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Trajectories of Marijuana Use among HIV-seropositive and HIV-Seronegative MSM in the Multicenter AIDS Cohort Study (MACS), 1984–2013

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Abstract

To construct longitudinal trajectories of marijuana use in a sample of men who have sex with men living with or at-risk for HIV infection. We determined factors associated with distinct trajectories of use as well as those that serve to modify the course of the trajectory. Data were from 3658 [1439 HIV-seropositive (HIV+) and 2219 HIV-seronegative (HIV−)] participants of the Multicenter AIDS Cohort Study. Frequency of marijuana use was obtained semiannually over a 29-year period (1984–2013). Group-based trajectory models were used to identify the trajectories and to determine predictors and modifiers of the trajectories over time. Four distinct trajectories of marijuana use were identified: abstainer/infrequent (65 %), decreaser (13 %), increaser (12 %) and chronic high (10 %) use groups. HIV+ status was significantly associated with increased odds of membership in the decreaser, increaser and chronic high use groups. Alcohol, smoking, stimulant and other recreational drug use were associated with increasing marijuana use across all four

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Compliance with Ethical Standards

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declares that they have no conflict of interest.

trajectory groups. Antiretroviral therapy use over time was associated with decreasing marijuana use in the abstainer/infrequent and increaser trajectory groups. Having a detectable HIV viral load was associated with increasing marijuana use in the increaser group only. Future investigations are needed to determine whether long-term patterns of use are associated with adverse consequences especially among HIV+ persons.

Resumen

Construir unas trayectorias longitudinal del uso de marijuana por hombres que han tenido relaciones sexuales con otros hombres y tienen o son inclinado a tener VIH. Hemos determinado los factores distinto que son asociado con las trayectorias del uso y tambien los que sirven a modificar el curso de la trayectoria. Se analizó datos de 3.658 hombres (1.439 VIH-sero-positivo y 2.219 VIH-sero-negativo) del estudio Multicenter AIDS Cohort (MACS) que han tenido relaciones sexuales con otros hombres. La frecuencia del uso de marijuana se colecto semi anual sobre 29 años (1984–2013). Utilizamos modelos de trayectoria basado en grupos para identificar las trayectorias, determinar los indicadores y modificadores de las trayectorias sobre tiempo. Identificamos cuatro distinto trayectorias del uso de marijuana: [1] abstinente/infrecuente 65 % (2) disminución de uso 13 % (3) uso creciente 12 % y (4) crónico 10 %. Se nota una correlación significativamente con hombres VIH-positivo en grupos 2, 3 y 4, En el análisis de hombres solo VHI-positivo, uso del alcohol, cigarrillos, estimulantes y otras drogas tuvieron asociado con el uso de marijuana mas creciente sobre todos los groupos de la trayectorias. Hombres que practican terapia antiretroviral estuvieron asociado con grupos 1 y 3. Hombres con niveles de *viral load* detectable estuvieron asociado con group 3 solamente. Se requiere mas estudios para mejor analizar si el uso a largo plazo son asociadas con las consecuencias especialmente entre personas VIH-positivo.

Keywords

Marijuana use; MSM; Trajectories; Persons living with HIV

Introduction

Marijuana use is common among persons living with HIV as studies have reported prevalence rates of current marijuana use between 24 and 56 % [1–6] as compared to approximately 7 % in the general United States population [7]. Men who have sex with men (MSM) report higher rates of current and past-year marijuana use than their heterosexual counterparts [8, 9]. Several studies report that persons living with HIV use marijuana to alleviate stress, anxiety, depression, HIV-related symptoms and side effects of antiretroviral therapy (ART) [2, 6, 10, 11]. In one recent study, among HIV-seropositive (HIV+) persons who inject drugs and who recently seroconverted, heavy cannabis use was associated with lower plasma viral load levels [12]. The therapeutic effects of marijuana are proposed to be mediated via the actions of active cannabinoid chemicals in marijuana—cannabidiol—at specific receptor sites: cannabinoid receptors (CB2) located mainly on cells and tissues of the immune system [13, 14]. In contrast the primary psychoactive cannabinoid in marijuana: tetrahydrocannabidiol (THC) binds to and activates another receptor site: cannabinoid receptor (CB1) located mainly in areas of the brain [15] to produce the euphoric and

cognitive impairing effects of marijuana [16]. Accordingly, there are concerns that marijuana use may be associated with poorer HIV treatment outcomes. Previous studies have found marijuana use to be associated with decreased cognitive function [17, 18] as well as reduced ART adherence [11, 19], which is crucial for persons living with HIV as optimal adherence to ART medications is required for long-term viral suppression [20].

Effective prevention strategies to reduce unhealthy or harmful marijuana use require an in-depth understanding of subgroups with different patterns of use. Despite the published evidence that marijuana use is common among HIV+ individuals and MSM and the potential adverse health outcomes associated with its use in these populations, very little is known about the patterns of marijuana use or how patterns of marijuana use may change over time in these populations.

Developmental research suggests different rather than similar pathways via which individuals initiate and progress to unhealthy or problem substance use [21, 22] over the life course. For instance, individuals who start using substances at an early age have increased risk of progressing to problem use and developing use disorders [23, 24]. Among HIV+ women, depressive symptoms and the presence of hepatitis C infection was associated with a pattern of persistent heavy drinking over time [25]. Another study found that low income and concurrent substance use were factors that predicted consistent hazardous drinking among HIV + MSM [26]. Therefore, understanding the natural history of marijuana use and the identification of different trajectories of use over time is important in order for intervention programs to be most effective. For instance, the identification of different patterns of marijuana use over time can help characterize subgroups of individuals with the greatest risk of progressing to heavy patterns of marijuana use and reveal unique predictors of such patterns of use which can be used to inform targeted intervention programs. To the best of our knowledge, there has not been a published report that has followed HIV+ individuals and MSM longitudinally over an extended period to characterize the natural history of their marijuana use. Past studies on substance use patterns in these populations have often focused on alcohol or heavy episodic drinking [26, 27], cigarette smoking [28] or stimulant use [29]. Therefore, the objectives of the current study are to characterize the longitudinal trajectories of marijuana use in a sample of HIV-seropositive (HIV+) and HIV-seronegative (HIV−) MSM over a period of 29 years, and to identify factors associated with unique trajectories of marijuana use, as well as those that can change over time that may modify the course of the trajectory.

Methods

The Multicenter AIDS Cohort Study (MACS)

The MACS is an ongoing prospective cohort study of the natural and treated history of HIV infection among MSM in the United States. A total of 6972 men were enrolled during the history of the project in three waves: 4954 men in 1984–1985, 668 in 1987–1991, and 1350 in 2001–2003 and at four centers located in Baltimore/Washington DC, Chicago, Los Angeles, and Pittsburgh. The study design of the MACS has been described previously [30–32] and only the design relevant to the current analysis is described here. The study questionnaires used in the MACS are available at: www.statepi.jhsph.edu/macs/forms.html.

