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EFFECT OF BASELINE CD4 CELL COUNT ON EFFICACY OF HIGHLY-ACTIVE ANTIRETROVIRAL THERAPY FOR HIV PATIENTS

RUNNING HEAD: BASELINE CD4 CELL COUNT TO INITIATE HAART

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ABSTRACT

Background**:** Comparison of transition rates between CD4 cell count states for individuals starting HAART at different baseline CD4 cell counts controlling for gender, age and drug abuse.

Methods**:** Observational study of 122 adult patients who started HAART at the AIDS Research Center in Tehran, Iran. CD4 cell counts were categorized as >500, 351-500, 200-

350 and <200 T-cell/ml) with one additional state for death considered. The continuous time multi-state Markov model was used to model the probability of transition between and intensity of CD4 cell count states and death.

Results**:** There was no significant difference in the rate of transition between CD4 states when starting HAART at a CD4 cell count ≥200 than at < 200 cells/ml when adjusted for gender, age and drug abuse. Individuals co-infected with HIV/TB who started HAART after TB treatment showed a significantly faster rate of progression to worse states. Males with HIV progressed significantly faster than females (HR = 1.9).

Conclusions**:** The study trajectory for CD4 count during HAART shows a significant effect for gender and TB. This should be considered with baseline CD4 in HIV positive patients.

Keywords: CD4 cell count, HAART, Markov model, TB/HIV co-infection

INTRODUCTION

It was estimated that about 35.0 million (33.2 to 37.2 million) people were living with HIV worldwide by the end of 2013. By June 2014, 28 of the 58 WHO HIV focus countries had policies offering antiretroviral therapy (ART) to HIV-positive persons. At the end of 2013, about 12.9 million people were receiving ART globally (1).

WHO guidelines before 2010 recommended that ART should begin in patients with CD4 cell counts of <200 T-cell/ml (2). In 2010, WHO recommended that, in addition to previous patients, ART should start when a person has a CD4 count of 200-350 T-cell/ml. In 2013, WHO published new guidelines that recommended a new cut-off for CD4 cell count of >500 T-cell/ml. The protocols of countries such as Brazil, France and the US state that every person with HIV should receive ART, irrespective of the CD4 T-cell count (3). The standard treatment is a combination of at least three drugs, usually one protease inhibitor or non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors; this is known as highly active antiretroviral therapy, or HAART.

HAART has been used since 1995-96, but the optimal time to begin remains controversial. Hogg et al. used Kaplan-Meier methods to estimate and compare mortality rates of HIV patients with baseline CD4 cell counts of <50 T-cell/ml and those with counts of 50-199 T-cell/ml who began ART between August 1996 and September 1999. They concluded that the first

group was 3.41 times more likely to die than those in the second group (4).

Egger et al. used a stratified Weibull model for CD4 T-cell count and transmission group to model the progression of HIV to AIDS/death in adult patients starting HAART. They found that initial CD4 T-cell count was the most important prognostic factor for patients starting HAART (5). Van Leth et al. investigated the risk of virologic failure (not reaching plasma HIV-1 RNA concentrations (PVL) of <400 copies/ml or a rebound to two consecutive values of more than 400 copies/ml) in 7 strata at baseline CD4 T-cell counts and 5 PVL strata at baseline (6). They used Cox proportional hazard analysis. Palella et al. found that HIV-infected persons with CD4 T-cell counts of 201-350 T-cell/ml who initiated ART had lower mortality rates than those who delayed ART to a CD4 of <200 T-cell/ml (7). They stated that increased survival for earlier ART initiation at CD4+ cell counts of 351-500 T-cell/ml were possible. Other researchers had already proposed CD4 modeling using different statistical models.

