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ORIGINAL RESEARCH ARTICLE

Continuous Time Semi-Markov Model to Optimise the Efficacy of World Health Organization HIV- naïves Staging Criterion in Nigeria

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ABSTRACT
Continuous Time semi-Markov model to study the transition among the various categorised HIV/AIDs stages has been presented in this paper. The model was used to appraise the staging of HIV- infected clients reported at General Hospital Minna, Niger State, Nigeria, for 10 years. The result indicated no transition from the asymptomatic stage of HIV to late/advanced AIDs $\varphi_{14}(n)=0$. However, transition occurs among the other stages due to the presence of Opportunistic Infections (OIs), which translate to gradual increment in the graphs of interval transition probabilities for all $n \in N$. Specifically, this study shows some increase in the transition probability from stages 2, 3 and 4 to stage 1 from about 0.081718, 0.011421 and 0.003908 in the first month to about 0.331054, 0.189427 and 0.061666 in the fifty months $n=50$. The graph derived from virtual transition probabilities shows the gradual monotone decrease after fifty (50) months. The result indicates that $\phi_{11}(n), \phi_{22}(n), \phi_{33}(n)$ and $\phi_{44}(n)$ attained the values of about 0.778442, 0.490655, 0.504554, and 0.614515 for the first few months. In fifty months, the percentage decrease is about 33.1%, 18.9%, and 6.1% for stages 2, 3 and 4, respectively. However, there is a slow drop followed by stability in the client's trajectory at various better threshold stages when infinity is attained. These underscore that all HIV-naïve clients eventually transition to the AIDs stage, especially when therapeutic intervention is lacking. The model established in this study could assist Health Care Providers (HCP), Epidemiologists, Medical Statisticians, and other funding organisations in planning for the treatment, surveillance, management, and intervention for the ever-increasing scourge of HIV/AIDs.

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Continuous Time, HIV-naive, Holding Time, Interval Transition Probability, Semi-Markov process, Opportunistic Infection.

INTRODUCTION
Nigeria ranks third among countries with the highest burden of human immune-deficiency Virus (HIV) infection in the world. The 2019 Nigeria National HIV/AIDS Indicator and Impact Survey (NNHAIIS, 2019) found that 1.9 million people are living with HIV and AIDS in Nigeria as of 2018. Over time, this low level of inflammation takes a toll on the body, putting the person with HIV at greater risk for health conditions such as cardiovascular disease, kidney disease, diabetes, bone disease, liver disease, cognitive disorders, and some types of cancer. Further, the HIV epidemic not only affects the health of individuals it also impacts households, communities, and the development and economic growth of a nation. Many of the countries hardest hit by HIV also suffer from other infectious diseases, food insecurity, and other serious problems.

With the pandemic spread of HIV/AIDs, a universally applicable staging system for HIV infection and disease became inevitable. World Health Organization (WHO), charged with global health assurance, devised an HIV/AIDs staging system. This system solely depends on clinical investigations as they exhibit on HIV-naïve individuals before staging them into any of WHO's four staging thresholds (i.e., Stages 1, 2, 3, and 4). Like many developing Nations, the WHO staging system is in place in Nigeria because it is easier applicability. However, with the availability of FACS machines for CD4 counts in most settings, Clinicians encourage the counselled and tested

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HIV-naïves to go for a CD4 count before staging. This scenario indicates a strong inclination to the United States Centre for Disease Control (US-CDC) approach to HIV/AIDs staging. Observing CD4 counts could be the surer method because machine measuring is involved.

Qi Cao *et al.* (2016) asserted that representing all relevant stages of clinical disease processes using a standard Markov model have large, unwieldy structures. In such situations, a more parsimonious, and therefore easier to grasp, model of a patient's disease progression can often be obtained by assuming that the future state transitions do not only depend on the present state (Markov assumption) but also the past through time since entry in the present state (semi-Markov assumption). Despite that, these so-called semi-Markov models are still relatively straightforward to specify and implement, they are not yet routinely applied in health economic evaluation to assess the cost-effectiveness of alternative interventions. The best-known continuous-time STM is the Markov model, which is based on the premise that the future state transitions only depend on the present and are independent of any knowledge from the past, such as time since entry into the present state or the sequence of prior states leading to the present (Aalen *et al.,* 2008; Lagatos *et al.,* 1978).

Instead of trying to represent complex clinical disease processes using a standard Markov model, Foucher *et al.* (2005) proposed to relax the Markov assumption by assuming that the future state transitions depend not only on the present but also on the past through time since entry in the present state. These so-called semi-Markov models allow for a more concise representation of complex healthcare processes in situations where time dependence needs to be incorporated into the model, but health economics assessments for assessing the cost-effectiveness of alternative healthcare interventions (see Lagatos *et al.,* 1978; Kang *et al.,* 2007 and Titman *et al.,* 2010).