The MACS study protocols were approved by the institutional review boards at the respective recruitment centers and their community affiliates and informed consent was obtained from all participants. MACS participants return every 6 months for a physical examination, collection of blood specimens and completion of a detailed interview and questionnaires. The interview and questionnaires include demographic, psychosocial, behavioral and medical history data. The questions about their recreational drug use, including marijuana, alcohol, poppers, cocaine, crack, heroin, methamphetamine, ecstasy, injection drug use as well as smoking history since their last visit were collected using Audio Computer Assisted Self-Interviewing (ACASI), an approach previously demonstrated to provide more accurate assessments of 'sensitive behaviors' than interview-administered questionnaires among MSM [33].

This analysis included data collected from standardized marijuana use questions from semiannual study visits 1 (data collection in April 1984–September 1984) through visit 59 (data collection ending in April 2013–September 2013). The study sample included 3658 participants who had data about marijuana use for at least 25 % of their possible study visits during the follow-up period. Specifically, the men enrolled in 1984–1985 and 1987–1991 had 15 and 13 visits or more respectively, whereas, the men enrolled in 2001–2003 had 6 or more visits. The median years of follow-up was 11.5 years [interquartile range (IQR): 9.5–21.0).

Measures

Outcome Measure: Marijuana Use—Marijuana use at each study visit was assessed with the following question "*Have you used any pot, marijuana or hash since your last visit*?" Participants who responded '*No*' to this question were classified as non-users. Among those who responded 'Yes', frequency of use was asked with the following question "*How often did you use pot, marijuana or hash since your last visit*?" with the following response options: "Daily"; "Weekly"; "Monthly" and "Less often".

Covariates

Sociodemographic Characteristics—The baseline visit (or index visit) was used to define a three level categorical variable for race/ethnicity status (non-Hispanic, white, non-Hispanic black and Other), educational attainment (high school diploma or less, some college or college degree, graduate work or more) and employment (employed or unemployed). Participants were classified according to the MACS study center they were enrolled and whether they were enrolled prior to or after 2001.

Depressive Symptoms—The Center for Epidemiologic Studies Depression (CES-D) scale, was used to measure clinically significant symptoms of depression [34]. This assessment was developed for use with community populations and includes components of depressed mood, feelings of worthlessness, sense of hopelessness, sleep disturbance, loss of appetite, and concentration difficulties. Scores on the CES-D of 16 or more suggests a clinically significant level of psychological distress [34].

Alcohol Use—Using data regarding frequency of drinking and average number of alcoholic drinks, alcohol consumption at baseline and at each study visit was categorized as hazardous drinking (defined as consumption of ≥14 drinks per week or any binge drinking i.e. 5 or more drinks per occasion) [35], low or moderate use (any drinking not meeting criteria for hazardous use) or no alcohol use.

Tobacco Use—Participants were classified as never, former and current smokers of cigarettes at each study visit. Participants were asked two questions including: whether they ever smoked cigarettes and whether they smoke cigarettes now. Participants were considered to be current smokers if they responded 'Yes' to both questions. Participants were categorized as former smokers if they answered 'Yes' to ever smoking cigarettes and 'No' to the smoking cigarettes now. Never smokers included participants who answered 'No' to both questions. In addition, among current smokers, pack-years of smoking at initial visit and at each subsequent visit was calculated using participants' responses to questions about the number of packs of cigarettes smoked per day.

Stimulant/Recreational Drug Use—Participants were considered to be users of stimulant drugs if they reported the use of any of the following drugs at baseline and at each study visit: (1) crack cocaine, (2) other forms of cocaine, (3) methamphetamines (or speed, meth or ice), (4) other recreational drugs such as "ecstasy" or MDMA (3,4-methylenedioxy-*N*-methylamphetamine).

Clinical Factors—HIV serostatus was assessed using an enzyme-linked immunosorbent assay with confirmatory Western blot tests on all MACS participants at each participant's initial visit and at each study visit for participants who were initially HIV−. Standardized flow cytometry was used to quantify CD4 + T-lymphocyte subset levels by each MACS site [36] and categorized as ≤200/mm^3, 201–500/mm^3, and >500/mm^3. Levels of plasma HIV RNA were measured using either the standard reverse transcription-polymerase chain reaction assay (Roche Nutley, NJ) or with the Roche ultrasensitive assay (Roche Diagnostics. Standardized viral load measures (across different assays) were used to create a dichotomous variable to denote detectable (>400 copies per mL) versus undetectable viral load. Hepatitis C virus (HCV) infection status was categorized as HCV negative if HCV antibody testing was negative. Participants were classified at each MACS study visit as HCV positive if they were found to be in the process of seroconversion, acute infection, chronic infection, clearing (between RNA + and RNA−), or previously HCV positive, but now clear of HCV RNA. In addition to the aforementioned covariates, we considered that the trajectories of marijuana use over time among HIV+ participants may be influenced by factors specific to HIV-infection. ART use was dichotomized as use of any ART since the last study visit versus no therapy used.

Attrition—Two binary variables were constructed and used as covariates to adjust for the effect of attrition: one for participants who dropped out or were lost to follow up (n = 1394) and the other for those who died within the follow-up period (n = 643).

Data Analysis

We used participant's self-reported frequency of marijuana use across the follow-up period to identify trajectories using a semi-parametric group-based mixture model: PROC TRAJ SAS procedure [37]. This approach sorts each participant's frequency of marijuana use over their follow-up period into 'clusters' and estimates a single model—consisting of distinct trajectories. The procedure calculates the probability of each participant belonging to each trajectory group and assigns individuals into trajectories based on their highest probability of trajectory membership [37, 38]. Participants were followed from the time of enrollment until either the time of death, lost to follow up or until the end of the study period (i.e. MACS visit 59 or September, 2013). We began by fitting a series of models with two to five trajectories by assuming linear, quadratic and cubic shape of the trajectory group curves. Several factors were considered in determining model fit and the optimal number of trajectory groups (and trajectory shape) that best represented the heterogeneity of groups within the data: including, a priori knowledge from previous research on trajectories of marijuana use [39–45], model fit statistics including Bayesian information criterion (BIC) [46], Akaike Information Criterion (Both BIC and AIC; smaller values suggesting better fit) [47], average posterior probability (entropy) of group membership (a measure of classification quality; greater than 0.7 suggests adequate internal reliability) [38], significance of the shape of the trajectory group curves (e.g., linear, quadratic), and size of the group membership (≥5 % per each group size). Model fitting was an iterative process, starting with a quadratic specification for the shape of the trajectory group curves and assessing whether an additional group resulted in a better model fit based on the aforementioned criteria. We then estimated higher order shapes of the trajectory group curves (e.g., cubic) and subsequently dropped non-significant terms. Models used a zero-inflated Poisson distribution to account for the large number of participants who reported not using marijuana.

