Application of Semi-Markov Process For Model Incremental Change in HIV Staging with Cost Effect

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Abstract: In the recent past, both non-parametric and parametric approaches have consistently been used to model cost effectiveness in a variety of health applications. This study applies the semi-Markov model while presenting the sojourn time with well-defined probability distributions. We employed the Weibull distribution to model the hazard function for each of the defined transition paths. We defined three distinct states of the semi-Markov process using the quantity of HIV virus in the blood of an HIV-infected person i.e., viral load (VL) copies in a milliliter (copies/mL). The three states were defined; VL < 200 copies/mL, 200 copies/mL < VL < 1,000 copies/mL, VL > 1,000 copies/mL and an absorbing state which is naturally death. We also developed a cumulative cost function, purposely to determine the average estimated cost per patient in each of the defined states. Incremental Cost Effectiveness Ratio (ICER) was utilized in the analysis of cost-effectiveness while comparing two program strategies i.e., Patients under the differentiated care model (DCM) and those who are not considered to be in any model of differentiated care during their respective ongoing clinical follow up. Results show the mean cost of the patients for each state 1, 2, and 3 was $765, $ 829, and $ 1,395 respectively. More so, the computed ICER ratio was $ 484/life-year-saved. In conclusion, the cost of keeping patients in state 1 (on DCM) was relatively cheaper and more efficient compared to the other states.

Keyword: HIV, Semi-Markov, Cost-effectiveness, Sojourn time, Viral load.

1. BACKGROUND

There has been a significant reduction of HIV/AIDs infection in the region within and around Sub-Saharan Africa (SSA) in the recent past, with slightly over 30% lower incidence rates [1]. The reduction is attributed to the global effort which largely targeted the regions that account for nearly 70% of persons living with HIV (PLHIV) [2, 3]. Kenya in particular has benefited from these efforts. The milestones achieved in reducing HIV/AIDs infections can be attributed to various programmatic strategies that are geared toward monitoring and enhancing the standard of life of people living with HIV. With these reductions, funding and investments in HIV support have dwindled. This has led to sustainability initiatives that warranted cost implications [4].

In this study, we revisit the application of semi-Markov processes in an attempt to model incremental change in HIV staging with a cost effect. This is designed to quantify the cost of keeping a patient in any of the HIV/AIDs stages. Utilization of semi-Markov chain models to account for competing risks (informative censoring), report censored data, numerous outcomes, repetitive outcomes, non-constant survival probabilities, and frailty [5, 6] provides an appropriate choice for this selection. Further, the clinical data used for this work was prone to right censoring hence semi-Markov models became appropriate for the analysis. The stochastic approach here describes the transition of individuals with a finite number of the defined state at a given time [5]. The possible movements between stages are represented with a state diagram. For this work, the death state is considered the absorbing state. The semi-Markov models considered here, intricately enable us to compute both probabilities and the rates of movement that are associated with each distinct transition between states in a single observed iteration as well as the estimated number of iterations spent in a given state. Naturally, the time spent in all states until eventual absorption is added to estimate the overall survival time. More so, the model is designed to incorporate analysis of multiple defined events simultaneously. Within the same framework, we are also able to include competing for risks within the states of the model, as well as consider individual associated frailty within subject-specific random effects [5, 7, 8].

Intrinsically, transitions can take place at any given time, and also considering that multiple unobserved transitions can take place between iterative assessments. Different authors have proposed different approaches i.e., half-iteration correction, where transitions are assumed to occur in the middle of a given observation iteration [9], have been proposed to reduce biases that results from the assumption that transitions can only take place at the start or the end an iteration. In this setting a semi-Markov model is considered a special case of the Markov chain with the following characteristics i.e., the time spent in the state of interest depends on both the prior and future adjoining states. This can also accommodate time-to-event interval-censored data [6, 10]. The stages of the semi-Markov process were determined by the level of VL. Here, we consider four different distinct customed states i.e.; VL < 200 copies/mL, 200

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copies/mL < VL < 1,000 copies/mL, VL > 1,000 copies/mL and an absorbing state which is naturally death. The Figure **1** below shows the four different states that were used. To define the model, an arrow will be attached to the diagram to show the probability of the transition and the waiting time it takes for a successful transition to occur.

