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# Association of HIV Viral Load and CD4 with HPV Detection and Clearance in HIV Infected Women Initiating HAART

**Minhee KANG, Ph.D.**[1] and **Susan CU-UVIN, M.D.**[2]

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health

[2]Obstetrics-Gynecology and Medicine, Brown University

## Abstract

**Objectives—**The extent to which highly active antiretroviral therapy (HAART) affects HPV acquisition and clearance in HIV-infected women is not well-understood. We sought to describe high risk HPV detection and clearance rates over time since HAART initiation, based on time-varying HIV viral load (VL) and CD4+ T-cell count (CD4) using novel statistical methods.

**Methods—**We conducted retrospective analysis of data from completed AIDS Clinical Trials Group (ACTG) A5029 study using multi-state Markov models. Two sets of high risk HPV types from 2003 and 2009 publications were considered.

**Results—**There was some evidence that VL>400 copies/mL was marginally associated with higher rate of HPV detection (p=0.068, hazard ratio [HR]=4.67), using the older set of high risk HPV types. Such association was not identified using the latest set of HPV types (p=0.343, HR=2.64). CD4>350 cells/mm$^3$ was significantly associated with more rapid HPV clearance with both sets of HPV types (p=0.001, HR=3.93; p=0.018, HR=2.65). There was no evidence that HPV affects VL or CD4 in all analyses.

**Conclusions—**High risk HPV types vary in studies, and they can affect analysis results. Use of HAART to improve CD4 may have an impact in the control of HPV infection, and the decrease in VL to a lesser degree.

### Keywords

HIV; human papillomavirus; HAART; cervical cancer; Markov models

## Introduction

Immuno-suppression is associated with prevalence and persistence of human papillomavirus (HPV), but the extent to which highly active antiretroviral therapy (HAART) affects HPV acquisition and clearance in HIV-infected women is not well-understood. A number of studies have shown that HPV infection and cervical dysplasia risks are elevated among women infected with HIV and immuno-suppressed (1–5), but there are mixed results on the effect of HAART on progression of HPV (1, 2, 6). Classification of high risk HPV types associated with cervical cancer vary in studies, as knowledge has evolved over time, and this may contribute to mixed results in literature. Also, data from HPV studies can be difficult to analyze due to: infrequent observations on HPV detection (every 6–12 months), small number of visits (over 3–5 years) and unknown rate and duration of transient HPV

Corresponding Author: Minhee Kang, Ph.D., Center for Biostatistics in AIDS Research, Harvard School of Public Health, 651 Huntington Avenue, Boston, MA 02115, 617-432-2819 (phone), 617-432-3163 (fax), mkang@sdac.harvard.edu.

infections (7, 8). For instance, HPV detections at two study visits 12 months apart may indicate a persistent infection or an infection that cleared and recurred between the visits.

To address the data limitations, a statistical approach using multi-state models was applied to describe HPV detection and clearance events that may be recurrent. We conducted a retrospective analysis on AIDS Clinical Trials Group (ACTG) A5029 data to describe and compare HPV detection and clearance rates with time-varying HIV viral load and CD4 count in HIV-infected women initiating HAART, when the exact times of HPV status changes are unavailable. Two sets of high risk HPV types from 2003 and 2009 publications were considered to evaluate how the analysis can be sensitive to evolving HPV types thought to be oncogenic.

## Methods

### ACTG A5029 Study

A5029 was an observational, prospective study to estimate prevalence of HPV DNA in treatment-naïve women initiating HAART and to explore association of HPV with CD4+ T-cell count (CD4) and HIV viral load (VL) (9). The study enrolled 147 women from 35 sites in the US and Puerto Rico between January 2001 and May 2003, who provided informed consent according to the ACTG procedures and each site's Institutional Review Board. Scheduled evaluations were infrequent: baseline (within 2 weeks of initiating HAART), weeks 24, 48 and 96. HAART was defined as a regimen of 3 or more drugs containing at least one protease inhibitor or non-nucleoside reverse transcriptase inhibitor or a triple nucleoside regimen containing abacavir. CD4+ T-cell count and plasma HIV-1 VL were conducted in laboratories at the ACTG sites using standardized techniques. Roche polymerase chain reaction/reverse blot strip assay was used to detect specific HPV types in the cervical swab specimens. HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82 were considered high-risk HPV types for cancer based on a 2003 publication (10) in A5029 (Set I). In addition to this set, we considered Set II based on the review of human carcinogens by the International Agency for Research on Cancer in 2009 (11). Types 26, 53, 66, 68, 73 and 82 were considered to have "limited evidence in humans for cervical cancer" and were placed in a separate category from types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 which had "sufficient evidence for cervical cancer" and were used as Set II.