After the optimal number of trajectory groups and shape of trajectory change were selected, we included covariates of interest to the trajectory models. For this analysis, two types of covariates were considered: time-fixed/risk factors of trajectory group membership and time-varying covariates. These time-fixed/risk factors comprise characteristics established before or at the time of the initial period of trajectories that may serve to predict membership in a given trajectory. Time-varying covariates measured during the course of the trajectory provide trajectory group-specific estimates of whether these covariates alter the course of the trajectory. One advantage of the PROC TRAJ software is that it allows for joint estimation of the parameters that describe the shape of the trajectory group curves, adjusted odds ratio (for risk factors for trajectory membership) and the coefficient estimates (for the time-varying covariates). We estimated models for all participants as well as by HIV serostatus. The analysis of all participants was adjusted for sociodemographic characteristics, depressive symptoms, substance use variables, hepatitis C infection status, attrition variables, and HIV serostatus. To account for potential differences in marijuana use by geographic region/site and MACS enrollment cohort, all models included variables for MACS center and enrollment cohort. In the analysis restricted to HIV+ participants, we included other clinical factors relevant to HIV+ status such as ART use, CD4 counts, and

viral load detectability. All analysis was performed in SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Sample Characteristics

The 3658 participants in this study contributed a total of 105,595 person-visits; the median number of visits was 23 (IQR: 19, 42) representing approximately 11 years (Table 1). Among those who were HIV+ (n = 1439 or 39 %), the mean age at baseline visit was 35 years [standard deviation (STD) = 7.7], median number of visits was 23 (IQR = 18, 38), the majority (62 %) were non-Hispanic whites and 24 % were non-Hispanic blacks (Table 1). At baseline, among the HIV+ participants, marijuana use was high (62 %: 52 % used less than daily and 10 % daily), 90 % used alcohol (including 25 % meeting criteria for hazardous use), 67 % reported stimulant/recreational drug use, 44 % were current smokers and 29 % were classified as having clinically significant depressive symptoms (CES-D ≥ 16; Table 1). At baseline, the HIV− participants in this study reported lower marijuana use (54 %; 48 % less than daily and 6 % daily use), stimulant/recreational drug use (59 %), rates of current smoking (35 %) and depressive symptoms (21 %) than the HIV+ participants. Both groups were similar with regard to alcohol use (Table 1).

Marijuana Trajectories—Using data for the entire sample, participants' self-reported frequency of marijuana use across the follow-up period identified four groups with distinct trajectories of marijuana use. We chose a four-group solution based on model parsimony, interpretability of trajectories, BIC and AIC values, significance of the polynomial growth terms, average posterior probabilities (which ranged between 0.95 and 0.99) and trajectory group size membership (all ≥5 %). Model fit information and average posterior probabilities of all models are displayed in supplemental Tables 2 to 5. Figure 1 displays the trajectories of marijuana use of these four groups, which we labelled as: "Abstainer/Infrequent", "Decreasers", "Increasers" and "Chronic high" trajectory groups. The *abstainer or infrequent use* group (65 % of the entire sample) was characterized by a group of men who abstained from or infrequently used marijuana during the follow-up period. The *decreaser* group (13 % of the entire sample) consisted of a group of men who reduced their marijuana use from nearly weekly use to infrequent use over the follow-up period. The *increaser* group (12 % of the entire sample) comprised a group of men who initially decreased their marijuana use during the first 10 years of follow-up, after which they began to increase their use over time. The *chronic high* group (10 % of the entire sample) represents a group of men who persistently used marijuana nearly daily over the follow-up period. Figure 2 displays trajectories of marijuana use among HIV+ participants: 61 % were in the *abstainer/ infrequent use* group, 14 % were in the *decreaser* group, 14 % in the *increaser* group, and 11 % in the *chronic high* group.

Table 2 displays the baseline characteristics of the entire sample by the four identified trajectory groups. The median number of visits was lower among those in the *increaser* trajectory group. Participants in the *abstainer/infrequent* use group were older at baseline compared to the other groups. Frequency of marijuana use at baseline varied across the

marijuana trajectory groups: as the proportion of daily users were < 1 % in the *abstainer/ infrequent*, 3 % in the *decreasers*, 10 % in the *increasers*, and 54 % in the *chronic high* groups. Racial status (among the whole sample), detectable HIV viral load and CD4 counts (among HIV+ participants) were similar across the marijuana trajectory groups.

Multivariable Analysis of Time-Stable and Time-Varying Factors of Marijuana Trajectories among All Men—A HIV+ status relative to being HIV− was associated with significant increased odds of membership in all groups reporting marijuana use: *decreaser* [adjusted odds ratio (AOR) = 1.61, 95 % confidence interval (CI) 1.27–2.05; $p < 0.001$], *increaser* (AOR = 1.63, 95 % CI 1.26–2.12; $p < 0.001$) and *chronic high* (AOR = 1.72, 95 % CI 1.32–2.23; $p < 0.001$) as compared to being in the *abstainer/ infrequent use* group (Table 3). The men who reported any marijuana use relative to those who *abstained or used infrequently* during the follow-up period were significantly more likely to be younger (Table 3). In addition, non-Hispanic blacks, compared to non-Hispanic whites had significantly increased odds of membership in the *decreaser* (AOR) = 1.42, 95 % CI 1.01–1.98; $p = 0.041$) and *increaser* (AOR = 1.43, 95 % CI 1.00–2.06; $p = 0.046$) groups relative to those in the *abstainer/infrequent use* group (Table 3). Those who had completed graduate work or more (at their baseline visit) as compared to those with a high school diploma or less had reduced odds of membership in *decreaser* (AOR = 0.61, 95 % CI 0.44–0.87; $p < 0.001$) and *chronic high* (AOR = 0.61, 95 % CI 0.41–0.89; $p < 0.001$) groups relative to the *abstainer/infrequent use* group. There were several significant associations with MACS study center on membership in the marijuana use trajectories. Those enrolled in the Los Angeles center as compared to nearly all other MACS centers had higher odds of reporting any marijuana use relative to being in the *abstainer/infrequent use* group (Table 3). Participants who were lost to follow-up and those who died during the follow-up period had significantly increased odds of membership in only the *increaser* trajectory group (Table 3).