The effect of the timing of initiation of ART on clinical outcomes has been controversial. ART improves the survival rates of infected persons; however, analysis based on time to death can be lengthy and progressive CD4 states can be used to model disease trajectory. The multi-state Markov model simultaneously models marker tracking and risk of death. Gentleman (1994) used a continuous time homogeneous multi-state Markov model to describe the transition through four states defined by CD4+ T-cell counts (>500, 200-499, 0-199, AIDS diagnosis). Their model assumed each person was observed for a specific time (8). Marshall et al. (1995) incorporated covariates using a Cox regression model (9). The models have enough parameters to allow them to fit different data about rates of transition for CD4 cell count trajectories.

METHODS

The present study included 128 patients that were sampled randomly from the Iranian Research Center for HIV/AIDS in Tehran. They were treated with HAART between 1999 and 2007 and were followed until either time of death or the end of the study period (October 2014). Their CD4 T-cell counts were measured every 3 months. The process of evolution of the CD4 cell count for each individual was observed at

discrete time points that were regularly or irregularly spaced. Age, gender, drug abuse, infection with tuberculosis at baseline, and baseline CD4 T-cell count was recorded for each patient. All adults who had had at least two follow-up visits in addition to the pre-HAART treatments were eligible for inclusion. Six patients were adolescents and were removed from the sample.

Statistical Analysis

The multi- state Markov model was used to analyze the disease trend. The states of the Markov processes were defined by the severity of the illness based on the CD4 cell counts in T-cells/ml. These states were: state 1 (CD4 count ≥ 500 T-cell/ml); state 2 (350 T-cell/ml ≤ CD4 count < 500 T-cell/ml); state 3e (200 T-cell/ml ≤ CD4 count <350 T-cell/ml); state 4 (CD4 count < 200 T-cell/ml); and state 5 (death). The time from initiation of HAART and the time intervals between checkups for each individual were recorded in months. It was possible in this model to represent transition as intensity q_{ij} which occurs from state i to adjacent state j.

The covariates of gender, age, drug abuse, infection with tuberculosis, and previous initiation of HAART (baseline TB) on the progression and regression of HIV was included to determine their effects on the model. The baseline CD4 count was incorporated as a covariate of the Markov model. Although before starting HAART patients were recorded to be in four different states, limitations in sample size restricted the number of categories to two: ≥200 T-cell/ml and 0-199T-cell/ml. These models were included as covariates of the Cox models as follows:

$$q_{ij}(t, Z) = q_{ij_0}(t)\exp(\beta_{ij} Z)$$

where Z is the vector of covariates.

In the second step of model fitting, each covariate was added to the Markov model. Univariate and multivariate models were compared using the likelihood ratio test and Akaike information criterion (AIC). Specific forward model selection based on the likelihood ratio test and AIC was used. In this procedure, the parameters of covariate effects considered different for each transition (full model), were the same for progression and regression (PR) or were the same for all progression transitions with the exception of a change in sign for regression. This last is called a progression mine regression model (PMR) (results not shown).

If a covariate based on the univariate model was found to be significantly associated with HIV progression, the best representation of this factor was later used for multiple regression analysis. The baseline CD4 cell count remained in the model because of its clinical importance. Unknown transition rates, first-hitting-time (time of first passage from one state to the desired state) and any covariate effects were estimated by maximum likelihood using the matrix product and the MSM package in software environment R (ver. 3.1.2).

RESULTS

The descriptive characteristics of the remaining 122 patients prior to initiation of HAART are given in Table 1. Of the patients in the CD4 cell count ≥200 T-cell/ml group, 9 deaths occurred. In the 0-199T-cell/ml group, 20 deaths occurred. Patients were followed for a median of 100 mo, with an interquartile range of 71.75–121 mo. The majority of patients (n = 106; 87%) started treatment with two nucleoside reverse transcriptase inhibitors (zidovudine/stavudine, lamivudine) and one protease inhibitor (nelfinavir) and the others initiated therapy with two nucleoside reverse transcriptase inhibitors (zidovudine/stavudine, lamivudine) and one non-nucleoside reverse transcriptase inhibitor (efavirenz/nevirapine) (n =16; 13%). Each patient was tested for TB before starting the HAART. All TB/HIV co-infected patients received the same TB therapy for at least 1 month before beginning HAART. The TB treatment included rifampin, isoniazid, pyrazinamide, ethambutol and vitamin B6.