Gillaizeau *et al.* (2014) asserted that many chronic and non-chronic diseases, except a few, exhibit stochastic clinical events. These events may denote disease incidences, progression, relapse, remission, recovery, etc. The biomedical dynamic processes can be stationary, progressive or non-progressive, respective to the adopted medical interventions and time index. Stochastic processes entail the trajectories within and among the various states within time t. The changes and duration among the diseased states are often unknown. Stochastic modeling becomes imperative to model such dynamic processes to understand the underlying mechanism inherent in disease progression. Thomas *et al.* (2006) showed that a semi-Markov process with sojourn times given as a general lifetime distribution of residence times can be approximated by a classical Markov process with an exponential distribution of residence times. This means that an exponentially distributed times sum replaces the general lifetime distribution. One way to estimate general lifetime span distributions with the semi-Markov model is to use expert judgment. Basta *et al.* (2008) used cross-sectional self-report data collected from 208 HIV seropositive individuals to determine the accuracy of Transtheoretical model (TTM) constructs to predict the stages of change for exercise behaviors in individuals living with HIV/ AIDS. Based on their sample, they discovered that predictive discriminate analysis classified HIV- naive individuals into the correct stages substantially better than chance alone, except that no one was accurately predicted in one of the stages out of four. Cox (1972) asserted that Markov models are widely used in medicine, particularly in the study of chronic diseases, extending classical survival models to the analysis of multi-state processes. In literature, conventional survival analysis has been used as a gold standard in modelling time to a single event. Here, one terminal event may be the onset of diseases or death. Time-to-event data may incorporate comparing hazard rates, intensities, or survival functions between states in these situations. Laird *et al.* (2013) asserted that the natural history of the disease could be modeled using a variety of approaches that fall under the general framework of multi-state modes, including Markov processes, non-homogenous Markov processes, semi-Markov processes, and hidden Markov processes. The authors further said that the most commonly used multi-state model is the Markov process model. However, to model the complex and stochastic duration-dependent processes usually encountered in epidemiology and biomedicine, the rigid Markovian assumption may be unrealistic and has to be relaxed. In this paper, the Semi-Markov model in continuous time was used to study the transition and staging of HIV/AIDs naïve clients into their threshold categories to improve the surveillance, management, and tracking of the HIV/AIDS pandemic in Nigeria.

MATERIALS AND METHODS

The data used in this research paper were collected at the Voluntary Counselling and Testing (VCT) clinic of General Hospital Minna, Niger State, Nigeria. This facility is one of the comprehensive HIV/AIDs referral sites. The clinic is responsible for data collation on HIV/AIDs clients of General Hospital Minna and other feeder sites within Minna and its environs. HIV/AIDs Patients' folders were x-rayed, and vital information for ten (10) years, i.e., from July 2010 to February 2020, was obtained. Over thousands of patient files, of which we included 634 randomly selected ART-naïve HIV-seropositive patients at various stages of disease progression based on the WHO staging system that has substantial complete retrospective follow-up data on Opportunistic Infections (OIs) were used.

We model the trajectory of HIV/AIDs clients among various threshold stages according to WHO staging criteria and stage the HIV/AIDs-naive clients into four stages using the Markov chain. We classified the stages as follows:

Stage 1: Asymptomatic stages
Stage 2: Early HIV stage
Stage 3: Intermediate HIV stage
Stage 4: Late/Advance stage

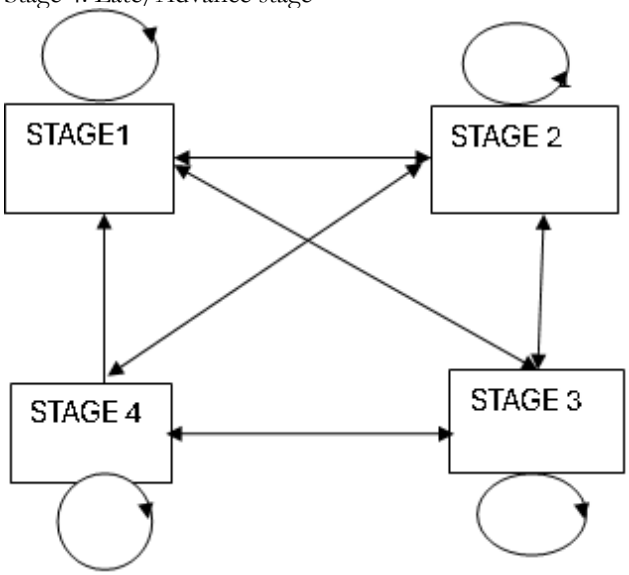

Figure 1 The transition diagram for the WHO staging criterion based on Opportunistic Infections.

The above transition diagram shows that stages 1, 2, and 3 communicate while stage 1 and stage 4 are transients. All possible transitions between stages 1, 2, 3, and 4 were made. Even if the next stage is the same as the last stage, we want the transition to occur at the point of stay in a stage. These are called virtual transitions and are represented by loops in Figure 1.

In Figure 1, we record the transition probability matrix P for the process, as shown in Equation 1.

$$P = \begin{pmatrix} p_{11} & p_{12} & p_{13} & 0 \\ p_{21} & p_{22} & p_{23} & p_{24} \\ p_{31} & p_{32} & p_{33} & p_{34} \\ p_{41} & p_{42} & p_{43} & p_{44} \end{pmatrix} \quad (1)$$

To analyse the process using the Markov theorem, we use the continuous-time semi-Markov process technique. Translations are easily identified from the transition probability matrix P. To study this process, we specify the stochastic nature of the transition. Think of this process as one in which the transition probabilities determine the occupancy of successive stages. However, the fate at any stage is described by a random variable that depends on the stage at which the next transition occurs. This results in a semi-Markov model being translated.