The results for the effects of time-varying covariates are displayed in Table 3. These estimates are trajectory group-specific: they indicate whether a covariate measured over time alters the trajectory of marijuana use within that trajectory group only. The estimates for the time-varying covariates are growth parameters that describe the amount of change/deviation from the average long-term trajectory of marijuana use within the trajectory. Depressive symptoms were significantly associated with increasing marijuana use within the *abstainer/ infrequent* ($p < 0.05$), *decreaser* ($p < 0.01$), *and chronic high* group*s* ($p < 0.001$). Alcohol use (low/moderate and hazardous use), being a current cigarette smoker, stimulant/recreational drug use, and intravenous drug (IDU) user were each significantly associated with increasing marijuana use within all marijuana trajectory groups (all ps < 0.01).

Multivariable Analysis of Time-Stable and Time-Varying Factors Associated with Marijuana Trajectories among HIV+ men—HIV+ participants who reported any marijuana use were significantly younger relative to those in the *abstainer/infrequent use group* (Table 4). Non-Hispanic, blacks as compared to non-Hispanic, whites, had increased odds of membership in the *decreaser* group (AOR = 1.82, 95 % CI 1.10–2.99; $p = 0.021$). Results for the effect of time-varying covariates on trajectory levels are also displayed in Table 4. Alcohol use over time was associated with increasing marijuana use in all trajectory

groups (all ps < 0.001); however, hazardous use was not associated with increasing marijuana use in the *chronic high* group ($p > 0.05$). Current cigarette smoking and stimulants/recreational drug use during follow-up was significantly associated with increasing marijuana use across all trajectory groups (all ps < 0.001). ART use was significantly associated with decreasing marijuana use in the *abstainer/infrequent* ($p = 0.047$) and *increaser* groups ($p = 0.045$). Detectable HIV RNA over time was significantly associated with increasing marijuana use in the *increaser* group ($p = 0.002$).

Discussion

This study utilized data from the MACS cohort to assess different patterns of marijuana use and to examine both risk factors and time-varying correlates associated with the different trajectories of marijuana use. Our analysis revealed that MSM in the MACS exhibited four distinct trajectories of marijuana use over time, including: *abstainer/infrequent, decreasers, increasers* and *chronic high* groups. Most of the men in this cohort displayed a pattern of abstaining or infrequent use over time (65 %) whereas approximately 10 % who used daily or near daily at their index visit continued this pattern of use over their follow-up visits. About a quarter of the men changed their pattern of use over time, either decreasing (~13 % of the men) or increasing use (~12 % of the men). Overall, our analysis suggested that these patterns of marijuana use over time were similar for both HIV+ and HIV− participants. In the analysis among all men, HIV+ status was associated with membership across all three trajectory groups reporting any marijuana use. Among HIV+ participants, having a detectable HIV RNA over time was associated with increasing marijuana use only among the men who increased their marijuana use during the follow-up period. Self-reported ART use over time in HIV+ men was associated with reducing marijuana use in the *abstainer/infrequent* and *increaser* groups. Overall, alcohol consumption, cigarette, stimulant/recreational drug use and IDU over time were associated with increasing marijuana use in nearly all trajectory groups.

To the best of our knowledge, we are not aware of any previous study that has examined trajectories of marijuana use among HIV+ and HIV− MSM over a long period of follow-up. Prior studies that have assessed trajectories of marijuana use have focused on adolescents transitioning into young adulthood [39–45] or racial/ethnic minorities [48–50], with a few studies reporting trajectories of use covering adulthood [51–53]. Direct comparisons of the results from our study with prior research may not be straightforward due to the different populations studied and age periods covered. However, nearly all studies on trajectories of marijuana use have identified a group that abstained or used infrequently, with some identifying a *chronic high* user group and a few identifying groups that increased [42, 44] and decreased [43, 44] their use.

The current study found that a HIV+ status was associated with membership in the *decreaser, increaser* and *chronic high* marijuana trajectory groups, a finding that suggests that overall HIV+ MSM in the MACS were more likely to use marijuana as compared to HIV− MSM. This finding is consistent with a number of studies reporting higher rates of marijuana use among HIV+ individuals as compared to HIV-uninfected populations [2–7]. HIV+ individuals report using marijuana to alleviate symptoms related to HIV-infection as

well as side effects of ART, although a substantial proportion of HIV+ individuals use marijuana recreationally [2]. Approximately 16 % of the HIV+ men in this study reported decreasing their marijuana use over time. This pattern of decreasing substance use over time was recently observed in a study of trajectories of stimulant use among MACS participants [29]. The authors also found that the men who decreased stimulant drug use reported significant reduction in risky sexual practices over time. Among the HIV+ MSM in this study, having a detectable HIV RNA over time was associated with increasing marijuana use among individuals in the *increaser* group, but not among the men in the *decreaser* or *chronic high* groups. Accordingly, we found that ART use over time was associated with decreasing marijuana use in the *abstainer/infrequent* and *increaser* groups. It is important to note that the assessment procedures used in this study make it difficult to ascertain that ART use preceded marijuana use. However, these findings provide some reassurance that there may not be an urgent need to intervene; however, there is a need to continue to study the long-term effects of marijuana use on other health outcomes both in HIV+ and HIV− individuals.

In the data presented here, among the entire sample as well as HIV+ individuals, younger age was associated with membership in all marijuana trajectory groups and being non-Hispanic, black was associated with membership in the *decreaser* and *increaser* groups. In addition, alcohol use, cigarette smoking, stimulants/recreational drug use, and depressive symptoms over time served to increase marijuana use within nearly all marijuana trajectory groups. This finding is consistent with previous studies that found substantial overlap between several types of drug use and other psychosocial health problems [54–56]. Accordingly, any prevention approaches to mitigate these behaviors should not focus on one of these behaviors or conditions but must consider these co-occurring conditions holistically.

