A Multistate Markov Model Based on CD4 Cell Count for HIV/AIDS Patients on Antiretroviral Therapy (ART)

Gurprit Grover[1], Adesh Kumar Gadpayle[2], Prafulla Kumar Swain[1,*] and Barnali Deka[1]

[1]*Department of Statistics, University of Delhi, Delhi, India*

[2]*Ram Manohar Lohia Hospital, New Delhi, India*

Abstract: The main purpose of this study is to assess the impact of Antiretroviral Therapy (ART) by using a multistate Markov model to estimate transition intensities and transition probabilities among various states (transient as well as absorbing) of the AIDS patients. A total of 580 AIDS patients were included in this study who are undergoing Antiretroviral Therapy treatment in the ART centre in New Delhi during the period of April 2004 to April 2011. The patients are classified in different states on the basis of their available CD4 cell counts. The authors also estimated the mean sojourn time and total length of stay in each state before absorption, and also examined the effects of explanatory variables (i.e Age, Sex, Mode of transmission) on the rates of transition using Cox's proportional hazard model.

Keywords: AIDS, ART, CD4 count, Cox PH Model, Multistate Markov Model, PLHA.

INTRODUCTION

Policy makers and biomedical researchers are facing formidable challenges in tackling the global pandemic of Human Immunodeficiency Virus (HIV) and subsequent development of Acquired Immunodeficiency Syndrome (AIDS). Current estimates put the number of People Living with HIV/AIDS (PLHA) worldwide at 34 million at the end of 2010, up 17% from 2001 [1, 2]. However, the development of antiretroviral drugs to treat HIV and subsequent introduction of Antiretroviral Therapy (ART) have singular effect upon the HIV epidemic, with an estimated gain of 14.4 million life-years globally among adults on ART between 1995 and 2009 [3, 4].

There is an estimated 23.9 lakh PLHA in India with an adult prevalence of 0.31 percent in 2009 [5]. Given the massive population density in India, even a low prevalence means large number of PLHA. However, the analysis of epidemic projections reveals a 50% decline of HIV incidence during last decade, which shows an evidential picture of impact of various intervention and prevention strategies. Since the initiation of free ART programme in 2004, a steady decline has been observed in trends of annual deaths due to AIDS related causes. Also a dramatic decrease in mortality was reported as 25 to 5 deaths per 100 person years in HIV infected individuals between 1997 and 2003 after initiation of ART [6].

HIV infection progressively weakens the immune system as reflected by the reduction in the CD4 cell counts; thus making patients vulnerable to various opportunistic infections. The antiretroviral drugs work by crippling the enzymes that are crucial in the replication of HIV. Currently available drugs have been reported to have achieved high levels of viral load suppression [7, 8]. Thus, CD4 cell count has been an important factor in the clinical investigation of HIV patients as well as used as prognostic marker for assessing HIV progression. Apart from being a leading marker of disease progression, CD4 counts have been used as an indicator of ART initiation. WHO Treatment Guidelines (2006) [9] state that all adolescents and adults including pregnant women with HIV infection and CD4 count of 200 cells/mm^3 or lower should start ART regardless of the presence or absence of clinical symptoms. However, 2010 revision of WHO Guidelines [10] recommends that ART should start when CD4 count is below 350cells/mm^3.

Multistate Markov model based on CD4 cell count has been extensively used to evaluate the disease progression of HIV/AIDS patients. Longini *et al*. (1989) used a 5-staged Markov model based on clinical indicators for progression of disease through the stages of HIV infection. Another study developed a 8-states Markov model based on the decline of CD4 cells in HIV infected individuals [11, 12]. Hendriks *et al*. (1998) also used a 8-staged Markov model based on CD4 cells to estimate the incubation period distribution of AIDS in a prevalent cohort of Injecting Drug Users (IDU) [13]. Alioum *et al*. (1998) [14] employed a multistate Markov model to estimate the effect of gender, age, mode of transmission and ART on the progression of HIV and recently a very similar work has been done by Reedy (2011) in South Africa [15].

*Address correspondence to this author at the Department of Statistics, University of Delhi, Delhi-11007, India; Tel: +919015146613;
E-mail: prafulla86@gmail.com

E-ISSN: 1929-6029/13

Present study has been undertaken in an attempt to evaluate the disease progression of HIV/AIDS patients receiving ART based on hospital records. To the best of our knowledge, no such study has been carried out in India. We have tried to estimate the transition intensities between various states of HIV/AIDS, defined by the ranges of CD4 cell counts, using multi-state Markov model for incomplete event-history data. Apart from this, we have estimated total length of stay in different states, and also estimated the effect of covariates – age, sex and modes of transmission (MOT) on disease progression.