Holding time and waiting time

Let (P_{ij}) be the probability that the HIV-naïve client in its last transition will enter the stage j of its next transition $i, j = 1, 2, 3,4$. The transition probabilities must satisfy the following:

$P_{ij} \geq 0,\ i, j = 1, 2, 3,4$ and

$$\int_{ij} P_{ij} = 1 \quad i = 1, 2, 3,4. \quad (2)$$

Whenever the HIV-naïve client enters the stage i, the client remains there for a time T_{ij} in a stage i before making a transition to the stage j. T_{ij} This is called the holding time on stage i. The holding times are positive integer-valued random variables, each governed by a probability distribution density function $f_{ij}(\ )$ called the holding time distribution function for a transition from stage i to stage j (Howard 1971).

Thus, $P(T_{ij} = m) = f_{ij}(m)\ i, j = 1, 2, 3,4 \quad (3)$

We assume that the means μ_{ij} of all holding time distribution are finite and that all holding times are at least one month long. That is, $f_{ij}(0) = 0$.

To completely describe the semi-Markov process in this study, we must specify four holding time distribution functions in addition to the transition probabilities.

For a fixed value of i, T_{ij} it is the same for each value of j $(i, j = 1, 2, 3,4)$

Let $f_{ij}(\ )$ be the probability distribution of continuous random variable T_{ij}

$$F_{ij}(n) = p(T_{ij} \leq n) = \int_{m=0}^{n} f_{ij}(m)dm \quad (4)$$

And

$\bar{F}_{ij}(\ )$ be the complementary cumulative probability distribution of T_{ij}

$$\bar{F}_{ij}(\ ) = 1 - f_{ij}(n) = p(T_{ij} > n) = \int_{m=n+1}^{\infty} f_{ij}(m)dm \quad (5)$$

Suppose the HIV-naïve client enters the stage i. Let Y_i be the time he/she spent on stage i before moving out of the stage i. Then Y_i is called the waiting time in the stage i.

We let $W_i(\ )$ be the probability distribution function of Y_i

Then: $W_i(m) = p(Y_i = n) = \sum_{j=1}^{4} p_{ij} f_{ij}(m)$ (6)

The probability distribution $W_i(\ )$ and the complementary probability distribution $\bar{W}_i(\ )$ for the waiting times are given as follows

$$W_i(n) = p(Y_i \le m) = \int_{m=1}^{n} W_i(m)dm \quad (7)$$

$$= \sum_{j=1}^{4} p_{ij} F_{ij}(n) \quad (8)$$

And $\bar{W}_i(m) = p(Y_i > n) = 1 - W_i(n)$ (9)

$$= \int_{m=n+1}^{\infty} W_i(m)dm$$
$$= \sum_{j=1}^{4} p_{ij} \bar{F}_{ij}(n) \quad (10)$$

Interval Transition Probability in Continuous-time

We define $\phi_{ij}(n)$ as the probability that the condition of an HIV-naïve client will be in stage j in a month n given that the client entered stage i in month zero. This is called interval transition probability from stage i to stage j in the interval $(0, n]$.

Then

$$\phi_{ij}(n) = \delta_{ij} \bar{W}_i(n) + \sum_{k=1}^{4} p_{ik} \int_{1}^{n} f_{ik}(m)\varphi_{kj}(n-m)dm \quad (11)$$

$$\delta_{ij} = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases} \qquad i, j = 1,2,3,4 \; n = 1,2,3,4$$

Equation (11) is the interval transition probability from stage i to stage j in the interval $(0, n]$

Application

The Voluntary Counseling and Testing (VCT) clinic at General Hospital Minna is one of the comprehensive HIV/AIDs referral sites. The clinic is responsible for data collation on HIV/AIDs clients of General Hospital Minna and other feeder sites within Minna and its environs. We included 634 randomly selected ART-naïve HIV-seropositive patients at various stages of disease progression based on the WHO staging system with substantial complete retrospective follow-up data on Opportunistic Infections (OIs). The reported data are summarised in Table 1, 2, and 3 below:

Table 1: A summary of the HIV/AIDs-naïve patients according to WHO staging criterion from 2010-2020.

Class interval (MW)	Stages	Frequency
Asymptomatic stage	1	138
Early HIV stage	2	197
Intermediate HIV stage	3	214
Advance stage	4	85
Total		634

Table 2: The Transition Count Matrix for the WHO Staging among HIV/AIDS-naive from 2010 – 2020.

	Stage 1	Stage 2	Stage 3	Stage 4	Total
Stage 1	***9***	***3***	***3***	***0***	***15***
Stage 2	***54***	***62***	***50***	***12***	***178***
Stage 3	***43***	***67***	***70***	***28***	***208***
Stage 4	***32***	***65***	***91***	***45***	***233***
Grand total	138	197	214	85	634

The transition probability Matrix of Table 2 above is presented as follows:

$$P = \begin{bmatrix} 0.7736 & 0.1321 & 0.0943 & 0 \\ 0.3333 & 0.4872 & 0.1026 & 0.0769. \\ 0.2000 & 0.1538 & 0.6419 & 0.1693 \\ 0.0645 & 0.0645 & 0.2742 & 0.5968 \end{bmatrix} \quad (12)$$

The Exponential holding time in stages (Continuous time)

Suppose that the holding times in each stage before transitioning to another stage follow the exponential distribution with the parameter λ. This implies that the mean holding time in each stage is $1/\lambda$ (in months). The mean holding time in each stage is presented in Table 3. It shows that HIV/AIDs clients recorded the highest mean holding time in stage 3 then, followed by stage 4, stage 1, and stage 2, respectively.