Our study has some limitations which we highlight in order for some caution to be exercised in the interpretation of our study findings. We restricted our analysis to MACS participants who had at least 25 % or more study visits in order to estimate stable trajectory models. However, at baseline, those included in the study differed from those not included on a number of sociodemographic, clinical characteristics as well as use of substances including marijuana (Supplemental Table 1). Therefore, it is possible that different trajectories of marijuana use may have emerged if these participants had been included in our study. Furthermore, in the MACS, data on substance use (including marijuana use) was obtained via Audio Computer- Assisted Self-Interview (ACASI). Although this method has demonstrated good accuracy in obtaining sensitive information such as drug use in studies of HIV+ individuals [57] as well as the MSM samples [33], the data reported here related to substance use may be subject to social desirability bias and most likely an under reporting with a potential underestimation of the true trajectories of marijuana use. Related to this issue is the effect of other biases related to participation in a large ongoing cohort study such as the MACS, along with participant attrition due to drop outs and mortality, which may result in an underestimation of long-term marijuana use. Indeed, in the current study, we found that men who increased their marijuana use and those with *chronic high* use over time were significantly more likely to die or to drop out during follow-up as compared to the *abstainer/infrequent* group. What this suggests is that the attrition in these groups may have precluded us from identifying what their patterns of marijuana use would have been if they had remained in the study. Also, participants in the MACS represent a highly cooperative

cohort of MSM who have been retained in an ongoing cohort study; thus, our findings may not be generalizable to the larger MSM population. Finally, the semi-parametric group based modeling approach used in this study has been criticized for its tendency to over identify trajectory groups [58]. Accordingly, Nagin and Tremblay [38, 59] caution that groups extracted from the group-based trajectory models should be thought of as approximations of the more complex underlying reality of individual-level trajectories of a behavior; thus, reification of trajectory groups should be done with caution.

In summary we used data from a large sample, with a long follow-up period, and utilized frequency measures of marijuana use to describe the natural history of marijuana use among HIV+ and HIV− MSM. Our study revealed different trajectories of use over time: with approximately 1 in 10 of the men emerging as chronic heavy users or increasing their use over time. Future investigations are needed determine whether long-term patterns of heavy use are associated with adverse consequences especially among HIV+ persons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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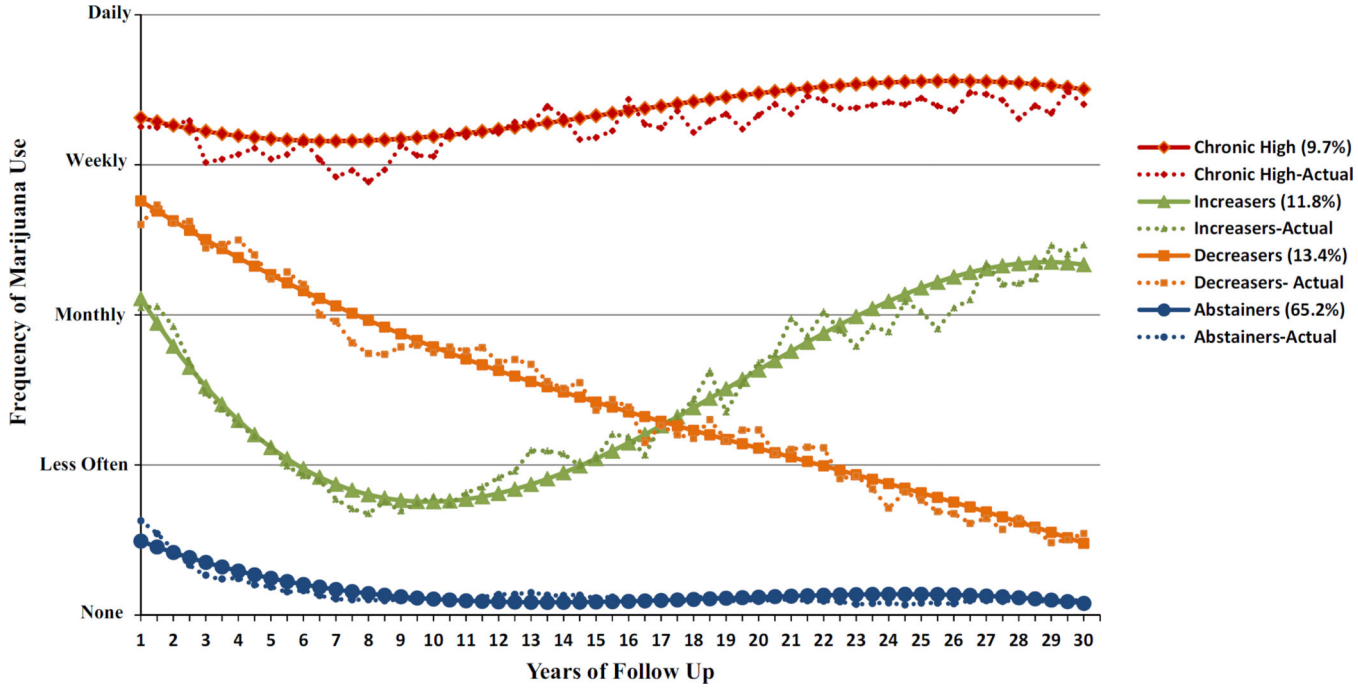

Fig. 1.

Trajectories of marijuana use among 3658 HIV+ and HIV− participants in the Multicenter AIDS Cohort Study (MACS) 1984–2013. The *solid lines* represent the predicted probabilities of frequency of marijuana use conditional on membership in one of the four marijuana trajectory groups, while the *dotted lines* represent the actual frequency of marijuana use given group membership. The y-axis represents the conditional probabilities of frequency of marijuana use, while the x-axis represents the years of follow-up