MATERIALS AND METHODS

Study Design

A retrospective follow-up study was conducted using solely hospital-based records of patients enrolled for ART programme at a public sector health facility.

Study Population

The study population consisted of HIV/AIDS patients who were enrolled for care at the ART centre of Ram Manohar Lohia Hospital in New Delhi, between April 2004 and November 2009. They were followed up through the routine ART register records till April 2011. Enrollments post November 2009 were not considered for this study to steer clear of any potential bias that could be introduced by way of new ART guidelines of November, 2009.

Taking the preliminary selection criteria as "*Age at Enrolment >= 18 years*", a total of 2710 patients were selected from the ART register for further screening. Due to incomplete information about exact date of death, 273 deaths had been excluded. Also, 332 lost to follow up cases (without any record of being alive or dead) as well as 598 cases with missing information on CD4 counts, date of collection of CD4 count, and MOT, etc., were further excluded from the analysis. Markov model was then fitted to the remaining 1507 patients. But the exercise yielded inconsistent results and errors due to less number of transitions between stages. After a number of reruns, it was decided to include only those patients with at least four complete records of CD4 counts. Thus 580 patients were finally found eligible for our study. At the end of the study period, 50 patients were dead and the remaining 530 patients were known to be alive with their CD4 cell count being unknown. Hence the data has been right censored for those patients who were alive at the end of the study period.

Data Collection

Data were extracted from the routinely maintained ART patient register. Date of entry into the study and subsequent follow up date of visits were noted. Follow up data on the key variable *CD4 cell count* (cells/mm^3) has been collected as and when available in the patient register. Follow up data were collected on weight and *haemoglobin* at each visit. Other variables considered are *age (in years), sex* and *MOT*. Also for such visits when CD4 cell counts were available, the outcome had been noted for each patient as – 'dead' at any subsequent visits and 'alive' either at subsequent visits (as evident from available records on *weight* or *haemoglobin*) or at end of the study period. In case of death, date of death was also noted down.

No personal identification details were available in the ART register except the registration identity number, which has not been abstracted. Also no information regarding HIV/AIDS status of a patient at enrollment or subsequent transition to AIDS during the study period (in case of a HIV patient) was available.

Statistical Analysis

Collected data were entered, cleaned, and managed in excel. A time-homogeneous Multistate Markov model was applied to analyze HIV/AIDS disease progression with the help of R package *msm* [16]. States associated with disease progression have been based on ranges of CD4 cell counts, defined as

States	1	2	3	4	5
Range of CD4 cell count (cells/mm^3)	>500	351-500	200-350	<200	Death

However, unlike some previous studies, transition from HIV to AIDS could not be incorporated into our study due to the unavailability of this particular information. Covariates were entered into the model as categorical variables – *Age* (≤35 yrs/ >35 yrs), *Sex* (male/female) and *MOT* (sexual/others). The category 'sexual' of the covariate *MOT* included both Homosexual and Heterosexual transmissions and the category 'other' included Injecting Drug Users (IDU) and Unknowns. Survival time of a patient, who was alive at the end of the study period, was considered as right censored.

Upon careful examination of CD4 count it became clear that reverse transitions need to be incorporated into the model. Bwayo *et al*. (1995) [17] were the first to include reverse transitions in CD4 count modeling. States 1 to 4 are transient states and death is the only