Table 3: Mean holding time in the stages.

Stage	Mean holding time
Stage 1	13
Stage 2	10
Stage 3	17
Stage 4	16

RESULTS

From equation (11), we obtain the interval probabilities presented in Tables (4), (5) and (6)

Table 4 shows the interval transition probabilities from stage 1 to stage 2, 3, stage 2 to 1, 3, 4, and stage 3 to 1 in continuous time for $n = 1, 2 \ldots\ldots 50$. This is shown in Figure 2.

Table 5 shows the transition probabilities from stage 3 to 2, 4, stage 4 to 1, 2, and stage 4 to 3 in continuous time, for $n = 1, 2 \ldots\ldots 50$. It is shown in Figure 3

Table 6 shows the virtual interval transition probabilities from stage 1 to 1, stage 2 to 2, stage 3 to 3, and stage 4 to 4 in continuous time, for $n = 1, 2 \ldots\ldots 50$. It is illustrated in Figure 4

Table 4: Interval Transition Probabilities for $\phi_{12}(n), \phi_{13}(n), \phi_{21}(n), \phi_{23}(n), \phi_{24}(n)$ *and* $\phi_{31}(n)$

N	$\phi_{12}(n)$	$\phi_{13}(n)$	$\phi_{21}(n)$	$\phi_{23}(n)$	$\phi_{24}(n)$	$\phi_{31}(n)$
1	0.009778	0.00698	0.081718	0.009764	0.007318	0.011421
2	0.018832	0.013443	0.060417	0.018598	0.01394	0.02219
3	0.027216	0.019428	0.086385	0.026592	0.019931	0.032343
4	0.034979	0.02497	0.103882	0.033825	0.025352	0.041917
5	0.042167	0.030104	0.131143	0.04037	0.030258	0.050945
6	0.048824	0.034853	0.150381	0.046292	0.034696	0.059456
7	0.054988	0.039253	0.167788	0.05165	0.038713	0.067482
8	0.060696	0.043328	0.183539	0.056499	0.042347	0.07585
9	0.065981	0.047101	0.19779	0.060886	0.045635	0.082185
10	0.070875	0.050594	0.210686	0.064856	0.04861	0.088913
11	0.075407	0.053829	0.222354	0.068447	0.051302	0.095256
12	0.079603	0.056825	0.232912	0.071677	0.053738	0.101238
13	0.083489	0.059599	0.243465	0.074638	0.055942	0.106977
14	0.087087	0.062167	0.251109	0.077299	0.057937	0.112195
15	0.090418	0.064545	0.258931	0.079707	0.059741	0.117209
16	0.093504	0.066748	0.266008	0.081885	0.061374	0.121937
17	0.09636	0.063737	0.272412	0.083857	0.062652	0.126395
18	0.099006	0.070676	0.278206	0.08564	0.064189	0.130598

Table 4 Continued

19	0.101455	0.072424	0.283449	0.087254	0.065398	0.134581
20	0.103724	0.074043	0.288193	0.088715	0.066493	0.138298
21	0.105824	0.075543	0.292485	0.090036	0.067483	0.141821
22	0.107769	0.076931	0.29637	0.091232	0.068379	0.145144
23	0.10959	0.078217	0.299884	0.092313	0.06919	0.148276
24	0.111237	0.079407	0.303069	0.093292	0.069924	0.15123
25	0.112782	0.080509	0.305941	0.094178	0.070588	0.154015
26	0.114211	0.08153	0.308545	0.09498	0.071188	0.156641
27	0.115536	0.082475	0.3109	0.095705	0.071732	0.159117
28	0.116762	0.083351	0.313032	0.096361	0.072224	0.161451
29	0.117837	0.084661	0.314961	0.096955	0.072669	0.163653
30	0.118948	0.084911	0.316706	0.097492	0.073071	0.165728
31	0.119922	0.085606	0.318285	0.097978	0.073436	0.167685
32	0.120823	0.08625	0.319714	0.098418	0.073765	0.169531
33	0.121658	0.086846	0.321007	0.098816	0.074064	0.171271
34	0.122431	0.089398	0.322177	0.099176	0.074334	0.172911
35	0.123146	0.087908	0.323235	0.099502	0.074578	0.174458
36	0.123809	0.088382	0.324193	0.099797	0.074799	0.175917
37	0.124423	0.08882	0.32506	0.100063	0.074988	0.177292
38	0.124991	0.089225	0.325843	0.100305	0.07518	0.178589
39	0.125517	0.089601	0.326553	0.100523	0.075343	0.179811
40	0.126004	0.089949	0.327195	0.100721	0.075492	0.180964
41	0.126456	0.090271	0.327776	0.10081	0.075626	0.182051
42	0.126873	0.090569	0.328302	0.101061	0.075745	0.183076
43	0.12726	0.090845	0.328778	0.101208	0.075857	0.184043
44	0.127618	0.091101	0.329308	0.10134	0.075956	0.184954
45	0.12795	0.09134	0.329597	0.10146	0.076046	0.185813
46	0.128257	0.091557	0.32995	0.101569	0.076127	0.186623
47	0.128542	0.09176	0.330269	0.101667	0.076201	0.187384