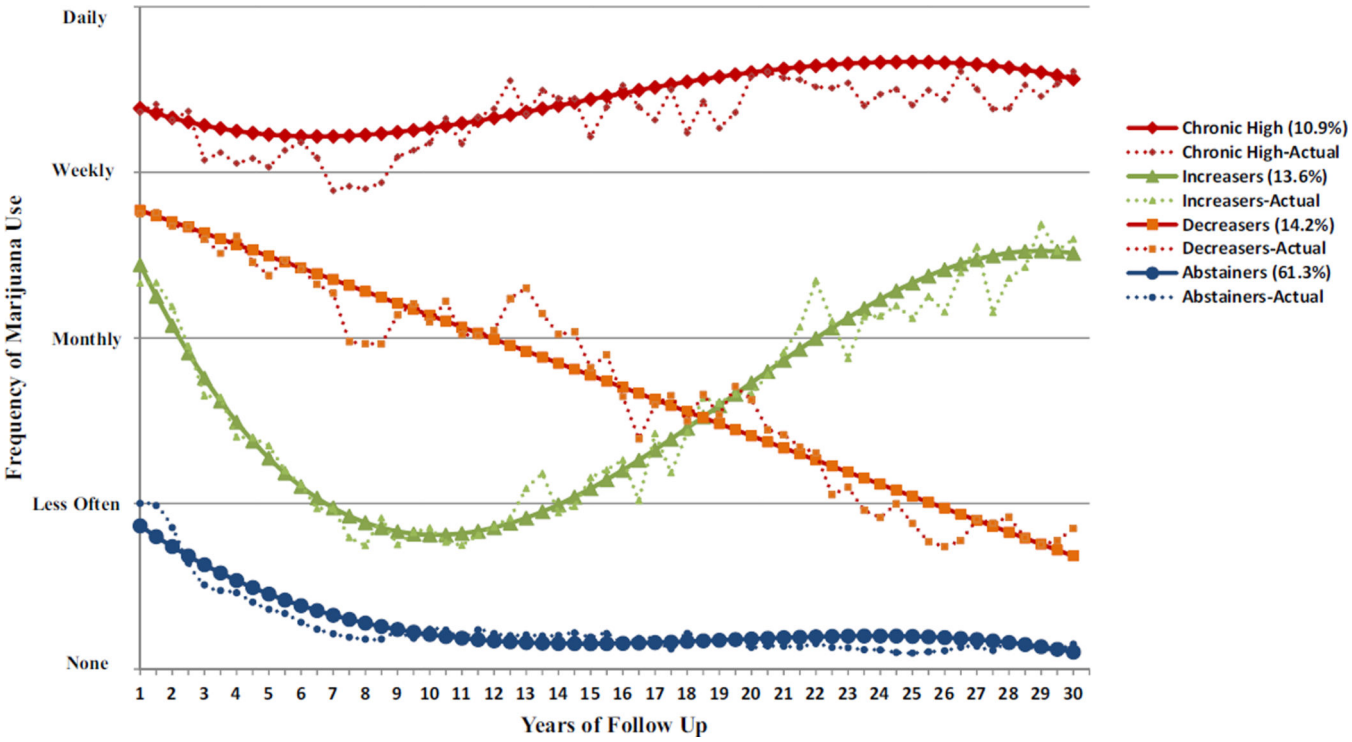

Fig. 2.

Trajectories of marijuana use among 1439 HIV+ participants in the Multicenter AIDS Cohort Study (MACS) 1984–2013. The *solid lines* represent the predicted probabilities of frequency of marijuana use conditional on membership in one of the marijuana trajectory groups, while the *dotted lines* represent the actual frequency of marijuana use given group membership. The y-axis represents the conditional probabilities of frequency of marijuana use, while the x-axis represents the years of follow-up

Table 1

Characteristics of MACS men used in the trajectories at baseline visit by HIV serostatus

	All men[a] (N = 3658) n (%)	HIV−[a] (n = 2219) n (%)	HIV+[a] (n = 1439) n (%)
No of visits, median, IQR	23 (19, 42)	22 (20, 44)	23 (18, 38)
Age (mean, SD)	35 (8.2)	35 (8.4)	35 (7.7)
Race, n (%)			
Non-Hispanic, Whites	2692 (74)	1797 (81)	895 (62)
Non-Hispanic, Blacks	620 (17)	278 (13)	342 (24)
Other	346 (9)	144 (6)	202 (14)
Education, n (%)			
High school diploma or less	621 (17)	289 (13)	332 (23)
Some college or college degree	1797 (49)	1057 (48)	740 (52)
Graduate work or more	1227 (34)	864 (39)	363 (25)
Unemployed, n (%)	370 (10)	200 (9)	170 (12)
Study center, n (%)			
Baltimore/Washington DC	942 (26)	622 (28)	320 (22)
Chicago	766 (21)	424 (19)	342 (24)
Pittsburgh	813 (22)	557 (25)	256 (18)
Los Angeles	1137 (31)	616 (28)	521 (36)
Study enrollment, n (%)			
Pre 2001	2726 (75)	1818 (82)	908 (63)
Post-2001	932 (25)	401 (18)	531 (37)
Depressive symptoms, n (%)			
CES-D < 16	2642 (76)	1669 (79)	973 (71)
CES-D ≥ 16	844 (24)	449 (21)	395 (29)
Alcohol use, n (%)			
None	312 (9)	177 (8)	135 (10)
Low/moderate	2441 (68)	1533 (70)	908 (65)
Hazardous use[b]	826 (23)	468 (22)	358 (25)
Smoking, n (%)			
Never	1494 (41)	968 (44)	526 (37)
Former	733 (20)	461 (21)	272 (19)
Current	1394 (39)	774 (35)	620 (44)
Cumulative pack-years, median (IQR), y	2.2 (0, 18)	1.0 (0, 18)	3.9 (0, 18)
Stimulants/recreational substance use, n (%)[c]	2259 (62)	1308 (59)	951 (67)
IDU, n (%)	296 (8)	109 (5)	187 (14)
Positive Hepatitis C virus antibody, n (%)	262 (7)	104 (5)	158 (11)
Detectable HIV RNA (>40 copies/ml), n (%)	–	–	1090 (91)
Current $CD4^+$ count (cells per cubic milliliter)			
<200	–	–	129 (9)

	All men[a] (N = 3658) n (%)	**HIV−[a] (n = 2219) n (%)**	**HIV+[a] (n = 1439) n (%)**
≥200 and <500	–	–	517 (36)
>500	–	–	779 (55)
ART use, n (%)	–	–	345 (24)
History of AIDS, n (%)	–	–	557 (39)
Marijuana use, n (%)			
None	1578 (43)	1031 (46)	547 (38)
Less than daily	1791 (50)	1054 (48)	736 (52)
Daily	258 (7)	123 (6)	135 (10)

IQR interquartile range, *SD* standard deviation, *CES-D* Center for Epidemiological Depression Scale, *ART* antiretroviral therapy, *IDU* intravenous drug use

[a] Data do not always sum up to total due to missing data for specific variables

[b] Hazardous alcohol use defined as >14 drinks per week or Binge Drinking (i.e. 5 or more drinks per occasion)

[c] Includes crack cocaine, other forms of cocaine, methamphetamines (or speed, meth or ice), Ecstasy

