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Mixed Membership Trajectory Models of Cognitive Impairment in the Multicenter AIDS Cohort Study

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Abstract

Objective—The longitudinal trajectories that individuals may take from a state of normal cognition to HIV-associated dementia are unknown. We applied a novel statistical methodology to identify trajectories to cognitive impairment, and factors that affected the “closeness” of an individual to one of the canonical trajectories.

Design—The Multicenter AIDS Cohort Study (MACS) is a four-site longitudinal study of the natural and treated history of HIV Disease among gay and bisexual men.

Methods—Using data from 3,892 men (both HIV-infected and uninfected) enrolled in the neuropsychology substudy of the MACS, a Mixed Membership Trajectory Model (MMTM) was applied to capture the pathways from normal cognitive function to mild impairment to severe impairment. MMTMs allow the data to identify canonical pathways and to model the effects of risk factors on an individual’s “closeness” to these trajectories.

Results—We identified three distinct trajectories to cognitive impairment – one “normal aging” (low probability of mild impairment until age 60), one “premature aging” (mild impairment starting at age 45–50), and one “unhealthy” (mild impairment in 20s and 30s) profile. Second, clinically defined AIDS and not simply HIV Disease, was associated with closeness to the premature aging trajectory. And, third, Hepatitis-C infection, Depression, Race, Recruitment Cohort and Confounding Conditions all affected individual’s closeness to these trajectories.

Conclusions—These results provide new insight into the natural history of cognitive dysfunction in HIV disease and provide evidence for a potential difference in the pathophysiology of the development of cognitive impairment based on trajectories to impairment.

Keywords

HIV; Dementia; HIV Associated Neurocognitive Disorder; Epidemiology

Introduction

HIV infection affects the nervous system [1], frequently resulting in neurobehavioral disturbances and HIV-associated neurocognitive disorder (HAND)[2, 3]. The advent of combination antiretroviral therapy (cART) has reduced the prevalence of HIV-Associated Dementia, but not of the milder syndromes[4–7]. HAND is still present in approximately 40% of HIV-infected individuals [8], and a number of risk factors have been identified. These can be host or HIV-disease based, and include older age, less education, the presence

of depression, hepatitis C virus (HCV) infection, AIDS, and the presence of other severe medical comorbidities[1, 2, 9].

The Multicenter AIDS Cohort Study (MACS) is a four-center study of the natural and treated history of HIV infection among gay/bisexual men. The MACS has tracked cognitive test performance for 25 years in a subcohort of men who formed the neuropsychological substudy[10]. Logistic regression, survival analysis, and similar methods have been used to determine how various risk factors influence the development of cognitive impairment in HIV disease[11–13], but they do not consider the possibility of multiple temporal patterns or trajectories to cognitive dysfunction.

In order to investigate the possibility of the existence of multiple patterns, or “trajectories” to cognitive impairment, we adapted the novel, data-driven Mixed Membership Trajectory Model (MMTM) technique [14] to fit these data. This technique has been used to model trajectories toward physical disability [15] as well as pathways to dementia in the elderly [16, 17]. MMTMs combine features of longitudinal Multivariate Latent Trajectory Models [18] to identify distinct, canonical profiles, with features of cross-sectional Grade of Membership Models[19] to allow individuals to have weighted memberships in each profiles.

An advantage of the MMTMs relative to other trajectory modeling techniques is that the MMTM also expresses each individual participant’s pathway as a *weighted combination* of the canonical trajectories. In addition to expressing an individual’s closeness to the canonical trajectories (or profiles), the membership weights can also be interpreted as reflecting each individual’s health propensities (i.e., disease and death).

The primary purpose of this study was to identify trajectories to impairment in a large cohort of gay/bisexual men with as much as 25 years of follow-up, and to determine the effects of HIV infection, AIDS, HCV infection, race, education and medical comorbidities on the closeness of each individual to the canonical trajectories.

Methods

This research was reviewed and approved by the Institutional Review Boards at each MACS site. Each participant signed a written statement of informed consent prior to starting any research-related activities.