Table 4 Continued

48	0.128805	0.091918	0.330557	0.101756	0.076267	0.188107
49	0.129049	0.092122	0.330818	0.101836	0.076327	0.188787
50	0.129275	0.092283	0.331054	0.101909	0.076382	0.189427

Table 5: Interval Transition Probabilities for $\phi_{32}(n), \phi_{34}(n), \phi_{41}(n)$ *and* $\phi_{42}(n)$

N	$\phi_{32}(n)$	$\phi_{34}(n)$	$\phi_{42}(n)$	$\phi_{43}(n)$
1	0.008783	0.009668	0.003908	0.016613
2	0.017064	0.018784	0.007579	0.032219
3	0.024872	0.027379	0.011028	0.04688
4	0.032235	0.035483	0.014267	0.060653
5	0.039177	0.043125	0.017311	0.073591
6	0.045722	0.05033	0.02017	0.085745
7	0.051321	0.057124	0.022856	0.097163
8	0.057713	0.063529	0.026153	0.107889
9	0.0632	0.069569	0.027749	0.117966
10	0.068374	0.075264	0.029976	0.127431
11	0.073252	0.085698	0.032067	0.136324
12	0.077852	0.085698	0.034032	0.144677
13	0.082189	0.090472	0.055878	0.152524
14	0.086278	0.094973	0.037612	0.159896
15	0.090134	0.099218	0.039241	0.166822
16	0.093769	0.10322	0.040772	0.173327
17	0.097198	0.106993	0.042709	0.179439
18	0.10043	0.110551	0.04356	0.18518
19	0.103477	0.113906	0.04483	0.190574
20	0.106351	0.117069	0.04642	0.195646
21	0.109061	0.120052	0.04714	0.2004
22	0.111615	0.122864	0.048191	0.204871
23	0.114024	0.125516	0.049175	0.209072

Table 5 Continued

24	0.116296	0.128016	0.050108	0.213018
25	0.118437	0.130374	0.05098	0.216725
26	0.120457	0.132596	0.051799	0.220207
27	0.122361	0.134692	0.052569	0.223478
28	0.124156	0.136669	0.053292	0.226551
29	0.125849	0.138532	0.05397	0.229438
30	0.127445	0.140289	0.054609	0.23215
31	0.12895	0.141946	0.055953	0.234698
32	0.130369	0.143508	0.055771	0.237091
33	0.131707	0.144987	0.0563	0.239339
34	0.132969	0.146369	0.056797	0.241451
35	0.134158	0.147679	0.057263	0.243436
36	0.13528	0.148914	0.057702	0.2453
37	0.136338	0.150078	0.058114	0.247051
38	0.137335	0.151175	0.058501	0.248695
39	0.138275	0.15221	0.058864	0.250241
40	0.139162	0.153186	0.059206	0.251692
41	0.139997	0.154106	0.059526	0.253056
42	0.140786	0.154974	0.059828	0.254337
43	0.141529	0.155792	0.060111	0.25554
44	0.14223	0.156563	0.060377	0.256671
45	0.14289	0.157291	0.060626	0.257733
46	0.143513	0.157977	0.060881	0.258731
47	0.144101	0.158623	0.061082	0.259668
48	0.144655	0.159233	0.061289	0.260548
49	0.145177	0.159808	0.061483	0.261375
50	0.145669	0.16035	0.061666	0.262152

Table 6: Virtual transition probabilities $\phi_{11}(n), \phi_{22}(n), \phi_{33}(n)$ *and* $\phi_{44}(n)$

N	$\phi_{11}(n)$	$\phi_{22}(n)$	$\phi_{33}(n)$	$\phi_{44}(n)$
1	0.983243	0.951201	0.970129	0.975571
2	0.967725	0.907045	0.941963	0.952623
3	0.953356	0.867092	0.915406	0.931065
4	0.940051	0.83694	0.890365	0.910812
5	0.927731	0.798229	0.866754	0.891787
6	0.916323	0.768631	0.844492	0.873915
7	0.905759	0.741849	0.824073	0.857125
8	0.895977	0.717676	0.802908	0.839904
9	0.886916	0.695689	0.775046	0.826545
10	0.878531	0.674849	0.767449	0.812617
11	0.870764	0.657396	0.750857	0.799544
12	0.863572	0.641652	0.735213	0.787258
13	0.856913	0.625954	0.720362	0.775719
14	0.850746	0.613655	0.706554	0.764879
15	0.845036	0.601621	0.693439	0.7553
16	0.839749	0.590733	0.681074	0.745129
17	0.834852	0.58106	0.669415	0.735142
18	0.830319	0.571965	0.658421	0.72764
19	0.82612	0.563899	0.649036	0.719767
20	0.822233	0.5566	0.638282	0.711513
21	0.818875	0.549957	0.629066	0.705319
22	0.815301	0.544019	0.620377	0.698745
23	0.812194	0.538613	0.612184	0.692578