We assume the waiting time at each phase matches the probability distribution that relies on both the current state and the entry state. The main cause of premature deaths in the limited resource setting remains to be HIV/AIDs despite the many HIV management kinds of research done [1]. According to UNAIDS report [11], Kenya has significantly improved in responding to this deadly disease to a prevalence below 5%. This achievement has led to dwindling financial aid in support of HIV programs from global donors, causing challenges in the sustainability of Kenya's HIV response [4]. Health policymakers are now faced with the challenge of efficient resource allocation to take care of HIV prevention, care, and treatment service interventions. Furthermore, operational program development and refinement of work plans that effectively reduce the cost of running HIV programs remain a problem in the limited resource setting [12]. For all the reasons mentioned above and more, it is essential to analyze and understand the cost and cost-effectiveness of keeping patients within the WHO staging in the resource-limited setting.

The main objective of this study is to use semi-Markov models in determining the incremental cost-effectiveness of keeping patients on World Health Organization (WHO)- state one versus higher staging on a DCM in a resource-limited setting. We also assessed the average total cost per state and the cumulative cost of each health state by combining the semi-Markov modeling process and the regression approach.

In the next section (section 2), we focus on the methodology and revisit the modeling framework including the distribution of sojourn time, modeling both the average cost and the cumulative costs in each state, and assessing the incremental cost-effectiveness using ICER. In section 3 we cover the overall results. Finally, in section 4, we discuss the overall results and provide the study's concluding remarks.

2. METHODOLOGY

2.1. The Modeling Framework

Suppose S is a discrete stage space and each patient is observed for some time t for h successive stages. That is $X = \{X_0, X_1, \cdots, X_h\}$, where the initial and final stages are denoted by X_0 and X_h respectively. Assuming $X \in S$ and the number of possible stages to be finite, the process $X = X_h$; $h \geq 0$ is considered to be a semi-Markov chain with h transitions [13]. In this case, the entry times sequence T_n for each stage X_h after h transitions is described as s sequence $\boldsymbol{T} = (T_0, T_1, \cdots, T_h)$, where the initial point T_0=0. Consider the transition probabilities from a given defined state to another i.e., $(i \rightarrow j)$, to be represented as $P_{ij} = P(X_{h+1} = j | X_h = i)$ and is homogeneous since P_{ij} doesn't depend on t. The conditional distribution function $G_{ij}(t) = P(T_{h+1} - T_h \leq t | X_{h+1} = j, X_h = i)$ *defines* the sojourn time between two stage (i, j).

2.2. Distribution of Sojourn Times

The transition probability of a given patient on HIV care from one state to another relies on how much time he/she spends in that state [14]. Supposing the sojourn time for a patient is random and follows a given distribution $G_{ij}(t)$, the following waiting time distributions will be considered in modeling and accessing the best distribution that describes the HIV/AIDs patients' progression.

Exponential Distribution: The hazard function under exponential distribution is constant for a Markovian case [15]. The distribution is defined by $G_{ij}(t) = 1 - exp(\lambda_{ij}), t \geq 0$ where, $\lambda_{ij} = \frac{1}{\sigma_{ij}}$ and $\sigma_{ij} > 0$. λ_{ij} is the expected time that a patient stays in a specific stage X_h before transiting to stage j from stage i. The hazard

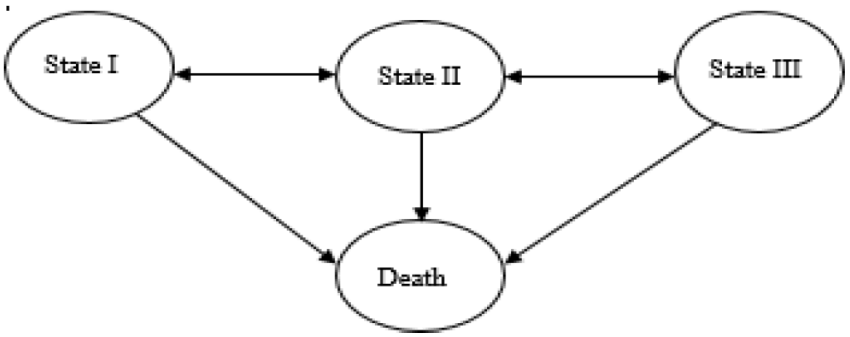

Figure 1:

function of the exponential distribution is given by $\lambda_{ij} = \frac{1}{\sigma_{ij}}$, $\forall X \geq 0$ *and* $\sigma_{ij}\, j > 0$.