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Table 2

Characteristics of MACS men at baseline visit by marijuana trajectory groups

Characteristics	Abstainer[a] (n = 2380)	Decreasers[a] (n = 483)	Increasers[a] (n = 425)	Chronic high[a] (n = 370)	χ^2/F	*P* value
No of visits, median (IQR)	23 (19, 43)	23 (19, 45)	21 (18, 28)	23 (18, 45)	10.5	<.0001
Age, mean (SD)	36 (8.4)	33 (7.8)	33 (7.2)	32 (6.8)	28.3	<.0001
Race, n (%)					8.2	.2173
White, non-Hispanic	1769 (74)	334 (69)	313 (79)	276 (75)		
Black, non-Hispanic	389 (16)	95 (20)	79 (19)	57 (15)		
Other	222 (10)	54 (11)	33 (8)	37 (10)		
Education, n (%)					61.7	<.0001
High school diploma or less	375 (16)	96 (20)	81 (19)	69 (19)		
Some college or college degree	1101 (46)	275 (57)	208 (49)	213 (58)		
Graduate work or more	896 (38)	111 (23)	134 (32)	86 (23)		
Unemployed, n (%)	225 (9)	65 (13)	37 (9)	43 (11)	8.9	.0302
Study center, n (%)					54.1	<.0001
Baltimore/Washington DC	667 (28)	98 (20)	114 (27)	63 (17)		
Chicago	495 (21)	108 (22)	89 (21)	74 (20)		
Pittsburgh	555 (23)	95 (20)	73 (17)	90 (24)		
Los Angeles	663 (28)	182 (38)	149 (35)	143 (39)		
Study enrollment, n (%)					7.3	.0611
Post-2001	626 (26)	132 (27)	90 (21)	84 (23)		
Depressive symptoms, n (%)					20.6	.0001
CES-D ≥ 16	503 (21)	140 (30)	97 (24)	104 (30)		
Alcohol use, n (%)					113.1	<.0001
None	261 (11)	17 (4)	16 (4)	18 (5)		
Low/moderate	1635 (70)	305 (64)	274 (67)	227 (62)		
Hazardous use[b]	432 (19)	152 (32)	120 (29)	122 (33)		
Smoking, n (%)					193.5	<.0001
Never	1141 (48)	135 (28)	134 (32)	84 (23)		
Former	481 (21)	78 (16)	88 (21)	86 (23)		
Current	734 (31)	267 (56)	194 (47)	199 (54)		

Characteristics	Abstainer[a] (n = 2380)	Decreasers[a] (n = 483)	Increasers[a] (n = 425)	Chronic high[a] (n = 370)	χ^2/F	*P* value
Cumulative pack-years, median (IQR), y	0.05 (0, 15)	5.6 (0, 18)	5.2 (0, 22)	9.4 (0.13, 22)	17.9	<.0001
Stimulants/recreational substance use, n (%)[c]	1231 (52)	397 (83)	332 (79)	299 (81)	100.4	<.0001
IDU, n (%)	143 (6)	72 (16)	40 (10)	41 (12)	52.7	<.0001
Positive Hepatitis C virus antibody, n (%)	158 (7)	49 (10)	29 (7)	26 (7)	7.4	.0588
HIV+	817 (34)	231 (48)	207 (49)	184 (50)	71.9	<.0001
ART use, n (%)[†]	236 (29)	48 (21)	29 (14)	32 (17)	27.7	<.0001
Detectable HIV RNA (>400 copies/ml), n (%)[†]	619 (76)	172 (74)	162 (78)	137 (74)	1.2	.7417
Current CD4$^+$ count (cells per cubic milliliter)[†]					10.8	.0927
<200	84 (10)	16 (7)	18 (9)	11 (6)		
≥200 and <500	310 (38)	79 (35)	64 (31)	64 (35)		
>500	416 (52)	133 (58)	124 (60)	106 (59)		
History of AIDS[†]	283 (35)	99 (43)	100 (48)	75 (41)	15.7	.0013
Lost to follow up	935 (39)	159 (33)	179 (42)	119 (32)	15.3	.0015
Died	336 (14)	95 (20)	104 (24)	83 (22)	41.1	<.0001
Marijuana use, n (%)					2231.0	<.0001
None	2049 (92)	218 (50)	140 (36)	20 (6)		
Less than daily	155 (7)	199 (46)	207 (54)	132 (40)		
Daily	4 (< 1)	15 (3)	39 (10)	181 (54)		

IQR interquartile range, *SD* standard deviation, *CES-D* Center for Epidemiological Depression Scale, *ART* antiretroviral therapy, *IDU* intravenous drug use

[†]Among HIV+ participants. Chi square tests (for categorical variables) and ANOVAs (for continuous variables) were used to examine differences in trajectory groups

[a]Data do not always sum up to total due to missing data for specific variables

[b]Hazardous alcohol use defined as >14 drinks per week or Binge Drinking (i.e. 5 or more drinks per occasion)

[c]Includes crack cocaine, other forms of cocaine, methamphetamines (or speed, meth or ice), Ecstasy

Table 3

Multivariable analysis of risk factors for marijuana trajectory group membership among all men (N = 3658)[†]

Characteristics	Abstainer (n = 2380) AOR 95 % CI	Decreasers (n = 483) AOR 95 % CI	Increasers (n = 425) AOR 95 % CI	Chronic high (n = 370) AOR 95 % CI
Age, per year increase	Reference	0.96 (0.95–0.98)***	0.96 (0.95–0.98)***	0.95 (0.94–0.97)***
Race (vs. White, non-Hispanic)				
Black, non-Hispanic	Reference	1.42 (1.01–1.98)*	1.43 (1.00–2.06)*	1.01 (0.68–1.51)
Other	Reference	0.79 (0.53–1.18)	0.62 (0.39–0.98)**	0.75 (0.48–1.18)
Education (vs. HSD or Less)				
Some college or college degree	Reference	1.04 (0.78–1.39)	0.86 (0.62–1.18)	0.94 (0.68–1.30)
Graduate work or more	Reference	0.61 (0.44–0.87)***	0.85 (0.60–1.21)	0.61 (0.41–0.89)***
Unemployed	Reference	1.23 (0.87–1.74)	1.14 (0.77–1.69)	1.17 (0.79–1.74)
Study center (vs. Los Angeles)				
Baltimore/Washington DC	Reference	0.66 (0.50–0.88)***	0.74 (0.55–0.99)*	0.53 (0.38–0.75)***
Chicago	Reference	0.81 (0.61–1.09)	0.72 (0.52–0.99)*	0.76 (0.55–1.05)
Pittsburgh	Reference	0.60 (0.44–0.82)***	0.57 (0.41–0.79)*	0.78 (0.57–1.07)
Study enrollment (vs. Pre 2001)				
Post-2001	Reference	0.99 (0.74–1.38)	0.81 (0.56–1.17)	0.74 (0.51–1.08)
HIV-Serostatus (vs. HIV−)				
HIV+	Reference	1.61 (1.27–2.05)***	1.63 (1.26–2.12)***	1.72 (1.32–2.23)***
Lost to follow up	Reference	1.01 (0.78–1.28)	1.66 (1.28–2.17)***	0.82 (0.63–1.08)
Died	Reference	1.24 (0.90–1.69)	2.22 (1.60–3.07)***	1.22 (0.88–1.71)
Time-Varying Covariates Influencing Trajectory of Marijuana Use Within Each Trajectory Among All Men (N=3,658)[†] *Trajectory-specific growth parameters (95% CI)*				
Depression (CES-D ≥ 16)	0.01 (0.00–0.02)*	0.06 (0.03–0.09)**	(0.01 (−0.02–0.05)	0.13 (0.10–0.17)***
Low/moderate alcohol use	0.08 (0.07–0.10)**	0.69 (0.64–0.73)***	0.72 (0.67–0.77)***	0.24 (0.19–0.29)***
Hazardous alcohol use[a]	0.16 (0.14–0.19)**	0.81 (0.76–0.86)***	0.83 (0.76–0.89)***	0.25 (0.20–0.31)***
Current Smoker	0.07 (0.05–0.08)*	0.29 (0.26–0.33)***	0.25 (0.21–0.29)***	0.21 (0.18–0.24)***
Stimulants/Recreational drug use[b]	0.24 (0.22–0.25)***	0.44 (0.41–0.47)***	0.49 (0.45–0.52)***	0.23 (0.19–0.26)***
IDU	0.14 (0.08–0.21)***	0.22 (0.13–0.32)***	0.46 (0.31–0.61)***	0.17 (0.04–0.30)***
Positive Hepatitis C virus antibody	−0.02 (−0.04 to 0.00)	−0.00 (−0.04 to 0.04)	0.04 (−0.15 to 0.09)	0.07 (0.02–0.13)***

