4.37; $p = 0.31$) for patients at WHO clinical stage IV. These findings are inherent to those of a study conducted among ART patients in Kombolcha Town that established fair drug adherence (AHR = 6.88, 95% CI: 4.31 - 24.04), Poor drug adherence (AHR = 9.58, 95% CI: 8.72 - 30.97), CD4 count < 50 cell/μL (AHR = 9.38, 95% CI: 1.48 - 59.31), CD4 count 50 - 99 cell/μL (AHR = 9.67, 95% CI: 1.80 - 51.73), bedridden (AHR = 9.5, 95% CI: 4.49 - 18.66), opportunistic infections (AHR = 4.58, 95% CI: 1.20 - 5.65), weight < 60 kg (AHR = 2.48, 95% CI: 1.59, 10.38), WHO stage III (AHR = 3.56, 95% CI: 1.71 - 17.89), WHO stage IV (AHR = 4.42, 95% CI: 1.75 - 25.93) as predictors of poor survival time [31]. Similarly, our study findings are inherent in those of a trial conducted at Eswatini, which established that UTT reduced HIV disease progression overall and was not detrimental for cli-

ents with more severe HIV [32]. Also, the findings of this study are consistent with those of an Ethiopian study, which showed that mortality among HIV patients on treatment decreased significantly since the start of the test and treat strategy and that patients under this treatment strategy had a higher survival probability throughout the follow-up period than those not in it [33].

5. Limitations

This study is retrospective in design and not all the desired data was available for collection due to poor documentation, incomplete data and absence of data of some key variables. A prospective design of the study will lead to more comprehensive findings that will best inform programming. Some of the missing data was due to individual client and health system challenges including non-compliance to appointment schedules, stock out of commodities, breakdown of machines and inadequate work force or untrained personnel in some cases. This study had confirmed improved survival with early ART initiation meaning focusing and strengthening this aspect, we will only have to ensure stringent implementation of processes and strategies of compliance to appoints and proper documentation of compressive data. The evaluation of the impact of the universal test and treat strategy on the survival of patients used the time from HIV diagnosis to ART initiation as the base to compare survival. However, there are likely to be major differences in the time of HIV infection of the participants, introducing significant differences in the time from HIV infection to diagnosis and many factors are playing during this time interval with the likelihood of influencing their survival even after ART initiation.

6. Conclusion

Results from this study have revealed that there is no difference in the viral load suppression rate of clients initiated early on ART compared with those initiated late in the Northwest Region of Cameroon. There was strong evidence that early ART initiation improves survival, with females having improved survival over males. Strengthening the processes of the universal test and treat strategy will ensure that the right people are initiated early on ART and will remain in it thus leading to an improved survival experience.

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Conflicts of Interest

The authors hereby declare that they have no conflicts of interest.

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