The estimated prevalence was interpolated for all times and plotted against the expected prevalence according to the fitted model. The observed and expected prevalence of each state from the time of initiation of HAART based on the multi-state Markov model is shown in Figure 1. Figure 2 shows the estimated survival curves for each state. Each survival curves represents one of four transient stages after starting treatment. The survival rates for 4 years were 96%, 95%, 93% and 87% for stages 1, 2, 3 and 4, respectively, at the start of HAART. Thus, a typical HIV positive person in state 1 that starts HAART has a probability of 0.04 of death after 4 years from onset of treatment, while this probability is 0.13 for apatient in state 4.

The probability of survival decreased over a period of 8 years to 0.90%, 89%, 87% and 81%, for state 1, 2, 3 and 4, respectively. These probabilities and Figure 2 also show that the risk of HIV progression to death was faster from state 4 (CD4 T-cell count of ≤199), although it was not statistically significant. These probabilities were calculated after adjusting for age, gender, drug abuse, baseline TB and baseline CD4 cell count.

Table 2 gives the estimated hazard ratio for each covariate effect for the transitions at a 95% confidence interval (CI). The hazard rate for gender in the progressive transitions was significant but was not significant for regressive transitions. The hazard ratio for progress to a worse state was approximately twice more fast for men than for women.The categories of age at the beginning were not significant for progression or regression. The baseline CD4 cell count and drug abuse showed no significant effects at any transition intensity. Patients with TB at the onset of the study progressed to worse states significantly faster than those who did not have TB. Regression was significantly slower for the TB-HIV positive patients.

The expected first-hitting-time $T_{i\to j}$, denotes the expected time spent in state i until first reaching state j. This parameter and the estimated transition rate from the multivariate model are shown in Table 3.

DISCUSSION

The use of ART for the treatment of HIV infected persons decreases viral replication and increases the CD4 T-lymphocyte count to delay progression of the disease (10). The best time to initiate HAART is a challenging question for medical researchers. The study of how CD4 cell count trajectory affects treatment over time can be useful for addressing this question.

Researchers have studied the mortality and morbidity of patients using different baseline CD4 cell counts using general non-parametric and semi-parametric survival methods. ART helps patients live longer and also possibly recover immunity to achieve CD4 cell counts >800 cells/ml after HAART (11-12). Common survival models experience problems related to the large amount of censored data.

Information about the progress of HIV can be shown using transitions between intermediate immunologic statuses. The multi-state Markov

model is useful for assessing the characteristics of HIV progression. Studies have proposed CD4 cell count modeling with a Markov model prior to the introduction of HAART (8, 13). The present study used the multi-state Markov model for continuous time and covariate effects to investigate the effect of baseline CD4 cell count on HAART effectiveness.

Characterization of changes in CD4+ cell count showed two group trajectories for probability of survival. Three states represent patients that are approximately the same who start therapy with high CD4 cell counts (states 1, 2 and 3) and one state for patients with a low CD4 cell count (state 4) at the beginning the therapy, although the differences are not statistically significant. This was confirmed by Cox regression analysis adjusted for gender, age, drug abuse, baseline TB and pre-HAART viral load levels. The results are consistent with results of previous studies (14-15)and conflict with other reports (16-17). These previous studies were not restricted to adult patients and their definition of the virological endpoint CD4 cell category and the type of statistical model used differed. Wood et al. concluded that, given good medical adherence, mortality rates would not increase by delaying the start of HAART for patients with <200 CD4 cell counts(18).

The fitted model showed the probability of a patient starting therapy in state 1 and staying in that state for 1, 3 and 8 years is 0.53, 0.37 and 0.29 respectively. The same model for state 2 was 0.29, 0.24 and 0.21, for state 3 was 0.32, 0.22 and 0.20 and for state 4 were 0.58, 0.30 and 0.17, respectively. There was insufficient evidence suggesting that starting therapy at ≥200 T-cell/ml instead of at <200 T-cell/ml increased the immunological benefit at 1, 3 or 8 years after starting HAART.