IQR interquartile range, *SD* standard deviation, *CES-D* Center for Epidemiological Depression Scale, *ART* antiretroviral therapy, *IDU* intravenous drug use, *OR* odds ratio, *AOR* adjusted odds ratio

*$P < 0.05$;

**$P < 0.01$;

***$P < 0.001$

[†]Models were estimated simultaneously within the Proc Traj software

[a]Hazardous alcohol use defined as >14 drinks per week or Binge Drinking (i.e. 5 or more drinks per occasion)

[b] Includes crack cocaine, other forms of cocaine, methamphetamines (or speed, meth or ice), Ecstasy

Table 4

Multivariable analysis of risk factors for marijuana trajectory group membership among HIV+ men (N = 1439)[†]

Characteristics	Abstainer (n = 820) AOR 95 % CI	Decreasers (n = 235) AOR 95 % CI	Increasers (n = 207) AOR 95 % CI	Chronic high (n = 177) AOR 95 % CI
Age, per year increase	Reference	0.98 (0.95–1.00)*	0.97 (0.95–0.99)*	0.95 (0.93–0.98)**
Race (vs. White, non-Hispanic)				
Black, non-Hispanic	Reference	1.82 (1.10–2.99)*	1.15 (0.70–1.91)	1.30 (0.76–2.22)
Other	Reference	1.24 (0.71–2.14)	0.66 (0.36–1.20)	0.70 (0.37–1.30)
Education (vs. HSD or Less)				
Some college or college degree	Reference	0.98 (0.64–1.51)	1.11 (0.71–1.74)	1.02 (0.65–1.60)
Graduate work or more	Reference	0.56 (0.32–0.98)*	1.21 (0.72–2.02)	0.62 (0.35–1.10)
Study center (vs. Los Angeles)				
Baltimore/Washington DC	Reference	0.64 (0.39–1.05)	0.72 (0.46–1.12)	0.55 (0.33–0.91)**
Chicago	Reference	1.00 (0.65–1.55)	0.69 (0.45–1.07)	0.77 (0.48–1.23)
Pittsburgh	Reference	0.73 (0.43–1.24)	0.54 (0.32–0.90)*	0.75 (0.45–1.23)
Study enrollment (vs. Pre 2001)				
Post-2001	Reference	0.53 (0.32–0.89)**	0.70 (0.42–1.17)	0.51 (0.29–0.87)*
History of AIDS	Reference	1.04 (0.64–1.69)	1.16 (0.74–1.82)	0.81 (0.49–1.32)
Lost to follow up	Reference	1.36 (0.86–2.14)	1.02 (0.63–1.65)	0.87 (0.54–1.42)
Died	Reference	1.24 (0.74–2.08)	1.36 (0.84–2.20)	1.07 (0.63–1.82)
Time-Varying Covariates Influencing Trajectory of Marijuana Use Within Each Trajectory Among HIV+ Men (N=1,439)[†] *Trajectory-specific growth parameters (95 % CI)*				
Depression (CES-D ≥ 16)	0.01 (−0.00 to 0.04)	0.15 (0.09–0.20)***	−0.06 (−0.12 to 0.01)*	0.09 (0.03–0.15)**
Low/moderate alcohol use	0.11 (0.09–0.14)***	0.54 (0.47–0.62)***	0.78 (0.70–0.85)***	0.16 (0.08–0.25)***
Hazardous alcohol use[a]	0.20 (0.16–0.25)***	0.72 (0.62–0.82)***	0.93 (0.83–1.04)***	−0.00 (−0.10 to 0.09)
Current Smoker	0.07 (0.05–0.10)***	0.25 (0.20–0.31)***	0.51 (0.45–0.57)***	0.38 (0.32–0.43)***
Stimulants/Recreational drug use[b]	0.25 (0.22–0.27)***	0.53 (0.47–0.59)***	0.52 (0.46–0.58)***	0.34 (0.28–0.39)***
IDU	0.09 (0.01–0.18)*	0.02 (−0.11 to 0.16)	−0.18 (−0.34 to 0.03)*	0.41 (0.20–0.62)**
Positive Hepatitis C virus antibody	−0.00 (−0.03 to 0.03)	0.28 (0.20–0.36)***	−0.03 (−0.11 to 0.04)	0.25 (0.15–0.35)***
ART Use	−0.04 (−0.07 to 0.01)*	0.03 (−0.02 to 0.09)	−0.14 (−0.21 to 0.07)*	−0.02 (−0.09 to 0.05)
Detectable HIV RNA	0.00 (−0.02 to 0.02)	−0.01 (−0.06 to 0.04)	0.09 (0.04–0.14)**	0.00 (−0.05 to 0.06)
$CD4^+$ count				
≥200 and <500	−0.02 (−0.05 to 0.00)	0.02 (−0.04 to 0.09)	0.05 (−0.02 to 0.12)	0.03 (−0.04 to 0.12)
>500	−0.03 (−0.06 to 0.00)*	−0.03 (−0.10 to 0.04)	−0.04 (−0.12 to 0.04)	0.26 (0.18–0.34)***

IQR interquartile range, *SD* standard deviation, *CES-D* Center for Epidemiological Depression Scale, *ART* antiretroviral therapy, *IDU* intravenous drug use, *OR* odds ratio, *AOR* adjusted odds ratio

*$P < 0.05$;

**$P < 0.01$;

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***$P < 0.001$

†Models were estimated simultaneously within the Proc Traj software

[a]Hazardous alcohol use defined as >14 drinks per week or Binge Drinking (i.e.. 5 or more drinks per occasion)

[b]Includes crack cocaine, other forms of cocaine, methamphetamines (or speed, meth or ice), Ecstasy