### Statistical Models

Continuous-time, multi-state Markov models were applied to the status data on HPV detection, VL and CD4. The following four states were defined for VL Model (Figure 1A) to describe the high risk HPV detection and clearance rates with time-varying VL:

1. = none of the high risk HPV types (HPV negative) and HIV viral load (VL) >400 copies/mL,
2. = at least one of the high risk HPV detected (HPV positive) and VL>400,
3. = HPV negative and VL ≤ 400, and
4. = HPV positive and VL ≤ 400.

A multi-state model describes a process where an individual is in one of the specified states at any time. An individual's status at any time can be categorized as one of the four states above, and changes in the state can be followed. The choice of 400 copies was based on the lower limit of quantitation of the Roche assay at the time of A5029. To illustrate the assumed state structure, suppose a woman begins in State 1. She may acquire HPV without improvement of VL (transition to State 2), or she may remain HPV negative and improve on

VL (transition to State 3). State 4 may be reached from State 1 via State 2 (change in HPV status first) or State 3 (change in VL first), but not directly from State 1; that is, we assume that simultaneous changes in HPV status and VL do not occur biologically. (However, State 4 may be observed after State 1 in the previous visit.) From State 2, she may clear HPV and return to State 1, or she may retain HPV and transition to State 4 with decreased VL. From State 3, she may acquire HPV while maintaining VL status (transition to State 4), or her VL may increase while remaining HPV negative (transition to State 1). From State 4, she may clear HPV and transition to State 3, or remain HPV positive while her VL increases (transition to State 2). She may also remain in any of the states for the remainder of the study. Analysis methods by Kalbfleisch and Lawless (12) were applied to account for the lack of exact times of HPV detection and clearance times. The methods also account for different visit times, numbers of visits and varying initial states from different study participants.

The transition rates, or cause-specific hazard rates, are denoted by λ's in Figure 1. For instance, $\lambda_{12}$ represents the hazard rate for acquiring HPV when VL remains >400 and $\lambda_{34}$ represents the rate when VL remains ≤ 400. For HPV clearance rates, $\lambda_{21}$ represents the rate for clearing HPV when VL remains >400, and $\lambda_{43}$ when VL remains ≤ 400. To describe the changes in HIV-related status, $\lambda_{13}$ represents the rate from VL>400 to ≤ 400 without HPV, and $\lambda_{24}$ with HPV. Conversely, $\lambda_{31}$ represents the rate from VL ≤ 400 to >400 without HPV, and $\lambda_{42}$ with HPV. Inferences on the effect of VL on HPV detection and clearance, and the effect of HPV on VL, can be made by comparing these hazard rates. Hypotheses are tested by fitting unrestricted and restricted models and using likelihood ratio tests. Mathematical details are in the Appendix.

A similar model was used to assess HPV detection and clearance rates with varying CD4 (CD4 Model, Figure 1B). The cause-specific hazard rates are represented by γ's. The four states were defined as follows:

1. = HPV negative and CD4 ≤ 350 cells/$mm^3$,
2. = HPV positive and CD4 ≤ 350,
3. = HPV negative and CD4>350, and
4. = HPV positive and CD4>350.

Threshold of 350 cells was chosen to be consistent with guidelines on when to start antiretroviral therapy at the time of A5029. The parameter estimates (and standard errors) using Set II are shown in Figure 1, and model fits are presented in the Appendix. The times to final visit were compared between groups with different baseline characteristics (HPV, VL, CD4 statuses) using log-rank tests. Analyses were conducted using SAS 9.1 and R 1.8.1.

## Results

### HPV and HIV RNA Viral Load

Of the 147 study subjects in the analysis, 143 had both HPV and HIV RNA results at baseline, 119 at week 24, 103 at week 48 and 85 at week 96. The data from times outside the scheduled visits for some subjects were also included in the analysis. Seventy subjects had four visits; 41 had three, 18 had two, and 18 had only one visit. Of the 143 subjects with both HPV and HIV RNA results at baseline, 120 subjects (84%) had VL>400 and 80 subjects (56%) had HPV. There was a trend of earlier discontinuation for subjects starting with HPV than without HPV, but the time to final visit was not statistically different

(p=0.13). The final visit times for the subjects starting with VL>400 and ≤ 400 were not significantly different.