Women comprise about 50% of HIV-infected individuals worldwide (19). Patterson et al. showed that for 6 months follow-ups, the virological and immunological response to HAART for male and female patients were similar (20). Moore et al. investigated the virologic, immunologic and clinical responses after starting HAART and found no significant evidence of gender difference in these responses (21). Studies have suggested that women may progress at a faster rate than males for equivalent viral loads (22). The results of this study show that males with HIV who started

HAART progressed at a significantly faster rate than females. There was no statistical significance for regression to better states or recovery, which is in line with the fact that women are likely to have had higher CD4 cell counts at the start of HAART than males (21).

The effectiveness of HAART for age of patients has shown conflicting results. Some studies have reported that older HIV patients show worse immunological outcomes than younger patients (23-24). Greenbaumet al. studied a large urban clinic and found that, despite increased virologic suppression in patients >50 years compared to patients <40 years, there was no difference in immune response between these two groups (25). Some studies have shown similar viral responses between age groups and found that older patients have slower rates of CD4 recovery and a lower magnitude of CD4 increase (26-27). The fitted model used in the present study showed that transition between CD4 cell count states were similar in patients aged >40 years and ≤40 years did not show significant differences for progression or recovery.

Tuberculosis is a chronic infectious disease that is the cause of one in five HIV-related deaths. WHO recommends determining TB prevalence among people living with HIV to control these deaths (28). Several studies have reported that HAART increases the survival rate of TB/HIV co-infected patients (29). Kassa et al. compared HIV patient groups with and without TB and concluded that there was no significant difference in the increase in total CD4+ counts between groups (30). The present study found a significant difference between groups. TB/HIV co-infected patients progressed significantly faster and regressed significantly more slowly for CD4 cell count.

This study found no difference in progression and recovery of patients at each baseline CD4 category when adjusted for gender, age, baseline TB and drug abuse. Although the sample size limited obtaining consistent estimates of some transitions, this question requires more study and should be investigated using larger sample sizes with the multi-state Markov model adjusted for baseline CD4 cell count.

REFERENCES

1. World Health Organization, Global update On The Health

Sector Response to HIV, 2014. July, 2014.

2. World Health Organization, Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. 2005.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFile /AdultandAdolescentGL.pdf 2011, January 10, 1–166.
4. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. JAMA 2001;286(20):2568–2577.
5. Egger M, May M, Chêne G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of Hiv-1-Infected Patients Starting Highly Active Antiretroviral Therapy: a Collaborative Analysis of Prospective Studies. Infect. Dis. Clin. Pract.2002; 360: 119–129.
6. van Leth F, Andrews S, Grinsztejn B, Wilkins E, Lazanas MK, Lange JM, et al. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. AIDS 2005; 19: 463–471.
7. Palella F, Deloria-Knoll M, Chmiel J, Moorman A,Wood K, Greenberg A, et al. Survival Benefit of Initiating Antiretroviral Therapy in HIV-Infected Persons in Different CD4+ Cell Strata. Ann Intern Med 2003; 138(8): 620–626.
8. Gentelman RC, Lawless JF, Lindsey JC, Yan P. Multi-state markov models for analysing incomplete disease history data with illustrations for hiv disease. Stat. Med.1994;13: 805–821.
9. Marshall G, Jones RH. Multi-state models and diabetic retinopathy. Stat. Med.1995;14: 1975–1983.
10. Sabin C, Phillips AN. Should HIV therapy be started at a CD4 cell count above 350 cells/ l in

asymptomatic HIV-1-infected patients?. Curr. Opin. Infect. Dis.2009; 22: 1–11.