Table 6 Continued

24	0.809355	0.533715	0.604458	0.686766
25	0.806707	0.529293	0.597174	0.681315
26	0.804258	0.525287	0.590306	0.676195
27	0.801989	0.521663	0.58383	0.671585
28	0.799888	0.518383	0.577724	0.666866
29	0.796002	0.516416	0.571966	0.662621
30	0.79614	0.512731	0.566537	0.659633
31	0.794472	0.510301	0.561419	0.653394
32	0.792927	0.508103	0.556592	0.651367
33	0.791496	0.506114	0.552041	0.648061
34	0.790172	0.504314	0.547751	0.644955
35	0.788945	0.502685	0.543705	0.642038
36	0.787809	0.501212	0.53989	0.639297
37	0.786758	0.499889	0.536293	0.636722
38	0.785784	0.498672	0.532901	0.634303
39	0.784882	0.49758	0.529703	0.632031
40	0.784047	0.496592	0.526688	0.629897
41	0.783274	0.495698	0.523848	0.627891
42	0.782558	0.49489	0.521164	0.626008
43	0.781895	0.49416	0.518636	0.624238
44	0.781281	0.493396	0.516253	0.622576
45	0.780712	0.492897	0.514006	0.621014
46	0.780186	0.492355	0.511887	0.619507
47	0.779698	0.499186	0.509889	0.618169
48	0.779247	0.49142	0.508005	0.616874
49	0.778829	0.491019	0.506229	0.615658
50	0.778442	0.490655	0.504554	0.614515

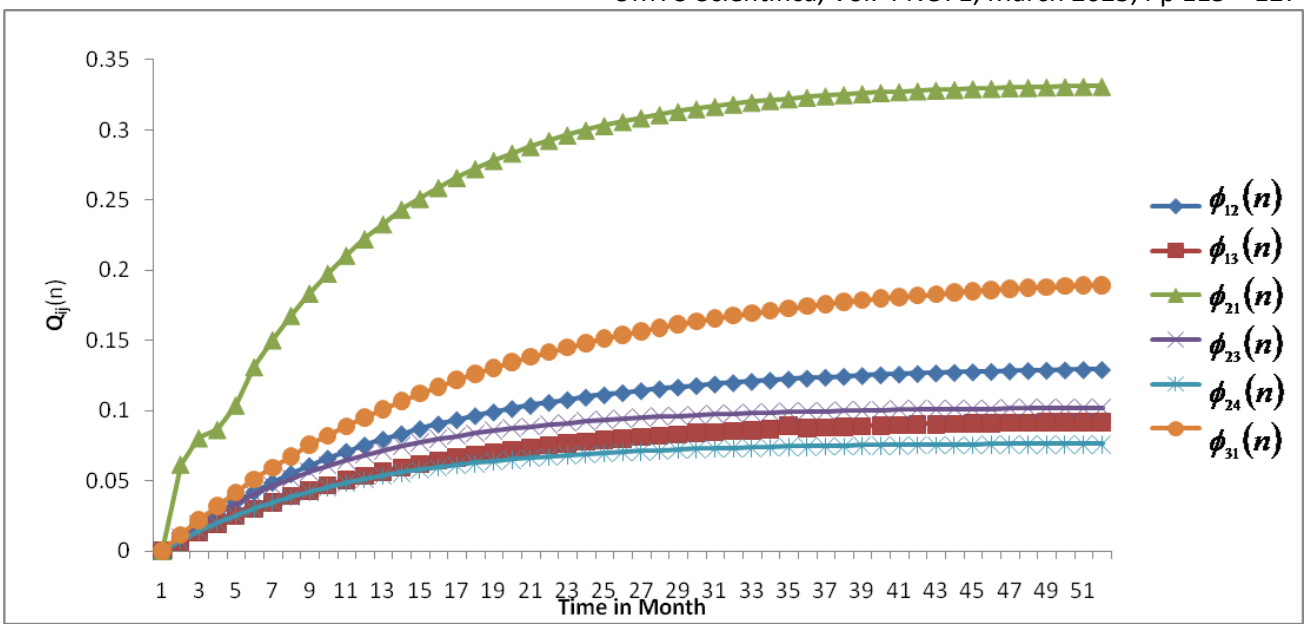

Figure 2: Interval Transition Probabilities Graph for $\phi_{12}(n), \phi_{13}(n), \phi_{21}(n), \phi_{23}(n), \phi_{24}(n)$ *and* $\phi_{31}(n)$ $n = 1, 2.\ldots\ldots 50.$