In VL Model (Figure 1A), comparison between $\lambda_{12}$ and $\lambda_{34}$ marginally suggested that a woman with current VL>400 was more likely to acquire HPV than with VL ≤ 400 using Set I (hazard ratio $\lambda_{12}/\lambda_{34}$ = 4.67, p=0.068). However, no such association was suggested using Set II ($\lambda_{12}/\lambda_{34}$ = 2.64, p=0.34). Other comparison results were similar with both HPV sets. There was no indication of a significant difference between subjects with VL>400 and VL ≤ 400 in clearance of HPV ($\lambda_{21}/\lambda_{43}$ = 0.632, p=0.55) and between HPV positive and HPV negative subjects in VL increase ($\lambda_{31}/\lambda_{42}$ = 0.656, p=0.69) and in VL decrease ($\lambda_{13}/\lambda_{24}$ = 0.983, p=0.98) using both sets of HPV (Set II results shown). Figure 2A presents model-based probability curves over 5 years for a woman initiating HAART, starting HPV negative and VL>400 (State 1), based on estimates using Set II. In half-year, the probability of remaining in State 1 is 0.20. The chances of being in the other states as HPV status changes and/or VL decreases are: 0.08 for HPV positive and VL>400 (State 2), 0.60 for HPV negative and VL<400 (State 3) and 0.12 for HPV positive and VL<400 (State 4). The probabilities stabilize in about 2.5 years to around 0.11, 0.08, 0.58 and 0.23 for the four states, respectively. They suggest that whereas the probability of being HPV positive and HPV negative are similar when VL>400 (at around 0.10), the probability of being HPV positive is about 0.4 times the probability of being HPV negative when VL ≤ 400.

### HPV and CD4+ T-Cell Count

There were 145 subjects in the analysis, because two of the subjects did not provide CD4. Of the 140 subjects with both HPV and CD4 results at baseline, 107 subjects (76%) started with CD4<350, and HPV was detected in 86 subjects (61%). Data availability trends over time were similar to those for the VL model above.

In CD4 Model (Figure 1B), similar conclusions were drawn from the two HPV sets (Set II results shown). Comparison between $\gamma_{21}$ and $\gamma_{43}$ suggested that a woman with current CD4>350 was more likely to clear HPV than with CD4 ≤ 350 (hazard ratio $\gamma_{43}/\gamma_{21}$ = 2.65, p=0.018). The statistical tests on other comparisons were not significant. There was no evidence to conclude that HPV detection rates differed between subjects with CD4 ≤ 350 and >350 ($\gamma_{12}/\gamma_{34}$ = 1.03, p=0.94), and HPV status did not seem to affect CD4 state transition rates ($\gamma_{13}/\gamma_{24}$ = .920, p=0.78; $\gamma_{31}/\gamma_{42}$ = 0.408, p=0.18). Figure 2B presents the model-based probability curves over 5 years for a HAART-initiating woman, starting HPV negative and CD4 ≤ 350 (State 1). The probabilities stabilize in about 3.5 years to around 0.12 in State 1, 0.11 in State 2 (HPV positive and CD4 ≤ 350), 0.56 in State 3 (HPV negative and CD4>350) and 0.21 in State 4 (HPV positive and CD4>350). The probability of being HPV positive is about 0.4 times the probability of being HPV negative when CD4>350.

## Discussion

Studies have shown varying effects of HAART on HPV infection and HPV-related cervical dysplasia. Several studies have shown higher HPV prevalence in women with lower CD4 and clearance of HPV with improving CD4 (9, 13, 14). Research on the association between HIV VL and HPV detection has been limited. One study showed that HIV VL and CD4 in combination appeared to be associated with HPV detection, with varying effects of HIV RNA level on HPV prevalence and incident detection depending on the CD4 stratum (4). Higher HIV VL may be associated with HPV detection due to a possible viral-viral interaction (15), or inflammatory responses induced by HIV may interfere with a woman's ability to mount an effective immune response to HPV infection (16). In vitro studies have shown an increased expression of HPV E1 and L1 viral genes with the presence of HIV tat

proteins (17). Our analysis using an older set of high risk HPV types suggested that higher VL may be associated with HPV detection and hinted at the role of HIV viral load in HPV acquisition. However, such association was not suggested using the latest set of high risk HPV types. Hence, our research shows the importance of considering the HPV types used when reviewing literature. It is postulated that immune reconstitution associated with HAART may lead to clearance of HPV, as has been the case with other viral or nonviral opportunistic infections, and this was consistent with our analyses where higher CD4 was associated with HPV clearance.