11. Lepri AC, Pezzotti P, Dorrucci M, Phillips AN, Rezza G. HIV disease progression in 854 women and men infected through injecting drug use and heterosexual sex and followed for up to nine years from seroconversion. BMJ 1994; 309(6968):1537–1542.
12. Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F. Risk of new AIDS diseases in people on triple therapy. Lancet 2000; 356(9226): 291–296.
13. Haberman S. HIV, AIDS, Markov processes, and Health and disability insurance, J. Actuar. Pract.1995; 3(1): 51–74.
14. Phillips AN, Weber R, Kirk O, Francioli P, Miller V, Vernazza P, et al. HIV Viral Load Response to Antiretroviral Therapy According to the Baseline CD4 Cell Count and Viral Load. JAMA 2001; 286(20): 2560–2567.
15. Lepri CA, Phillips AN, d'Arminio Monforte A, Castelli F, Antinori A, de Luca A, et al. When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. AIDS 2001; 15(8): 983–990.
16. Anglemyer A, Rutherford GW, Easterbrook PJ, Horvath T, Vitória M, Jan M, et al. Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review. AIDS 2014; 28(2): 105–118.
17. Grabar S, Pradier C, Le Corfec E, Lancar R, Allavena C, Bentata M, et al. Factors associated with clinical and virological failure in patients receiving a triple therapy including a protease inhibitor. AIDS 2000;14(2): 141–149.
18. Wood E, Hogg RS, Yip B, Harrigan PR, Shaughnessy MVO, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350× 109 cells/L. Ann. Intern. Med.2003; 139(10): 810–816.

19. Sidibé M. Global report: UNAIDS report on the global AIDS epidemic 2013, 2013.
20. Patterson K, Napravnik S, Eron J, Keruly J, Moore R. Effects of age and sex on immunological and virological responses to initial highly active antiretroviral therapy. HIV Med.2007; 8(6): 406–410.
21. Moore AL, Kirk O, Johnson AM, Katlama C, Blaxhult A, Dietrich M,et al. Virologic, immunologic, and clinical response to highly active antiretroviral therapy: the gender issue revisited. J Acquir Immune Defic Syndr.2003; 32(4): 452–61.
22. Farzadegan H, Hoover DR, Astemborski JS, Lyles CM, Margolick JB, et al. Sex differences in HIV-1 viral load and progression to AIDS. Lancet 1998; 352(9139):1510–1514.
23. Operskalski EA, Stram DO, Hang Lee YZ, Donegan E, Busch MP, Stevens CE, et al. Human immunodeficiency virus type 1 infection: relationship of risk group and age to rate of progression to AIDS. J Infect Dis 1995; 172(3): 648–655.
24. Belanger F, Meyer L, Carre N, Coutellier A, Deveau C. Influence of age at infection on human immunodeficiency virus disease progression to different clinical endpoints: the SEROCO cohort (1988-1994). Int J Epidemiol 1997; 26(6):1340–1345.
25. Greenbaum AH, Wilson LE, Keruly JC, Moore RD, Gebo KA, Effect of Age and HAART Regimen on Clinical Response in an Urban Cohort of HIV-Infected Individuals. AIDS 2008; 22(17): 2331–2339.
26. Viard J-P, Mocroft A, Chiesi A, Kirk O, Røge B, Panos G, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. J Infect Dis 2001; 183(8): 1290–1294.
27. Manfredi R, Chiodo F. A case-control study of virological and immunological effects of highly active antiretroviral therapy in HIV-infected patients with

advanced age. AIDS 2000;14(10): 1475–1477.

28. A guide to monitoring and evaluation for collaborative TB/HIV activities. WHO Library Cataloguing-in-Publication Data, 2015.
29. Tseng S-H, Jiang DS, Hoi H-S, YangS-L, Hwang K-P. Short report: Impact of HAART therapy on co-infection of tuberculosis and HIV cases for 9 years in Taiwan. Am. J. Trop. Med. Hyg.2009; 80(123): 675–677.
30. Kassa D, Gebremichael G, Alemayehu Y, Wolday D, Messele T, van Baarle D. Virologic and immunologic outcome of HAART in Human Immunodeficiency Virus (HIV)-1 infected patients with and without tuberculosis (TB) and latent TB infection (LTBI) in Addis Ababa, Ethiopia. AIDS Res. Ther.2013; 10(1): 18.