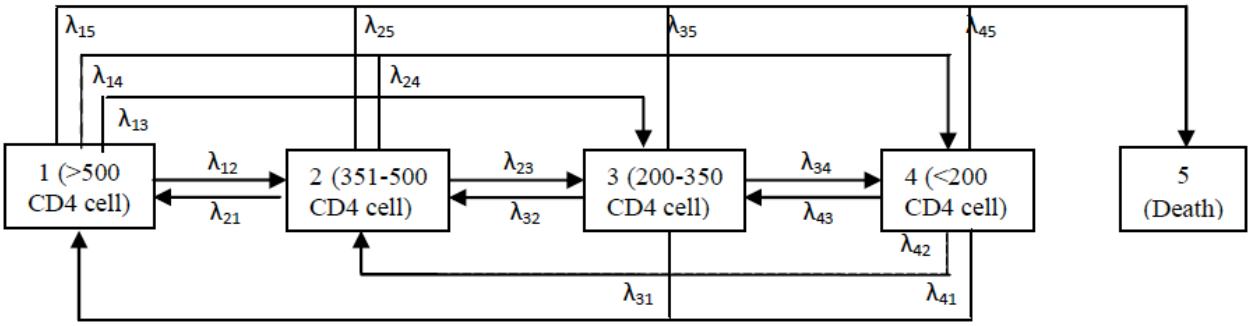

Figure 1: Graphical representation of the Multi-state Markov Model. The states of HIV/AIDS have been defined as the ranges of CD4 cell counts (cells/mm^3). Transition intensities between various states (λ"s) have been indicated along the transition lines.

absorbing state. A patient may move continuously among different transient states and also from any of the transient state to the absorbing state. The model useful for our study is depicted graphically in Figure **1**.

Multistate Markov Model

A patient, after getting enrolled to receive ART, can move along the discrete state space S={1,2,3,4,5}. If X(t)= r be the state of a patient at any time t, then the intensity with which the patient moves to state s during the interval (t, t+Δ*t*) is defined as

$$\lambda_{rs}(t) = \lim_{\Delta t \to o} \frac{P(X(t+\Delta t) = s / X(t) = r)}{\Delta t} \quad r,s = 1,2,...,5$$

This implicitly assumes that the multistate model is Markovian, i.e. the probability of going to a future state depends only on the present state and not on the history. The transition intensity matrix, defined as Q= $[q_{rs}]_{5x5}$, has the following properties: i) $\sum_{s \in S} \lambda_{rs} = 0$ for all r; and ii) $\lambda_{rr} = -\sum_{r \neq s} \lambda_{rs}$. The transition intensities can be estimated using the maximum likelihood estimation procedures (see Kalbfleish and Lawless (1986), and Kay (1986)) [18, 19].

The estimates of transition intensities can be used to compute the transition probability matrix P(t)= $[P_{rs}(t)]_{5x5}$, where $P_{rs}(t)$ is the probability of a HIV/AIDS subject being in state *s* at time (t+u), given that the subject was at state r at time t.

$$P_{rs}(t) = P(X(t+u) = s / X(t) = r)$$

The transition probability matrix in terms of the intensity matrix are obtained as $P(t) = e^{tQ}$ [19-20]

Mean Sojourn Time and Total Length of Stay

The mean sojourn time describes the average period in a single stay in each transient state before moving to either a higher or lower level of CD4 count. It is estimated by $-1/q_{rr}$ where q_{rr} is the *r*th diagonal entry of the estimated transition intensity matrix Q. It is also of interest to estimate the total length of stay in each transient state, which is defined as the expected amount of time spent by a subject in each state during the study period. In fact this feature might be more informative in the presence of reverse transitions.

Cox PH Model

Effect of covariate vector **z** on transition i→j for a HIV/AIDS patient is modeled by $q_{ij}(t)$, Cox proportional hazards regression on the transition hazard given by

$$q_{ij}(t) = q_{ij}(0)\exp(\beta_{ij}^T \mathbf{z})$$

where $q_{ij}(0)$ is the baseline intensity, β_{ij} is the regression coefficient and z_{ij} is vector of covariate specific transition i→j, defined for a patient based on covariates z, assuming that the covariate does not change over time [18, 21]. Maximum likelihood estimates for baseline intensities and regression coefficients can be obtained using procedures as detailed in Kalbfleish and Lawless (1986) [18].

RESULTS

Descriptive characteristics of 580 (409 male, 171 female) study subjects are presented in the Table **1**. Patients were followed for a median of 3.54 years (IQR 1.91 – 4.52 years) and had a median of 9 visits (IQR 4 – 13 visits). The median time between visits was 0.26 years. 76.49% of the participants had cd4 cell count less than 500 mg/mm^3 at the time of enrolment. 50 (8.6%) deaths occurred at the end of the study period.

Table **2** shows the observed transitions between follow up visits. The increase in CD4 cell counts is evident from this table as seen in the cases of back transitions – 2→1 (136), 3→2 (228) and 4→3 (337). A total of 701 (136+228+337) transitions has been observed from higher to lower states.