Weibull Distribution: The Weibull distribution sojourn time is given by; $G_{ij}(t) = 1 - exp(-\lambda_{ij}\, t^{V}ij\,)$, $t \geq 0$. Weibull distribution generalizes the exponential distribution and is highly used in modeling clinical progression because of its flexibility in nature [13, 15]. A Weibull distribution with two parameters $\{\sigma_{ij}, V_{ij}\}$ to take care of various shapes for monotone hazards. The Weibull distribution hazard function is defined as

$$\lambda_{ij}(x) = V_{ij}\left(\frac{1}{\sigma_{ij}}\right)^{v_{ij}} X^{v_{ij}-1}, X \geq 0.$$

2.3. Average and Cumulative Costs at each State

We used a regression approach according to Liu [16], to model the average cost in each state. The average time consumed in each state is distributed into k_h intervals and a regression model was constructed for each interval. Assuming $Y = (0, \tau]$ is the time of interest. Y is divided into K_h intervals such that $y_k = (a^h, a^h]$. The regression equation takes the form;

$$C_{k,i}^{h} = \alpha_0 + \alpha_1 Z_1 + \alpha_2 Z_2 + \cdots + \alpha_p Z_p \qquad (2.3)$$

Where C^h is the cost of patient *I* that was observed, z_i are covariates in state *h* in interval *k* and α_i are the corresponding co-efficiencies of the covariates. Equation 2.3 can be reduced to;

$$C_{k,i}^{h} = \alpha^{h} Z_i; \qquad i = 1, 2, \cdots, N\ ;\ h = 1, \cdots, H \qquad (2.4)$$

where;

α^h refers to a vector of unknown regression parameters within the interval *k* in the state,

Z_i is a vector of covariates, and i and h are several patients and health stages respectively. If a patient *i* within the interval *k* has no cost record, then $C^h = 0$. Taking the expectation of observed cost above (2.4); $E\left(C_{k,i}^{h}\right) = E(\alpha^h Z_i)$,

$$\hat{C}_{k,i}^{h} = \hat{\alpha}^h Z_i$$

where $\hat{\alpha}^h$ is the estimator of α^h and is defined as;

$$\hat{\alpha}^h = (\mathbf{Z}\mathbf{Z}^{J})^{-1}\mathbf{Z}^{J}\mathbf{C}^h$$

where $\mathbf{Z}$ is an $p \times N$ matrix of covariates $z_1, \cdots, z_N$ and $\mathbf{C}^h$ is the $N \times 1$ vector of the given costs $C^h, \cdots, C^h$ that have been observed. Using U^h to denote the total time spent by a patient *i* in state *h*, the cumulated cost function at time *t* of patient *i* is described as;

$$C_i^h(t) = \sum_{\forall k(\alpha_k^h \leq U_k^h;\, \alpha_k^h \leq t \leq \alpha_{k+1}^h)} \hat{C}_{k,i}^{h} + \hat{C}_{k+1,i}^{h}\left[\frac{U_k^h - \alpha_k^h}{\alpha_{k+1}^h - \alpha_k^h}\right]$$

The cumulative cost functions obtained are equivalent to the number of the heath stage (*H*) present.

To validate the best Markov model that describes the real data set we used the Akaike information criterion (AIC) for comparison between the above-discussed sojourn time distributions. According to Porte [17], the lower the AIC value the better the model.

2.4. Evaluating the Incremental Cost-Effectiveness using ICER

In this context, we employ cost-effectiveness analysis to evaluate the costs and related health outcomes [18, 19]. Results are expected to provide important critical information ranging from programs, policies, and clinical, epidemiologic, and economic benchmarks to strengthen health-related interventions. In assessing the incremental cost of patients on DCM and those who were not on DCM, we used the incremental cost-effectiveness ratio [20]. Mathematically it is defined as;

$$ICER = \frac{\bar{C}_{intervention} - \bar{C}_{control}}{\bar{E}_{intervention} - \bar{E}_{control}}$$

where $\bar{C}$ and $\bar{E}$ represent the average costs and average time levels, respectively.