There are a couple of limitations to our analysis. There was a trend of earlier discontinuation for subjects starting with HPV, suggesting possible informative censoring, and the small sample size did not allow models that adjust for covariates such as age, cigarette smoking, HPV type and sexual activity. There are several advantages of the statistical methods that we used. The multi-state modeling approach accommodates multiple and recurrent events using intermittent data. The hazard rates are estimated simultaneously in the model, eliminating the need to subset the data to estimate HPV detection rate among the HPV negatives and separately to estimate clearance among the positives. And while other HPV studies have used the midpoint between the visit times as the event time (e.g. time of HPV detection or clearance) or the time of the visit, the methods we used are appropriate when the exact event times are unknown. The approach utilized the incomplete data efficiently and provided a more comprehensive description of the HPV detection and clearance process.

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## Appendix

Let $p_{jk}(s,t)$ represent the probability that an individual in state $j$ at time $s$ is in state $k$ at time $t$, where $j,k$=1,2,3,4 and $s \leq t$. Since the process is assumed to be time-homogeneous, $p_{jk}(s,t) = p_{jk}(0,t-s)$. The intensity function for transition from state $j$ to state $k$, or cause-specific hazard at time t, is denoted by $\lambda_{ij}$ and defined as,

$$\lambda_{jk} = \lim_{\delta \to 0} \frac{p_{jk}(t, t+\delta)}{\delta}, \; j \neq k.$$

Let $P(s,t)$ and $\Lambda$ denote the 4×4 matrices of transition probabilities and intensities, respectively, where the $j$th diagonal element ($\lambda_{jj}$) is the negative of the rate of leaving state $j$:

$$\lambda_{jj}=-\sum_{k,k\neq j}\lambda_{jk}$$

The relationship between the transition probabilities and the transition rates is given by,

$$P(s,t)=\exp^{(t-s)\Lambda}=\sum_{m=0}^{\infty}\frac{\Lambda^m(t-s)^m}{m!}.$$

The time that the process stays in a state before making a transition to a different state is exponentially distributed, with the mean sojourn time in state $j$ given by $-1/\lambda_{jj}$.

The transition intensity matrix for the model in Figure 1 is given by,

$$Q=\begin{bmatrix} -(\theta_1+\theta_2) & \theta_1 & \theta_2 & 0 \\ \theta_3 & -(\theta_3+\theta_4) & 0 & \theta_4 \\ \theta_5 & 0 & -(\theta_5+\theta_6) & \theta_6 \\ 0 & \theta_7 & \theta_8 & -(\theta_7+\theta_8) \end{bmatrix}$$

where $\lambda_{12}=\theta_1$, $\lambda_{13}=\theta_2$, $\lambda_{21}=\theta_3$, $\lambda_{24}=\theta_4$, $\lambda_{31}=\theta_5$, $\lambda_{34}=\theta_6$, $\lambda_{42}=\theta_7$ and $\lambda_{43}=\theta_8$. The likelihood function for $\theta = (\theta_1, \ldots,\theta_8)'$ is given by,

$$L(\theta)=\prod_{i=1}^{n}\prod_{r=1}^{m_i}p_{y_{r-1}^i,y_r^i}(t_{i,r}-t_{i,r-1};\theta),$$

where the Markov process is observed intermittently at times $t_{i,0} < t_{i,1} < \cdots < t_{i,m_i-1} < t_{i,m_i}$, $i=1, \ldots, n$ individuals, each with $m_i$ observations. Kalbfleisch and Lawless provide a scoring procedure to obtain the maximum likelihood estimate (MLE) for θ and an estimate of its asymptotic covariance matrix.