Table 1: Descriptive Characteristics of all Study Subjects (N = 580)

Variables	Category	Number (%)
Sex	Male Female	409 (70.5%) 171 (29.5%)
Age Group	≤35 years >35 years	300 (51.7%) 280 (48.3%)
Mode of Transmission (MOT)	Sexual Others	135 (23.3%) 445 (76.7%)
Status	Alive Death	530 (91.4%) 50 (8.6%)

Initially, the Markov model without covariate has been used to study the overall disease progression. The estimates of transition intensities (λ_{ij}) with 95% confidence intervals (CI) are presented in Table **3**. It reveals that patients in state 1 are 10.4 times (0.458/0.044) more likely to move to state 2 than die in the state 1. Also, the rate of transition from state 2 to 1 is 1.2 times more likely than to state 3(200-350 CD4 cell). However, similar transition behavior has been observed in case of transition from states 3 and 4 to death. Patients in state 3 are 3.2 times (1.007/0.309) more likely to move to state 2 than to state 4(<200 CD4 cell). Once a patient is in state 4, he/she has 188.4 times (1.383/0.007) more chance to move to state 3 than to state 1.

The estimated one and five year transition probabilities are summarized in Table **4**. A patient in state 1 has a 67% chance of being in the same state at the end of one year, as opposed to 19% and 4% chances of being moved to state 2 (351-500 CD4 cell) and of dying respectively. A patient in the state 2 has- a 33% chance of being in the same state at the end of one year; a 38% chance of being moved to state 1; and 23% chance being moved to state 3 (200-350 CD4 cell) at the end of one year. A patient in the state 4 (<200 CD4 cell) has a 30% probability of still being in the same state at the end of one year and a 41% chance of moving back to state 3.

However a patient in state1 (>500 CD4 cell) is 41% likely to remain in the same state and 16% chance of being dead at the end of fifth year. A patient in the state 3 has- a 39% probability of moving back to state 1 and a 22% chance of moving back to state 2 (351-500 CD4 cell) at the end of fifth year. A patient in state 4 has 38%, 23% and 21% chances of being in states 1, 2 and 3 respectively at the end of fifth year.

The Table **5** shows the estimates of mean sojourn time along with 95% CI as well as total length of stay in each transient state. The average amount of time a patient spent in state1 (>500 CD4 cell) is 1.79 years (95% CI: 1.26, 2.55), the average period in state2 (351-500 CD4 cell) was 0.58 years (95% CI: 0.49, 0.67), before making any transition to other states. Again, an

Table 2: Number of Observed Transitions Between States (Rows to Columns)

To From	State1	State2	State3	State4	State5	Censored
State1	132	25	4	0	5	184
State2	136	144	70	6	6	143
State3	64	228	351	63	10	151
State4	13	90	337	324	29	52

Table 3: Estimates of Transition Intensities (95% Confidence Interval) for the Time Homogeneous Markov Model

States	1	2	3	4	5
1	-0.556 (-0.79, -0.391)	0.458 (0.298,0.706)	0.054 (0.013,0.228)	0	0.044 (0.019,0.097)
2	0.932 (0.778,1.116)	-1.732 (-2.02,-1.483)	0.768 (0.582,1.016)	0.014 (0.001,0.334)	0.017 (0.003,0.108)
3	0.032 (0.012,0.084)	1.007 (0.874,1.16)	-1.379 (-1.56,-1.22)	0.309 (0.233,0.412)	0.026 (0.012,0.071)
4	0.007 (0.001,0.043)	0.021 (0.003,0.135)	1.383 (1.224,1.561)	-1.432 (-1.60,-1.27)	0.025 (0.006,0.072)

Table 4: Estimated Transition Probabilities between States (Rows to Column) of HIV/AIDS Patients

States	1	2	3	4	5
1 year					
1	0.67101757	0.1930278	0.08710098	0.00985983	0.03899382
2	0.37740816	0.3347240	0.22698163	0.03489555	0.02599071
3	0.17782896	0.2862256	0.41503955	0.09382279	0.02708312
4	0.08152282	0.1842287	0.41291969	0.29732075	0.02400808
5 year					
1	0.4082158	0.2143533	0.1759466	0.03966745	0.1618169
2	0.4026372	0.2208800	0.1880413	0.04402905	0.1444124
3	0.3899731	0.2238994	0.1975576	0.04794493	0.1406250
4	0.3786757	0.2273666	0.2075706	0.05215452	0.1342325

Table 5: Mean Sojourn Time and Total Length of Stay

State	Mean Sojourn Time		Total Length of Stay (in yrs.)
	Estimate (in yrs.)	SE (95% CI)	
State1	1.79	0.322 (1.26, 2.55)	14.87
State2	0.58	0.045 (0.49, 0.67)	7.58
State3	0.73	0.045 (0.64, 0.82)	6.23
State4	0.69	0.041 (0.62, 0.78)	1.42

individual with CD4 cell count of more than 500 is expected to survive 15 years.