3. RESULTS

3.1. Data Definition and Description

Routine follow-up of PLHIV remains a pillar for nibble HIV service delivery programs. To retrospectively evaluate modalities, results, and costs of HIV/AIDS patient follow-up, we studied clinical data from the record of 738 patients obtained from 9 facilities namely Kiambu District Hospital, Ruiru Sub-District Hospital, Karuri Sub-District Hospital, Thika Level V Hospital, Kiandutu Health center, Wangige Sub District Hospital, Gatundu District Hospital, Igegania Sub-District Hospital, and Limuru Health Center. The available characteristics for each patient were Patient Id, and State.i, State.j time, Viral load, DCM (1=Patients on DCM, 2=Patients not on DCM), Age, Gender (1-male, 2- female), and facility location. Table **1** describes the percentage of patients in the study together with their respective characteristics. The mean costs for state I, State II and State III were about \$765, \$829 and \$1395 respectively.

3.2. Semi-Markov Setting

We consider a discrete stochastic process $\{X_t : t \in T\}$ that can move to states {1, 2, 3, 4}. The process

Table 1: Distribution of Patients according to their Characteristics

	DCM follow up (Percent)-1	No follow-up (percent)-2
Sex		
1	240 (0.52)	253 (0.52)
2	226 (0.48)	232 (0.48)
Tb-coinfection		
1	66 (0.13)	33 (0.07)
2	452 (0.87)	472 (0.93)
Facility location		
1	20 (0.03)	26 (0.04)
2	20 (0.03)	27 (0.04)
3	36 (0.05)	25 (0.04)
4	137 (0.2)	11 (0.02)
5	189 (0.27)	73 (0.11)
6	146 (0.21)	140 (0.21)
7	73 (0.11)	213 (0.32)
8	42 (0.06)	108 (0.16)
9	32 (0.05)	37 (0.06)
N (percent)	465 (0.49)	485(0.51)

typically begins in say state 1 and remains there for a random duration with mean μ_1, then it goes to another state i.e., 2 where it remains for a random duration with mean μ_2, then back to any of the states, and so on. The process can eventually end in state 4 (Absorption state). We consider a complete cycle whenever the process returns to say state 1. This is typically an extension of Markov processes where we remove the restriction of Markovian property and introduce the sojourn times of states.

Formally, we let the process $\{X_t: t \in T\}$ be a homogeneous Markov chain $\{X_n\} n \geq 0\}$ on states {1, 2…, *n*} where p_{ij} is the probability of *i*th ($i \geq 1$) jump from state *i* to state *j* for $i \neq j$. That is,

$$p_{ij} = P(X_n = j | X_{n-1} = i).$$

A state can either be absorbing or transient i.e.

$$\sum_{i \neq j} p_{ij} = \begin{cases} 1 \; absorbing \; state \\ 0 \; transcient \; state \end{cases}$$

The process $\{X_t: t \in T\}$ is called a semi-Markov process on the condition that, if the process enters state *i*, the next state is *j* with probability p_{ij} and given that the next state that will be entered is *j*, the duration until the transition from *i* to *j* is a random variable with cumulative distribution function $\Omega_{ij}(t)$:

$$\Omega_{ij}(t) = P(\tau_n \leq t | X_{n-1} = i, X_n = j), t \geq 0, \quad t \geq 0 ,$$

where $\tau_n = T_n - T_{n-1}$,

The process $\{X_t: t \in T\}$ therefore does not posses the Markovian property.

The objective of this study is to study the transition of patients in four different states as defined by their VL. Three states are defined (Figure **2**): 'stage 1, 'stage 2', and 'stage 3. Note that the stage 'dead' is absorbing because the probability to move out of this stage is null. Table **2** describes the frequency of the transitions. To get the most promising model, the data set was subjected to two distributions (Weibull and Exponential) and their AIC examined.

3.3. Cost

In this section, we assessed the mean costs. All treatment costs available for each patient were included. The mean cost per patient is assessed according to the method previously presented. A regression model is thus performed in this study. This helped in dropping all non-informative covariates and selecting those covariates that seemed to affect the mean cost. This was done by forwarding model selection. For convenience, the selected covariates were the same in each interval. To choose these covariates we plotted the cumulated costs according to the characteristics of patients observed in the database (Figure **2**) Costs seem to be different for each level of covariate 'TB-co-infection', 'Follow-up (DCM)', and 'stage' and very close for sex and location facility.