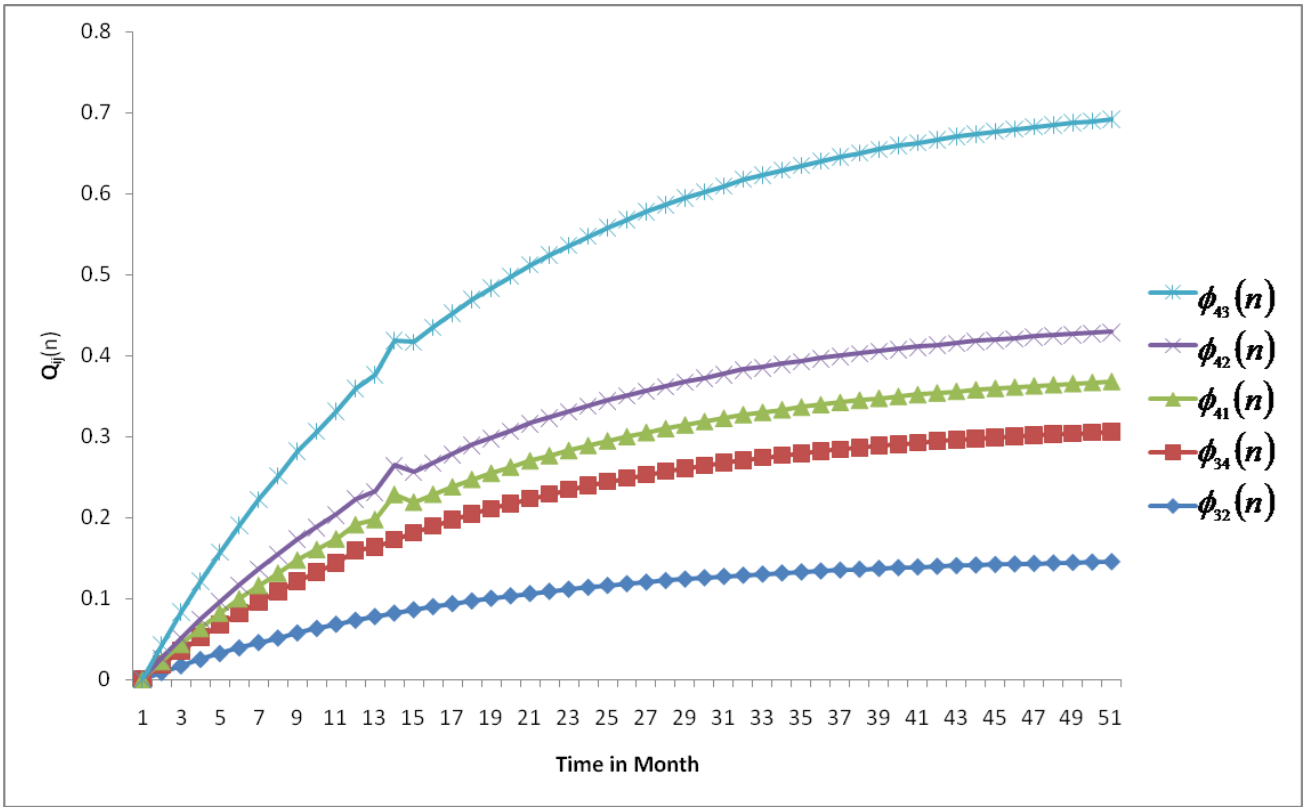

Figure 3: Interval Transition Probabilities Graph for $\phi_{32}(n), \phi_{34}(n), \phi_{41}(n), \phi_{42}(n)$ *and* $\phi_{43}(n)$ $n = 1, 2.\ldots\ldots 50.$