Subjects

The MACS enrolled a total of 6972 men from sites in Baltimore, Washington, Chicago, Los Angeles, and Pittsburgh at three separate time points: 4954 men enrolled in 1984–1985, 668 men enrolled in 1987–1991, and 1350 men enrolled in 2001–2003 (see [20, 21]). The men enrolled in 1984–1985 and 1987–1991 are considered cohort 1 (C1), and the men enrolled 2001–2003 are considered cohort 2 (C2). Details of the study enrollment have been reported previously [10] [22]. This study uses data from the NP study collected on or before March 31, 2012 [10].

Cognitive Classification

The NP evaluation includes measures from multiple cognitive domains related to classification of HAND[3, 22–25] including: executive functioning, speed of information processing, attention and working memory, learning, memory, and motor [10]. In order to classify a participant as normal, mildly or severely impaired, they needed to have completed at least one test in four of the six domains. If that criterion was met, a summary T-score was calculated for each domain; if only one test in a domain was completed, the T-score for that test was used as the Domain Score. For domains with two test scores, we averaged the T-scores to create the Domain Score. However, in the case of the Motor domain, we used the lowest T-score on either the dominant or nondominant hand of the Grooved Pegboard. If the T-score for one of the Grooved Pegboard measures was ≥ 40 and the other one was <40 then the Motor domain was assigned the lowest obtained T-score plus five.

Using the Antinori criteria [3], cognitive classifications were: 1) Normal, if one or fewer domains had T-scores 1 SD or more below the mean (i.e., $T \leq 40$); 2) Mild Impairment, if two or more domains had T-scores 1 SD or more below the mean, and the individual did not meet criteria for the more severe category that follows; and 3) Severe Cognitive Impairment, if two or more domains had T-scores 2 SDs or more below the mean (i.e., $T \leq 30$), or one domain had a T-score 2.5 SDs or more below the mean (i.e., $T \leq 25$).

To be included in the MMTM, participants needed to have at least one cognitive classification. Although the MMTM technique is able to process time varying covariates, it is difficult to produce visual representations of trajectories that include multiple time-varying factors. Therefore, in this initial implementation of MMTMs in HIV disease, we limited our sample to men who did not become infected during the follow-up period, and age was the only time-varying factor. Of the 6,972 men in the MACS, 3,892 met these criteria. The differences between the men who did and did not meet these criteria are summarized in Supplemental Table E-1. Fifty-four percent (2099/3892) of the men included in this study were HIV infected at their first cognitive classification. Table 1 presents the characteristics of the participants by serostatus. Cognitive classifications were made at multiple time points (ages) for each individual. There were a total of 25,471 observations for the 3,892 participants, an average of 6.54 observations per individual.

Trajectory Modeling

We assumed the existence of a small number of “canonical profiles” to describe distinct patterns in the development of cognitive outcomes over time (see Discussion for information regarding profile selection). The purpose of these analyses is to identify from the data, trajectories or pathways that individuals may take to one of the three cognitive outcomes (i.e., normal, mildly impaired, severely impaired) over time (and as they age). The MMTMs differ from other trajectory models in that each individual is not forced to follow a single trajectory exactly, but rather shares some properties of each trajectory to varying degrees. Thus, at the end of the analysis, we have membership weights for each individual for each trajectory.

At each study visit there is a cognitive classification that is coded for each individual: Normal, Mildly Impaired, Severely Impaired. For each of the three of the profiles, the probability of each diagnosis as a function of age is modeled as a multinomial ordered logistic regression [26] (See Eq. 1, Supplemental Materials), allowing the computation of the probability of each cognitive classification given age.

MMTMs are multilevel models which means that they offer insight both at a general level, and at the level of the *individual* pathway characterizing an *individual* participant. The trajectory of each individual can be modeled by the MMTM as a mixture of the canonical trajectories (See Eq. 3, Supplemental Materials). Because the membership weights capture general health status of each individual, it is reasonable to assume that particular outcomes, such as mental state or death [27, 28], are conditionally independent of one another, given these health status weights. This is analogous to the conditional independence of multiple indicators (observed scores, data), given factor scores, in typical factor analytic methodologies.

We tested the effects of seven time invariant, binary predictor variable: Cohort (C1), Race (White), Confounding Conditions (Ever) [29], Hepatitis C Infection (Ever), Depression (Ever), HIV (Present), and AIDS (Present Ever). AIDS was defined as occurring when HIV seropositive men developed an AIDS-defined illness (i.e., ignoring CD4+ cell count). We selected these seven variables in this first implementation of an MMTM either because we knew they were significant predictors within the MACS cohort (e.g., recruitment cohort, medical comorbidities), because they had been identified as risk factors by others (e.g., HCV, depression), or because they were related to HIV disease (i.e., infection status and AIDS).