Table 2: Frequency of Transitions and Summaries of the Sojourn Times

Transition	*n*	per cent	Sojourn times				
			Min	Max	Mean	Median	Std. dev
Transition 1 → censoring*	303	16.38	0.10	7.64	4.37	5.10	2.60
Transition 1 → 2	190	10.27	0.10	5.98	0.83	0.39	5.98
Transition 1 → 3	87	4.70	0.10	3.03	0.72	0.34	0.80
Transition 2 → 1	223	12.05	0.10	4.90	0.54	0.30	0.71
Transition 2 → 3	142	7.68	0.12	4.39	0.82	0.46	0.89
Transition 2 → censoring*	232	12.54	0.00	7.64	3.92	3.41	2.63
Transition 3 → 1	230	12.43	0.07	1.93	0.34	0.25	0.28
Transition 3 → 2	240	12.97	0.10	5.28	0.67	0.32	0.91
Transition 3 → censoring*	203	10.97	0.07	7.64	3.72	3.09	2.10
Total	1850	100					

Table 3: Estimates of Semi-Markov Parameters for Exponential and Weibull Distributions and the Significant Effects from the Set of Three Covariates

Model	Transition	Distribution	DCM	sd	Age	sd.1	Gender	sd.2	pij
Weibull	1–>2	Weibull	24.80	0.01	-1.06	0.02	0.14	0.16	0.59
Weibull	1–>3	Weibull	9.59	0.02	-0.84	0.01	0.14	0.04	0.41
Weibull	2–>1	Weibull	-0.92	0.01	-1.23	0.06	0.09	0.13	0.66
Weibull	2–>3	Weibull	10.20	0.02	-0.88	0.01	-0.07	0.02	0.34
Weibull	3–>1	Weibull	78.10	0.03	-4.84	0.00	0.09	0.13	0.37
Weibull	3–>2	Weibull	13.00	0.01	-1.15	0.01	-0.09	0.13	0.63
Exponential	1–>2	Exp	6.21	0.02	-0.35	0.01	0.05	0.13	0.62
Exponential	1–>3	Exp	4.53	0.02	-0.45	0.02	-0.15	0.21	0.38
Exponential	2–>1	Exp	-1.80	0.01	-0.17	0.01	0.48	0.11	0.65
Exponential	2–>3	Exp	3.60	0.04	-0.34	0.02	0.00	0.15	0.35
Exponential	3–>1	Exp	13.40	0.00	-0.82	0.01	0.06	0.13	0.37
Exponential	3–>2	Exp	4.77	0.02	-0.48	0.01	-0.00	0.11	0.63

Table 4: Measure of the Best Model

Model	AIC	Complexity
Weibull	717.44	33
Exponential	2395.17	27

Results show, there is no significant difference regarding the location cost and sex. Further, apart from the graphical analysis, we performed a regression model to estimate the total cost of the three stages for all patients. We used the least-square technique to estimate the regression parameters ($\hat{\alpha}_C$). Results are shown in the Table **5** below.

A plot of the cumulative functions obtained with the $\hat{\alpha}_k$ is shown in Figure **3** below. The DCM follow-up only applied for patients in stage 1 as stages 2 and 3 were considered critical hence close medical care. Notably, from the graph, the incremental cumulative cost for patients in stage 1 (in DCM) was significantly lower compared to the other stages (not in DCM). Though the differences in cumulative cost for patients was significant, the cumulative cost for the three stages had an increasing trend over time. Using the ICER equation presented in the methodology the incremental cost was about $483.83.

4. DISCUSSIONS

The main objective of the study was to use semi-Markov models in determining the incremental cost-effectiveness of keeping patients on WHO- state one versus higher staging while incorporating