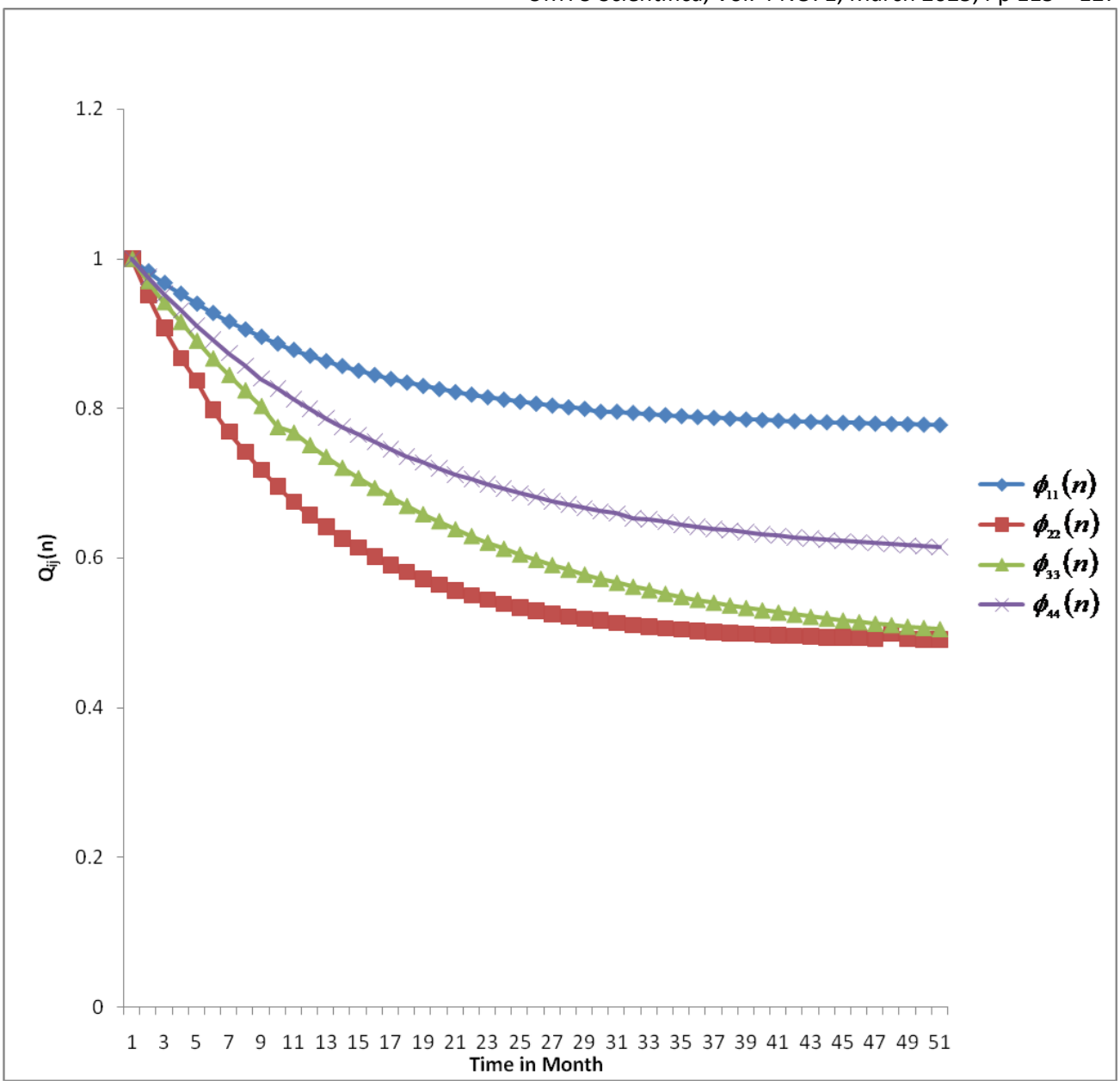

Figure 4: Virtual Transition Probabilities Graph $\phi_{11}(n)$, $\phi_{22}(n)$, $\phi_{33}(n)$ for $n = 1, 2, \ldots, 50$.

DISCUSSION

This paper presented a Semi-Markov model to examine the validity of the WHO staging system for HIV/AIDs–naïves patients reported in Nigeria using a continuous time Semi-Markov model. From the empirical analysis of the collected data, the results indicate no transition from stage 1 to stage 4: that is $\varphi_{14}(n) = 0$. This applies to the n^{th} period under consideration. In other words, there is no transition from the asymptomatic stage of HIV to late/advanced AIDs. The holding time in each stage is presented in Table 3. It shows that HIV/AIDs clients recorded the highest mean holding time in stage 3 then, followed by stage 4, stage 1, and stage 2, respectively.

Furthermore, if an HIV-naïves uninfected patient were in stage 1, he or she would more likely go to stage 2 more times than stage 3, and incidentally, there is no transition to stage 4. This is reasonable in the medical sense as there is rarely a case of HIV- naïve patient shunting directly to advance AIDs stage 4. Also, when HIV/AIDs patients were in virtual stages (i.e., transiting to the same stage), patients were in transient stages more of the time than any other stages.

In the continuous time, the results in Tables 4 and 5 and Figures 2 and 3 show that the transition probabilities from stages 2, 3, and 4 to state 1 increase by about 0.081718, 0.011421, and 0.003908 in the first month $(n = 1)$, indicating that it rises to 0.331054, 0.189427 and 0.061666 in the fifty months $n = 50$. The reduction rates are

approximately 33.1%, 18.9%, and 6.1% over fifty months for stages 2,3 and 4, respectively. Table 6 and Figure 4 show that in the first few months and years, $\phi_{11}(n)$, $\phi_{22}(n), \phi_{33}(n)$ and $\phi_{44}(n)$ reached values of approximately 0.778442, 0.490655, 0.504554, and 0.614515, respectively. However, they decay slowly, returning to zero at infinity. These indicate that, from a medical point of view, every HIV-naïve patient progresses to her AIDs stage, especially if no therapeutic intervention is performed. The results also suggest that if a patient translations to one of these stages, they will remain/persist in that HIV/AIDs stage for several days before an actual or hypothetical transition takes place. I'm here. Tier changes, therefore, occur less frequently over time. The behaviour of $\phi_{11}(n), \phi_{22}(n), \phi_{33}(n)$ and $\phi_{44}(n)$ for $n = 1, 2, 3, \ldots$ are very interesting. This is because they produced nearly identical probability values. This is evident in the graph as it forms an almost straight line $y = 1$.

Therefore, the Continuous Time Semi-Markov Model (CTSMM) can be used to determine prognosis and therapeutic adherence to treatment regimens by HIV-infected individuals. The model can also be used to predict the expected stage(s) that newly infected, HIV-naïve clients are likely to enter. Prediction model information may help track, monitor, and manage HIV/AIDs patients undergoing treatment.

CONCLUSION

A continuous time semi-Markov model was presented to assess the efficacy and staging of HIV-naïves patients using WHO criteria. This model determined the longitudinal staging of HIV/AIDs clients. It has also been shown that Predictions for each stage are well captured during a retrospective cohort study according to the opportunistic infection (01s) threshold. (OIs). This study showed that HIV-naïve patients stay longer in certain stages where therapeutic intervention is not readily available but can be easily obtained by applying. The results also indicate that, from a medical point of view, every HIV-naïve patient progresses to her AIDs stage, especially if no therapeutic intervention is performed. The prediction model information could be useful in the tracking, surveillance, and management of HIV/AIDs individuals undergoing treatment.

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