Our study of disease progression has further been extended to include covariates- *age, sex and MOT*, using Cox PH regression modeling. All the covariates were time-independent. Final model has been selected on the basis of the Likelihood Ratio (LR) test. Table **6** shows all the models along with their LR test statistics. The basic model had no covariate effect included in it. Then each of the factors were added to the 'no covariate' model- one at a time, two at a time and lastly all the three simultaneously. LR tests were performed for each model to assess its goodness-of-fit. However we have reported here only the final multivariable model (with Age+Sex+MOT).

The hazard ratios (HR) for each covariate (i.e Age, Sex and MOT) on each transition along with 95% CI are presented in the Table **7**. The only transition found to be significantly associated with female is from state 3 to 4. Patient aged more than 35 years are 20% less

Table 6: Likelihood Ratio (LR) Test for Model Selection

Covariates	-2*LLa	LR Test statistic	df	p-value
No Covariates	4794.169	_	_	_
Age	4766.441	27.728	15	0.02333*
Sex	4765.894	28.275	15	0.01991*
MOT	4677.146	117.023	15	0.000*
Age+Sex	4753.198	40.971	30	0.000*
Age+MOT	4655.545	138.624	30	0.0226*
Sex+MOT	4640.478	153.691	30	0.6203
Age+Sex+MOT	4627.712	166.457	45	0.0000*

[a]Log Likelihood.

Table 7: Estimates of Hazard Ratios (95% CI) for Transitions from Multivariate Cox PH Model

	Age[+]	Sex[$]	MOT[#]
	HR (95% CI)	HR (95% CI)	HR (95% CI)
State 1 - State 2	1.871 (0.813, 4.303)	0.491 (0.184, 1.310)	0.451 (0.194, 1.048)
State 1 - State 3	2.604 (0.009, 7.177)	2.683 (0.000, 6.38)	17.736 (0.000, 43.151)
State 1 - State 5	2.022 (0.274, 14.896)	31.075(0.000, 600.086)	0.100 (0.015, 0.644)*
State 2 - State 1	0.811 (0.414, 0.952)*	0.955 (0.668, 1.366)	1.158 (0.676, 1.983)
State 2 - State 3	1.030 (0.577, 1.836)	0.897 (0.489, 1.643)	2.157 (0.934, 4.981)
State 2 - State 4	0.030 (0.000, 5313.59)	15.286 (0.000, 382.998)	0.013 (0.000, 163.35)
State 2 - State 5	0.973 (0.298, 3.169)	47.617 (0.000, 938.277)	0.061 (0.007, 0.542)*
State 3 - State 1	1.128 (0.168, 7.422)	14.569 (0.000, 106.429)	0.002 (0.000, 179.31)
State 3 - State 2	0.947 (0.710, 1.262)	1.236 (0.928, 1.648)	1.574 (1.051,2.357)*
State 3 - State 4	0.797 (0.450, 1.408)	0.457 (0.202, 0.933)*	1.843 (0.799, 4.248)
State 3 - State 5	0.548 (0.027, 10.640)	12.608 (0.000, 390.905)	0.003 (0.000, 67.880)
State 4 - State 1	76.197 (0.000, 1555.03)	0.034 (0.000, 448.839)	16.898 (0.000, 36.038)
State 4 - State 2	0.028 (0.000, 6267.03)	14.237 (0.000, 1029.15)	0.031 (0.000, 161.580)
State 4 - State 3	0.835 (0.650, 0.973)*	1.186 (0.912, 1.542)	1.973 (1.442,2.699)*
State 4 - State 5	2.191 (0.261, 18.383)	0.347 (0.243, 4.957)	0.063 (0.000, 8.173)

[+]Reference Category: <35 yrs; [$]Reference Category: Male; [#]Reference Category: Others; *Significant.

likely to make the back transition from state 2 to 1 as compared to those aged less than 35 years (HR=0.81; 95% CI: 0.41, 0.95). Similar finding has been observed in case of transition from state 4 to 3 (HR=0.84; 95% CI: 0.65, 0.97). The effect of MOT is significant for the transitions 1→5, 2→5, 3→2 and 4→3 at 5% level of significance.