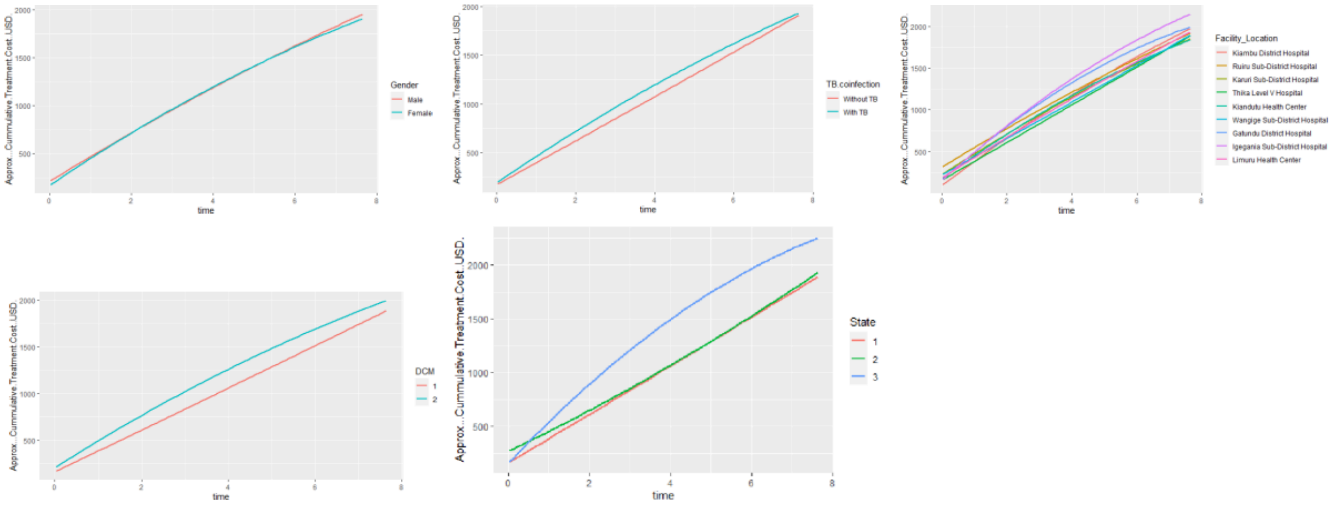

Figure 2: Cumulative costs of patients staying alive at time t according to their co-variates.

Table 5: Results of the Regression Model on Total Costs for all Patients within the Three Stages

	Cumulative total cost		
	□(*Pr*(> |*t*|)) Covariates		
	stage 1	**stage 2**	**stage 3**
Intercept	-633.895 (0.00)	-662.779 (0.00)	-918.843 (0.00)
DCM	-147.369 (0.00)	-92.315 (0.00)	-93.2921 (0.00)
Age	66.0635 (0.00)	64.4413 (0.00)	81.3969 (0.00)
Gender	4.20326 (0.00)	6.4529 (0.24)	10.6762 (0.15)

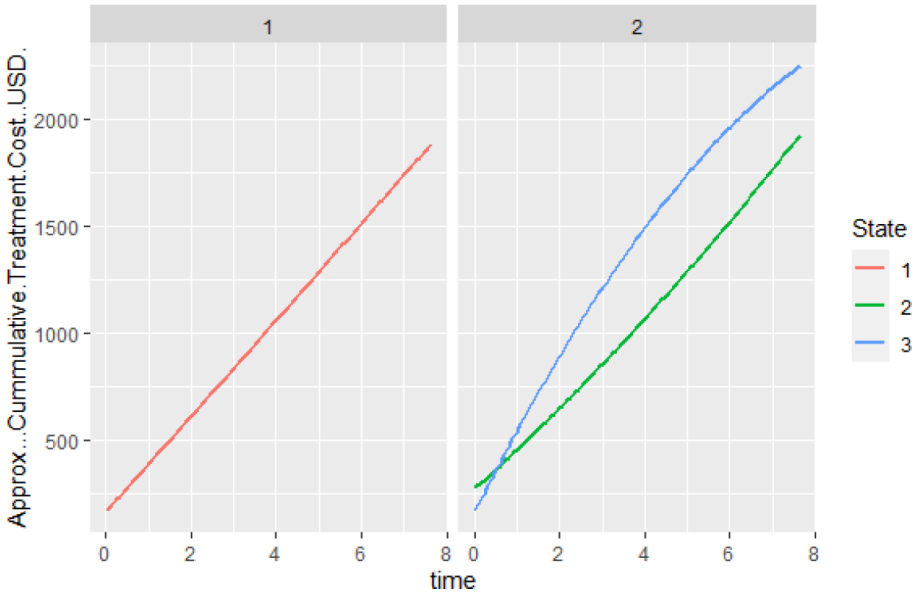

Figure 3: Cumulative costs function or DCM according to patient profiles.

Differentiated Care Model within resource-limited setting. We also analyzed the mean total cost per state and the cumulative cost of each health state by combining the semi-Markov modeling process and the regression model. This is an important attempt designed to enable policymakers to efficiently allocate resources among a spectrum of HIV services. In theory, the study demonstrates the use of the semi-Markov approach to assessing HIV/AIDS state cost-effectiveness while taking to account inter-state comparison.