Hypotheses to compare hazard rates can be tested by fitting unrestricted and restricted models and using likelihood ratio tests (LRT). For example, we can test $H_0$: $\theta_1=\theta_6$ by fitted the unrestricted model given in [1] and fitting the restricted model where the third row is replaced with $(\theta_5, 0, -(\theta_5+\theta_1), \theta_1)$. The likelihood ratio statistic, $2[\log L(\theta)_{unrestricted} - \log L(\theta)_{restricted}]$ has an approximately $\chi_1^2$ distribution if $H_0$ is true.

The observed transition frequencies and the corresponding expected numbers from the models (in parentheses) are listed below to examine the model fits. As an example, consider the 47 subjects who started in State 1: HPV negative and HIV VL>400 copies/mL (HIV VL Model). Of these, 11 subjects remained in State 1, two transitioned to State 2, 28 to State 3 and six to State 4 by Week 28. The model-estimations for these frequencies are 11.23, 3.57, 27.36 and 4.84, respectively. Overall, the comparisons of the observed and expected frequencies indicate adequate model fits.

**Table A1**

The HIV viral load (VL) model

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| 1 | 11 (11.23) | 2 (3.57) | 28 (27.36) | 6 (4.84) | 47 |
| 2 | 2 (2.85) | 9 (14.39) | 9 (7.97) | 31 (25.79) | 51 |
| 3 | 1 (1.21) | 1 (0.28) | 6 (7.67) | 2 (0.85) | 10 |
| 4 | 0 (0.25) | 2 (1.12) | 2 (1.53) | 3 (4.10) | 7 |

($t_0$=0,$t_1$=24)

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| 1 | 3 (2.87) | 1 (0.91) | 7 (6.99) | 1 (1.23) | 12 |
| 2 | 1 (0.61) | 7 (3.10) | 1 (1.72) | 2 (5.56) | 11 |
| 3 | 3 (4.94) | 4 (1.14) | 31 (31.45) | 3 (3.47) | 41 |
| 4 | 0 (1.05) | 1 (4.79) | 8 (6.57) | 21 (17.59) | 30 |

($t_0$=24,$t_1$=48)

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| 1 | 3 (0.68) | 0 (0.36) | 1 (3.10) | 1 (0.86) | 5 |
| 2 | 2 (0.72) | 4 (1.86) | 4 (3.38) | 1 (5.04) | 11 |
| 3 | 2 (4.91) | 2 (2.02) | 31 (26.58) | 4 (5.50) | 39 |
| 4 | 3 (1.16) | 1 (2.65) | 4 (6.15) | 10 (8.04) | 18 |

($t_0$=48,$t_1$=96)

**Table A2**

The CD4 model

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| 1 | 21 (21.55) | 4 (3.69) | 10 (9.34) | 1 (1.42) | 36 |
| 2 | 4 (5.05) | 30 (29.63) | 3 (3.89) | 13 (11.42) | 50 |
| 3 | 2 (0.95) | 0 (0.25) | 12 (15.66) | 5 (2.15) | 19 |
| 4 | 1 (0.13) | 0 (0.69) | 4 (2.13) | 2 (4.04) | 7 |

($t_0$=0,$t_1$ =24)

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| 1 | 13 (14.36) | 3 (2.46) | 6 (6.23) | 2 (0.95) | 24 |
| 2 | 4 (2.83) | 14 (16.60) | 1 (2.18) | 9 (6.40) | 28 |
| 3 | 2 (1.44) | 0 (0.38) | 23 (23.90) | 4 (3.27) | 29 |
| 4 | 1 (0.21) | 2 (1.09) | 3 (3.35) | 5 (6.35) | 11 |

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| ($t_0$=24,$t_1$=48) | | | | | |
| | **1** | **2** | **3** | **4** | |
| 1 | 7 (6.12) | 3 (2.07) | 5 (6.23) | 1 (1.59) | 16 |
| 2 | 2 (1.54) | 6 (4.62) | 1 (2.47) | 3 (3.36) | 12 |
| 3 | 1 (2.15) | 0 (1.01) | 25 (21.10) | 3 (4.73) | 29 |
| 4 | 0 (0.75) | 3 (1.95) | 10 (7.03) | 3 (6.26) | 16 |
| ($t_0$=48,$t_1$=96) | | | | | |