Table 1: Characteristics of the sample study according to the CD4 cell count prior to the initiation of highly active antiretroviral therapy (HAART).

		CD4 cell count before therapy		
Characteristic		**≥200**	**0-199**	**All patients**
Gender (%)	**Female**	**5 (14.3)**	**17 (19.5)**	**22 (18.0)**
	Male	**30 (85.7)**	**70 (80.5)**	**100 (82.0)**
Age (%)	**<40 year**	**11 (31.4)**	**45 (51.7)**	**56 (45.9)**
	>40 year	**24 (68.6)**	**42 (48.3)**	**66 (54.1)**
Drug abuse (%)	**Yes**	**19 (54.3)**	**40 (46.0)**	**59 (48.4)**
	no	**16 (45.7)**	**47 (54.0)**	**63 (51.6)**
Transmission (%)	**Injection Drug use**	**18 (51.4)**	**43 (49.4)**	**61 (50.0)**
	Sexual contact	**9 (25.7)**	**26 (29.9)**	**35 (28.7)**
	Blood transfusion	**7 (20.0)**	**18 (20.7)**	**25 (20.5)**
	Mother to child	**1 (2.9)**	**0 (0.0)**	**1 (0.8)**
Baseline TB	**No**	**30(85.7)**	**73(83.9)**	**103(84.4)**
	Yes	**5(14.3)**	**14(16.1)**	**19(15.6)**

Table 2: Estimates of Hazard Ratios (95% CI) for Transitions from Multivariate Cox Model

Covariate	Strata	Transition	HR	95% CI
Sex	**female**		**1.00**	
	male	$i \to j$ $i = 1,2,3,4 \mid j = 2,3,4,5$	**1.9012***	**(1.0118,3.5724)**
		$j \to i$ $i = 1,2,3 \mid j = 2,3,4$	**1.0123**	**(0.6162,1.6631)**
Age	**≤ 40 years**		**1.00**	
	>40years	$i \to j$ $i = 1,2,3,4 \mid j = 2,3,4,5$	**1.0697**	**(0.6907,1.6567)**
		$j \to i$ $i = 1,2,3 \mid j = 2,3,4$	**1.3552**	**(0.8984,2.0422)**

Drug using	**Yes**		**1.00**	
	No	$i \to j$ $i=1,2,3,4 \mid j=2,3,4,5$	**0.6462**	**(0.3560,1.1728)**
		$j \to i$ $i=1,2,3 \mid j=2,3,4$	**0.6263**	**(0.3688,1.0636)**
Baseline CD4	**≥ 200**		**1.00**	
	<200	$i \to j$ $i=1,2,3,4 \mid j=2,3,4,5$	**0.7603**	**(0.4337,1.3330)**
		$j \to i$ $i=1,2,3 \mid j=2,3,4$	**0.5973**	**(0.3245,1.0995)**
Baseline TB	**No**		**1.00**	
	Yes	$i \to j$ $i=1,2,3,4 \mid j=2,3,4,5$	**1.2458***	**(1.0391,1.5001)**
		$j \to i$ $i=1,2,3 \mid j=2,3,4$	**0.8009***	**(0.6666,0.9623)**
Reference Category: sex: female ,age: ≤ 40 years; drug using: yes, baseline CD4: ≥ 200; *Significant				

Table 3: Estimated transition rate (95% CI) and hitting time (in months) using HIV trajectory model

Transition rates [per month] (95% CI)	Hitting time (months)
$q_{12} = 0.0933(0.0426,0.2043)$	$T_{1\to 2} = 10.7154$
$q_{21} = 0.1233(0.0587,0.2589)$	$T_{1\to 3} = 31.3613$
$q_{23} = 0.1124(0.0617,0.2049)$	$T_{1\to 4} = 96.6149$
$q_{32} = 0.1122(0.0667,0.1887)$	$T_{2\to 3} = 20.6458$
$q_{34} = 0.0508(0.0319,0.0808)$	$T_{2\to 4} = 85.8995$
$q_{43} = 0.0495(0.0337,0.0729)$	$T_{3\to 4} = 65.2337$
$q_{45} = 0.0068(0.0046,0.0102)$	