Understanding the cost-effectiveness of the HIV/AIDS program remains critical due to the decrease in global HIV prevalence level which has eventually resulted in diminished donor funding. The semi-Markov

process considered here provides for flexible modeling of hazard functions [21-23]. We used both exponential and Weibull distributions to fit the data and compared it with Akaike Information Criteria (AIC) [28]. Weibull distributions performed better compared to the Exponential distribution. We consequently used Weibull to model the sojourn times. More so, we were able to successfully link the costs and states in this setting. We used a combination of semi-Markov and regression models to analyze the average cost depending on the state. On average the mean cost of managing individuals in state I, State II, and State III are $765, $829 and $1395 respectively. From the cumulative cost plots, the incremental cost of stage one is relatively lower compared to state II and State III. This difference is attributed to the differentiated care model (DCM) strategy during follow-up. In this study, we have shown that it is relatively cheap to keep a patient in the state I compared to II and III.

The cost-effectiveness analysis of DCM shows that putting patients on DCM is not only cheap but also more effective compared to treating patients, not on DCM. Results from this study indicate that the average cost for the interventions group (individuals not in DCM) was $213.3806 with an increase in time of 0.4410. Based on this, the ICER was $483.8268 for any additional time. Notably from Table **5**, the patients' cumulative cost within any stage is influenced by, age and a follow-up strategy. Gender was found not to be statistically significant in influencing the total cost within a stage. Literature shows, health care spending is an increasingly important economic and political issue [24]. The purpose of conducting incremental multi-stage cost research is to allow clinicians and policymakers to make more rational decisions regarding clinical care and resource allocation, especially in resource-limited areas. Incremental multi-stage cost analysis would significantly contribute to assessing the value of new medical strategies, by simultaneously examining incremental health benefits in light of incremental costs.

Lin *et al*. [25] pioneered a non-parametric method for estimating medical costs from incomplete follow-up data. The main principle of this methodology was to divide the entire period of interest into several intervals and then estimate the average total cost by the sum of the Kaplan-Meier estimator for the probability of dying in each time interval multiplied by the sample mean of the total costs from those who are observed to die in that interval. This method is limited due to its assumption of independent censoring.

Comparison of the performance of several broad approaches of modeling cost analysis i.e. typical linear models, a linear model with log-transformed cost, generalized linear models (GLMs), median regression, and proportional hazards models [26] reveal the demand to get an appropriate model has increased. Both survival and cost data are commonly censored; therefore, methods presented by Austin et al [26] were limited in that they could not account for censored data. This is, however, mitigated in our study.

Willan *et al*. [20] presented two different models i.e., for cost and survival data which utilizes the inverse probability of censoring weighted (IPCW) method to account for censored data and also address the covariance structure between survival and cost. The weak point of the piece of work presented by Willan *et al*. [20], however, is that regression assumption are not well suited for time-to-event data.

Recently, Liu *et al*. [16] proposed a shared random effects model for monthly medical costs and survival time. This model would account for the correlation between survival time and monthly medical costs.

The above-reviewed methods do not account for the whole clinical evolution of the disease in survival analysis. The literature presents several methods which would work well in studying the whole clinical evolution of the disease in survival analysis. Markov models are particularly useful when a decision probably involves a risk that is ongoing over time [9]. The decision trees are best used in performing cost-effective analysis [9]. They presented discrete time Markov Models for medical decision-making. The model eases the ability to describe all the patient's trajectories, which are applied with fixed transition rates computed from previous information.

Gardiner *et al*. [23, 27] presented a stochastic model for statistical inference in cost-effectiveness analysis. Multi-state models in this case fitted to data together with cost-effective analyses. A multi-state model (Markov model) and a regression method for estimating changes in health status and costs also fit well and are similar to our findings.

In most countries, policymakers and a variety of stakeholders use cost-effectiveness analyses in an attempt to understand effective interventions that provide the best value for money [19]. More so, also provide important critical information that can be of great value. Cost data are mostly skewed, with long-tailed distribution and so the assumption of normality for the cost distributions in the cost model presented, might not always apply. Additionally, it is not verifiable that the different intervals were independent. This approach can also be extended to scenarios where interventions that could affect cost were part of the study. Lastly, additional distributions like gamma

and log-normal could be considered in choosing the best sojourn time distribution.

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