In the MMTM, each of these predictor variables has a coefficient to describe its impact on the membership weight of each canonical profile. For example, Cohort (X_1) will have a coefficient, α_{11} , to describe the impact of Cohort on membership for canonical profile 1, a coefficient, α_{12} , to describe the impact of cohort on membership for canonical profile 2, and coefficient, α_{13} , to describe the impact of cohort on membership for canonical profile 3. The relative effect of a given predictor on the odds of an individual identifying more closely with one profile than the other, is described by the *difference* between these coefficients.

In addition to modeling the probabilities of the *cognitive* outcomes in each of the men while they are in the study, we also modeled the probability of death. This was important because we needed to account for censoring by death in order to obtain accurate estimates of the probabilities of mild and severe cognitive impairment at later ages, when these cognitive outcomes might be masked by (premature) death. For a more detailed description, see the Supplemental materials.

Results

There are three main findings from this study. First, we identified three distinct trajectories to cognitive impairment – one “normal aging”, one “premature aging”, and one “unhealthy” profile. Second, clinically defined AIDS and not simply HIV Disease, was associated with

closeness to the premature aging trajectory. Third, HCV, Depression, Race, Cohort and Confounding Conditions all affected individual's closeness to these trajectories.

Figure 1 shows the trajectories of the three canonical profiles: the probability of severe impairment as a function of age is shown by the red curves, the probability of mild impairment is shown by the black curves, and the probability of normal cognition is shown by the green curves. It is important to note that these curves should not be viewed or interpreted as if they were survival functions. These trajectories are the cross-sectional probabilities of the three states (normal, mildly and severely impaired) at each age; thus, at any given age, the sum of the three probabilities is equal to 1.00.

We arbitrarily refer to canonical profile 1, for which the probability of normal cognition is initially very high, as the “normal aging” profile; profile 2, for which the probability of mild impairment begins to climb at age 45–50 years, as the “premature aging” profile; and profile 3, for which the probability of normal cognition is near zero even at the youngest age, as the “unhealthy” profile.

For the normal aging profile, the probability of cognitive impairment is virtually zero until the age of 60. Thereafter, the likelihood of mild impairment increases, while that of normal cognition necessarily decreases. At age 80 the individuals close to the canonical profile have approximately equal likelihoods of having normal cognition or being mildly impaired. The likelihood of a severe impairment remains close to zero, reflecting, in part, the relatively small proportion of the sample in the 70+ year age range. Approximately 60% of the study sample is closest to this canonical profile.

The “premature aging” profile is similar to the “normal aging” profile, except that it is offset to the left by 25+ years. Individuals close to this profile (approximately 21% of the sample) have a approximately equal probability of normal cognition and mild impairment at age 50–55, and by age 80 the likelihood is greatest that these individuals will have a severe cognitive impairment.

Individuals closest to the “unhealthy” profile (approximately 19% of the sample) are either mildly or severely impaired across the entire age range. Even those individuals in their 20s have >80% likelihood of a mild impairment; by age 70 the probability of mild vs. severe impairment is approximately 50%.

The parameters of the MMTM, including the significant time invariant covariates, as well as the survival component are presented in Table 2. Cohort, AIDS, depression, HCV infection, confounding conditions, and the cohort by race interaction significantly affected closeness to the canonical profiles. Of particular importance were the findings related to HIV disease, AIDS, and HCV infection. The effect of AIDS on closeness to the canonical trajectories was the largest of all of the time invariant covariates that were tested. While infection with HIV moved individuals *towards* the premature aging profile, those individuals with AIDS moved *away* from the healthy profile towards the unhealthy, and also *towards* the premature aging profile. Infection with hepatitis C tended to move individuals *away* from the normal aging profile and *towards* the premature aging and unhealthy profiles. The effect of having been recruited into C2 was to move individuals *away* from the healthy profile.