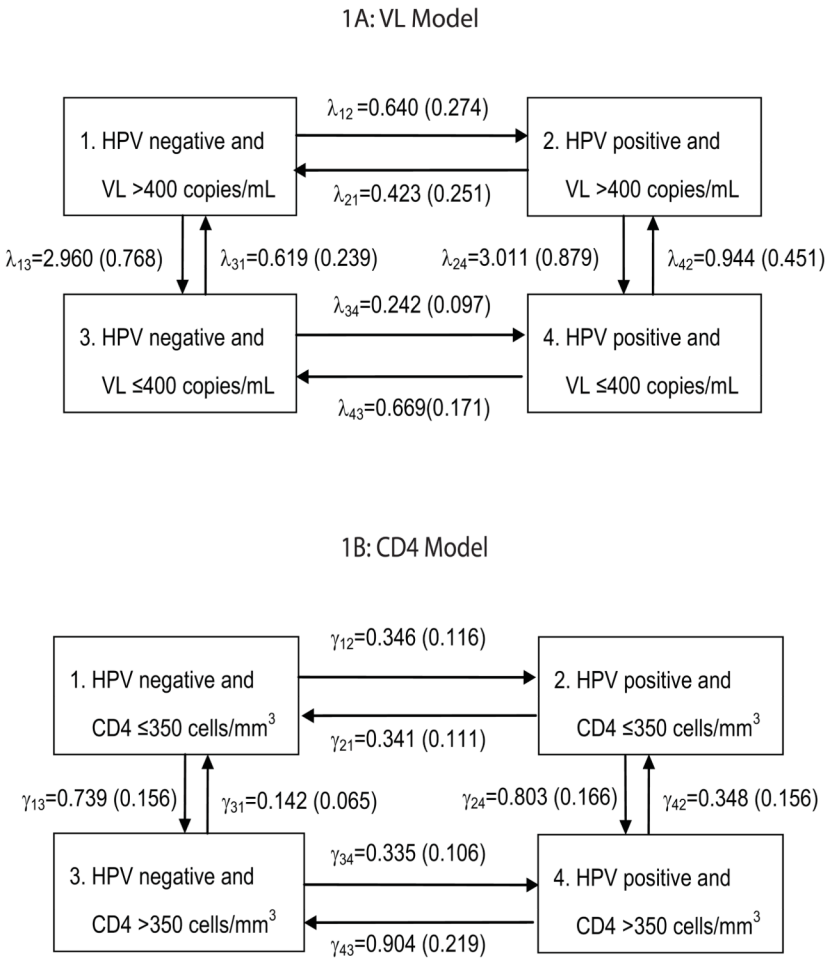


**Figure 1.**
Models to describe HPV detection and clearance with varying HIV-related statuses. Estimated cause-specific hazard rates and standard errors from Set II are presented.

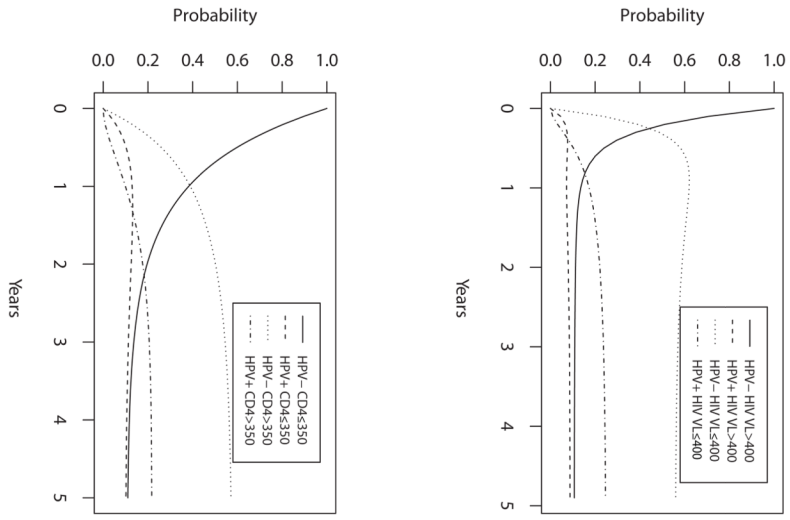


**Figure 2.**
State probability curves over 5 years from (A) VL Model and (B) CD4 Model, based on the model estimates using Set II. The initial state is State 1: high risk HPV negative and (A) VL>400, or (B) CD4 350.