DISCUSSION

Our analysis of disease progression towards death of HIV/AIDS patients on ART has some significant findings. The patients who had CD4 <200 cells/mm^3 showed a very less chance of immune recovery, and substantially higher risk of immune deterioration, which is comparable with the findings of previous studies [12, 13, 15]. A number of studies from India have showed a gain in CD4 cell counts after initiation of ART [22-25]. However, there is no Markov model-based study in India to compare the pattern of transitions to immune recovery after initiation of ART. This implies that if therapeutic interventions are initiated at the early stages of infection when the immune system is relatively intact, then immune recovery and slow progression to death may be contained. Our study clearly shows that there is considerable improvement in health condition of HIV/AIDS patients continuing ART for a longer duration as evident from our five year transition probabilities. The survival time of an individual, who had CD4 >500 cells/mm^3 at the time of ART initiation, has been estimated to be 15 years compared to 11 years as reported in previous studies where effect of ART interventions on disease progression was not considered.

In terms of covariate effect, HIV/AIDS patients who were more than 35 years of age at ART initiation tend to experience a rapid forward progression, though not all the hazard ratios for these transitions were significant. The progression to death is more pronounced in case of a person aged more than 35 years and presenting the advanced state of immune deterioration (CD4 <200 cells/mm^3) at the start of ART. Two studies from India [22, 26] too reported an increasing risk of death with increasing age, although both the studies are not comparable with ours in terms of study design. Many other studies have reported considerable impact of age at seroconversion to HIV on the future disease progression [14, 15, 27-30]. Our study thus confirms that it might seem plausible to start antiretroviral therapy at higher levels of CD4 cell counts for older people.

However, gender difference does not exhibit any significant effect on the disease progression concurring with the findings of earlier studies [15, 27, 31-34]. Comparison of disease progression rates between risk

groups by various MOT have revealed rather conflicting findings. A patient with sexually transmitted HIV infection (homosexual or heterosexual) tends to progress slowly to immune deterioration and death as well compared to a patient with other modes of transmission. However those patients with sexual modes of transmission and CD4 count between 500 to 200 cells/mm^3 showed a higher risk of progression to the next stage of immune deterioration. A number of earlier studies too reported similar conflicting findings in terms of effect of various modes of transmission on the HIV/AIDS disease progression [30, 35-36]. The differential responses of various MOT on the HIV/AIDS disease progression may be due to several reasons. The risk group IDU, being relatively more visible, has a higher chance of getting diagnosed at earlier stages. This in turn facilitates timely treatments leading to an increase in immune level. However other confounding factors might introduce co-morbid illnesses other than the opportunistic infections. This might have a larger role to play in bringing down the CD4 cell count as compared to those patients with sexual MOT receiving ART.

The implication of our findings is that it might be prudent on the part of treatment and care providers to target early therapeutic interventions to slow the progression of a PLHA towards immune deterioration; thereby, contributing towards some gain in life years and somewhat increased quality of life due to the reduced chances of opportunistic infections. India shares a major share of global burden of HIV/AIDS with the third largest number of PLHA. This highlights the requirements of wider access to HIV testing and counseling services, and also the need of comprehensive strategies to facilitate early detection in India. It is also need of the hour to carve out the high risk populations and start targeted intervention (TI) strategies to reduce incidences as well as further spread of HIV infection to the general population.

Our study however has some limitations. First, the patient records were often incomplete, particularly in regards of follow up data on clinical parameters. This forced us to discard a large portion of the data. Second, we have only considered data from one ART center which caters to patients mostly from Delhi and its adjoining regions like Haryana and Punjab. Therefore a strict generalization of our findings at national level would require utmost care and need to be substantiated by further multi-centric analyses. The third limitation is that our results are strongly dependent upon the assumption of time homogeneity. This simplifying assumption was incorporated to facilitate the analysis of disease progression in the presence of heavy censoring. There is a need to examine the appropriateness of this assumption by conducting longitudinal studies and making sure that data on parameters of the studies are collected properly. The hidden Markov model techniques may be used further to relax the assumption of time-homogeneity. The last and the important drawback is that our study was not able to estimate the transition rate from HIV seroconversion to AIDS and consequently incubation period.

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Received on 28-01-2013 Accepted on 05-03-2013 Published on 30-04-2013

http://dx.doi.org/10.6000/1929-6029.2013.02.02.08