In Table 3, we break down the sample into three groups, each representing those individuals who were closest to one of the three canonical profiles. That is, individuals listed under the “normal aging” profile were closest to the normal aging profile compared to either the premature aging or unhealthy profiles. The table then shows the percent of individuals within each of these broadly defined groups who had the condition represented by each covariate. That is, 34.9 percent of the individuals closest to the normal aging profile were HIV-infected. We did not test to determine whether there was a significant difference in the distribution of the covariates across the three canonical profiles because the variables used in Table 3 actually occur twice in the table – once in the MMTM (generating the column labels), and again in the table itself (as row variables).

In order to demonstrate the effect of the individual covariates on closeness to the canonical profiles, we identified five study participants who had different combinations of the covariates. Figure 2 shows the trajectories for these individuals relative to the canonical trajectories generated by the MMTM. The top panel shows the trajectories for Mild impairment; the bottom panel for Severe impairment. With an increasing number of covariates the individual profiles move away from the normal aging profile, through the premature aging profile, towards the unhealthy profile.

Discussion

We have identified, for the first time, three distinct, canonical profiles to cognitive impairment in HIV disease, and tested the effects of seven factors on the “closeness” of individuals to each of these profiles. The trajectories to cognitive impairment included: “normal aging”, “premature aging”, and an “unhealthy” profile. HIV, AIDS, HCV, cohort, confounding conditions, depression, and the interaction between cohort and race have a significant effect on the closeness of individuals to these profiles. These results provide new insights into the natural and treated history of HIV/AIDS by demonstrating that illness progression does not follow a single course. These results demonstrate that *within the data* there is evidence of three distinct pathways that individuals within this large group of men, both with and without HIV disease, can develop cognitive impairment. These results differ from traditional survival models, which assume the existence of only a single linear pathway, and from other trajectory models in that individuals’ trajectories are weighted combinations of the “canonical” trajectories. The analysis of the model covariates reveals how they affect individuals’ closeness to each of the three canonical profiles. Thus, these models provide a unique way of examining longitudinal data, and eventually may allow us to identify biologically meaningful subgroups of individuals based on the trajectories and the covariates, potentially affecting treatment and management.

Our finding of a “premature” aging trajectory is relevant to the ongoing discussions regarding the possibility that infection with HIV results in an accelerated or premature aging (see [30–32] for reviews). HIV disease moved individuals away from the healthy and unhealthy profiles, and towards the premature aging profile. A similar pattern was seen for AIDS, meaning that those HIV-infected individuals who ever met criteria for clinical AIDS also moved towards the premature aging profile. It is important to emphasize that while this profile is certainly consistent with what has been described as “premature aging” both in

terms of HIV disease but also other conditions (e.g., [33]), we did not directly test “aging” biomarkers such as telomere length or immune senescence.

One of the key strengths of the MMTM is that individuals are assumed to have weighted membership in each of the canonical profiles. It is possible for an individual to be an ideal member of one profile or to be a mixed member of all three profiles, allowing individuals to display characteristics of each profile to varying degrees. This can be seen not only in Figure 2, but also in Supplemental Figure 1 that presents 100 (total) random individuals’ trajectories to each cognition classification. This ability of individuals to have mixed memberships in the trajectories is important because there is variability in the prevalence and importance of risk factors, which directly influences membership as a function of age.

Under the MMTM, the covariates that we tested here should not be viewed in the traditional sense of affecting the risk of a certain cognitive classification, but rather as affecting the “closeness” of an individual’s profile to a canonical profile. For example, the presence of a confounding condition does not increase an individual’s risk for severe cognitive impairment, but rather increases the likelihood that that individual will identify more closely with the unhealthy profile than the healthy profile. This is a critical distinction for understanding the power of the MMTM as compared to other methods of analyzing epidemiologic data.

To decide how many trajectories to include in the final model, we explored both two and three trajectory models and were able to obtain estimates from both. We then compared the prediction accuracy of the two models using the method of posterior predictive checking (see Chapter 24 of [34]), replicating the original classifications to obtain 1,000 different simulated datasets. The models performed equally well with regard to overall accuracy (See Supplemental Materials), but the three trajectory model was easier to interpret, leading us to present those findings here. The model presented here should not be thought of as a “true” model, but rather the best solution for a three profile model. If we had more participants at the upper and lower ends of the age distribution, this could easily result in a change in the number and shape of the canonical profiles.