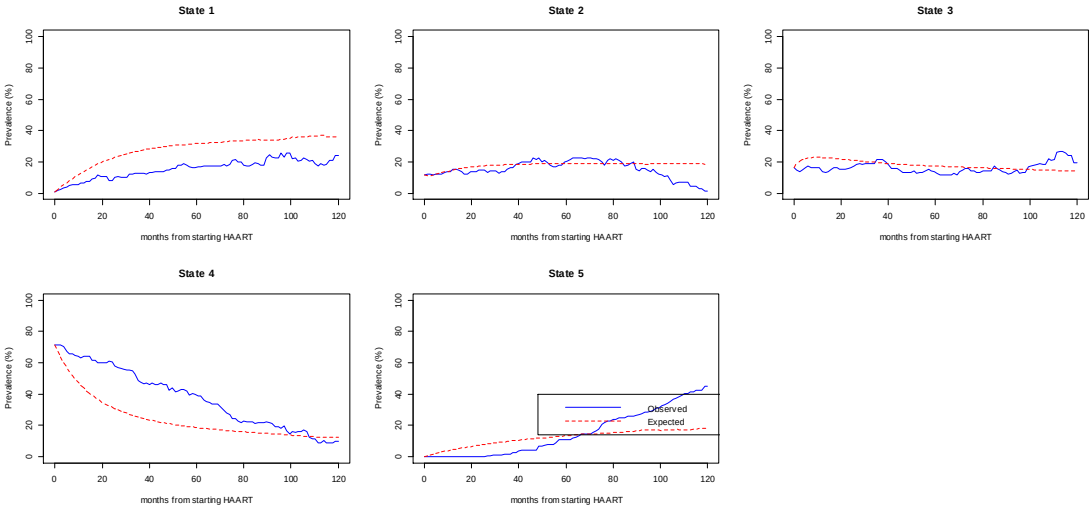

Figure 1: observed and expected prevalence of each HIV state over time of HAART

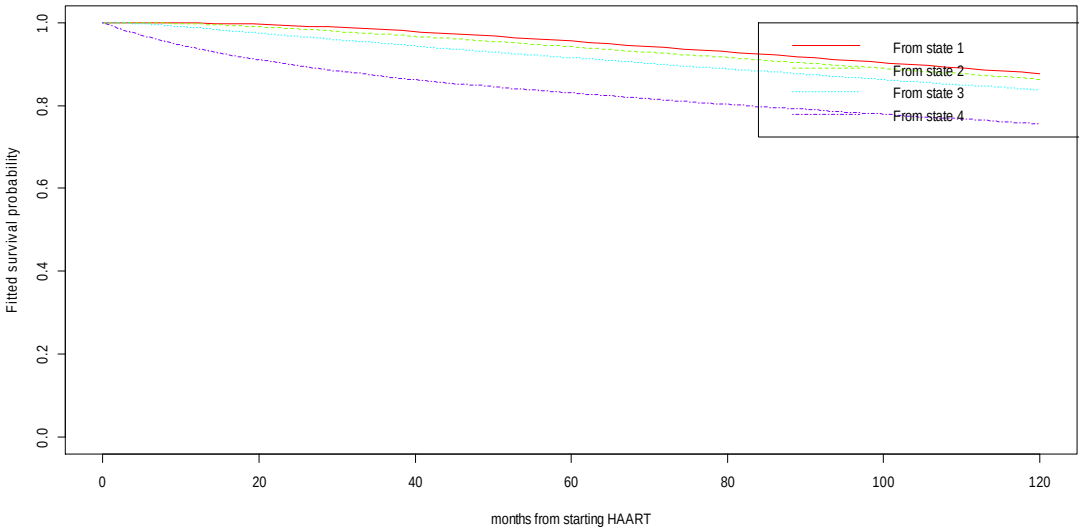

Figure 2: Survival-type curves for the probability of staying alive from each state