Individuals identifying more closely with the premature aging profile are also more likely to die sooner (See Supplemental Figure E-2), and individuals with HIV disease and those with AIDS are likely to be closer to this profile than the other two. This observation adds to our confidence in the interpretability and validity of these trajectories in that HIV-infected individuals with severe cognitive impairment have a higher risk of death [28, 35]. Additionally, the finding that cohort, HCV infection, confounding conditions, and depression, and AIDS affect the closeness of individuals to the normal aging profile (i.e., generally away from that profile) may be a direct reflection of the potential for each these conditions to negatively affect brain health.

The covariates in the model do not fully explain trajectory membership, suggesting that other factors may also influence individual trajectories. These may include ApoE genotype, recreational drug use, and access and adherence to combination antiretroviral therapies (cART). Unfortunately, genetic data were not available from a large enough number of

individuals to include ApoeE genotype as a predictor in the model. On the other hand, information on the use of both recreational drugs and cART are time varying predictors, and we had decided to delay including such variables in this first use the MMTM framework in the context of HIV Disease. Nevertheless, these results emphasize the value of MMTMs as a novel, analytic tool, and demonstrate their ability to identify patterns within large data sets that might have otherwise gone unnoticed.

There are several limitations to our study; first, MMTMs cannot easily account for time-varying covariates, such as incident infection or disease (or CD4+ cell counts), an obvious limitation in the study of HIV disease. Thus, additional work needs to be done in order to develop computationally efficient methodologies for the incorporation of time-varying covariates into the models, and to allow for the visualization of the effects of these covariates. Second, our data are restricted to gay and bisexual men evaluated as part of the MACS; we did not evaluate trajectories among women or among younger substance users. For the MMTM to be most useful, longer observation periods are essential, and while the Women's Intra-agency HIV Study (<http://statepiaps.jhsph.edu/wihs/>) has similar biological and medical comorbidity information, it has only limited neuropsychological evaluations. Therefore, at the present time, large, long-term follow-up studies that could be merged with this data set are not available.

In conclusion, the MMTM technique uses patterns *within the data* to identify distinct, canonical profiles; the results are not constrained by any *a priori* assumptions about the trajectories. These techniques are highly innovative in that they are able to: 1) account for "reversing" states – i.e., moving from HAD to mild impairment and even normal cognition, as might be expected following viral suppression; 2) express each individual's pathway as a weighted combination of the canonical trajectories; and, 3) determine the extent to which risk factors for cognitive impairment affect the "closeness" of an individual to each of the canonical trajectories. This tool has the potential for meaningful application in a variety of domains related to HIV disease, and holds the promise to reveal important data-driven insights into the natural and treated history of HIV disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The three canonical profiles with pointwise posterior 95% credible bands for each cognitive classification. The X-axis represents assembled cross-sectional probabilities of the three states (normal, mildly and severely impaired) across time/age. At any given age, the sum of the three probabilities is equal to 1.00. The Y-axis represents the age of the men in the cohort at the time of the examination.

A) The trajectories of the “normal aging profile” for the probability of normal cognition (green), mildly impaired cognition (black), and severely impaired cognition (red). B) The trajectories of the “premature aging profile” for the probability of normal cognition (green), mildly impaired cognition (black), and severely impaired cognition (red). C) The trajectories of the “unhealthy profile” for the probability of normal cognition (green), mildly impaired cognition (black), and severely impaired cognition (red).

Effects of Covariates on Closeness to Trajectories to Mild and Severe Cognitive Impairment

Figure 2.

The effects of individual covariates on individual trajectories to mild impairment (A) and severe impairment (B). Case 1 has none of the covariates of interest, Case 2 has only HCV infection, Case 3 has HCV and HIV infection, Case 4 has HCV, HIV, and AIDS, and Case 5 has HCV, HIV, AIDS, and confounding medical conditions.

Table 1

Characteristics of Study Participants at Time of First Cognitive Classification

Viral Status	HIV–	HIV+	Effect Size
N=	1793	2099	
Cohort (C1/C2)¹	71/29 (1275/518)	69/31 (1451/648)	0.022
Years between Baseline Visit & First Cognitive Classification¹	5.56 (7.1)	3.59 (4.3)	–0.340*
Age¹	40.96 (10)	38.20 (8.0)	–0.299*
Education Years¹	15.64 (2.7)	14.94 (2.7)	–0.258*
Race (White)¹	77.47 (1389)	71.32 (1497)	–0.006
Marijuana²	36.90 (655)	45.44 (942)	0.086*
Cocaine²	14.42 (256)	21.08 (437)	0.086*
IVD^{**2}	2.95 (52)	4.82 (98)	0.048*
Opiates²	2.54 (45)	2.17 (45)	0.103*
CD4+ Count¹	n/a	483.76 (280)	
Standardized Log₁₀ Viral Load¹	n/a	3.49 (1.4)	
AIDS²	n/a	6.10 (128)	
Cognitive Classification (none/mild/severe)²	78/18/4 (1392/327/74)	67/18/5 (1629/368/102)	0.019
Combination ART^{2***}	n/a	20.96 (440)	N/A
Speed of Processing³	50.5 (9.0)	49.8 (9.1)	.06
Executive Functions³	49.9 (9.4)	49.9 (9.5)	.01
Working Memory³	49.4 (9.3)	49.2 (9.0)	.02
Memory³	49.6 (9.4)	49.9 (9.6)	–.03
Learning³	49.5 (9.1)	49.5 (9.3)	–.004
Motor Function³	46.9 (10.4)	46.5 (10.5)	.04

¹ These characteristics are presented as Mean (SD), and their effect size is reported as Cohen's d statistic.² These characteristics are presented as Percent (N) 'Yes', and their effect size is reported with the phi statistic.³ Age and education adjusted T-scores (mean ± standard deviation); their effect size is reported as Cohen's d statistic.

* p<0.05

** IVD = Intravenous drug use.

*** Antiretroviral Therapy

Table 2

Parameters for the MMTM with all of the tested covariates included.

	Canonical Trajectory Parameters	Estimate (SD)		
		Healthy	Premature Aging	Unhealthy
Intercept	B_{0*}	13.629 (5.816)	5.500 (0.608)	1.061 (0.044)
Effect of Age	B_{1*}	-0.189 (0.027)	-0.155 (0.016)	-0.039 (0.004)
Mild/Severe Impairment Threshold	c_*	6.540 (3.882)	3.985 (0.540)	28.872 (18.931)

Covariate	Estimate [95% CI] for difference between Healthy and Unhealthy Profiles ¹	Estimate [95% CI] for difference between Healthy and Premature Aging Profiles ²	Estimate [95% CI] for difference between Unhealthy and Premature Aging Profiles ³
Cohort	-0.805 (-1.131, -0.484)*	0.738 (0.317, 1.269)*	1.588 (1.124, 2.127)*
Race (White)	-0.046 (-0.364, 0.277)	-0.318 (-0.688, 0.096)	-0.272 (-0.644, 0.171)
Confounding Conditions	-0.154 (-0.030, -0.014)*	0.592 (0.390, 0.798)*	0.746 (0.533, 0.959)*
Hepatitis C Virus Infection	-0.321 (-0.575, -0.058)*	-0.344 (-0.656, -0.020)*	-0.024 (-0.346, 0.287)
Depression	-0.433 (-0.606, -0.262)*	0.196 (-0.032, 0.402)	0.629 (0.365, 0.874)*
HIV	-1.267 (-1.569, -0.977)*	-3.795 (-4.176, -3.458)*	-2.529 (-2.963, -2.173)*
AIDS	-0.194 (-0.351, -0.034)*	-2.57 (-2.863, -2.253)*	-2.370 (-2.733, -1.994)*
HIV & Race Interaction	0.549 (0.167, 0.943)*	0.523 (-0.149, 1.119)	-0.026 (-0.744, 0.597)

¹ a positive value increases the odds of being closer to the Healthy Profile

² a positive value increases the odds of being closer to the Healthy Profile

³ a positive value increases the odds of being closer to the Unhealthy Profile

Table 3

Distribution of Risk Factors Across the Three Trajectories

	Normal Aging	Premature Aging	Unhealthy
Number	2028	704	630
HIV Infected²	34.6	59.6	41.0
AIDS	3.8	39.7	11.9
HCV Infected	6.7	11.9	13.4
Race (White)	73.9	86.7	60.7
Depressed	72.1	71.4	81.2
Medical Confounds	31.6	25.4	39.8
Cohort 1	65.7	95.3	53.8

¹ Participants are classified based on profile with the largest membership weight g_{ik}

² All numbers are percentages of the men closest to the trajectory who are positive for the risk factor (e.g., 34.6% of the men in closest to the “Normal Aging” trajectory are HIV-infected).