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Major depression disorder trajectories and HIV disease progression: results from a 6-year outpatient clinic cohort

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Abstract

Contradictory evidence exists on the role of Major depression disorder (MDD) as a predictor of human immunodeficiency virus (HIV) disease progression, particularly regarding the effect of MDD presence versus pattern of illness. The objective of this study was to examine whether MDD status and pattern of illness differentially predict HIV disease progression. Retrospective cohort data from a six-year follow-up of HIV patients at an outpatient clinic were analyzed. MDD trajectories were identified by latent class growth analysis and generalized linear mixed models were used to examine their relation to low CD4+ T-lymphocyte counts (<200 cells/μL) during follow-up. Among 1,494 HIV patients, four MDD trajectory groups were identified: Low-Chronic, Moderate-Ascending, High-Episodic, and High-Chronic. Trajectory group membership was predicted by male sex ($P = .04$), minority race ($P < .01$), older age ($P < .01$) and low baseline CD4 count ($P = .04$). The High-Chronic group had lower odds of having a low CD4 count than the Low-Chronic group (adjusted Odds Ratio [aOR]: 0.63; 95%CI: 0.49–0.81) while the Moderate-Ascending group had higher odds (aOR: 1.53; 95%CI: 1.08–2.19). The odds of having a low CD4 count were higher among male (aOR: 1.25; 95%CI: 1.03–1.52), minority races (American Indian [aOR: 1.85; 95%CI: 1.38–2.49] and African Americans [aOR: 1.58; 95%CI: 1.33–1.87]), Hispanic (aOR: 1.52; 95%CI: 1.06–2.18), and divorced/separated patients (aOR: 1.62; 95%CI: 1.16–2.28) but decreased over time ($P < .01$) across trajectory groups. In this study, because MDD trajectories and CD4 counts were determined based on secondary data abstracted from electronic medical records, the results should be interpreted cautiously due to the potential for selection and misclassification bias. Overall, study findings suggest the pattern of MDD illness among HIV patients can be classified into clinically meaningful trajectory groups that appear to be programmed by known risk factors, and are useful for predicting HIV disease progression. Targeted interventions among at-risk patients may be critical to altering MDD illness patterns and curtailing HIV disease progression.

Abbreviations: AIC = Akaike information criteria, AIDS = acquired immunodeficiency syndrome, aOR = adjusted odds ratio, ART = antiretroviral therapy, BIC = Bayesian information criteria, CD4 = cluster of differentiation 4, CI = confidence interval, EMR = electronic medical record, GLMM = generalized linear mixed model, HIV = human immunodeficiency virus, LCGA = latent class growth analysis, MDD = major depression disorder, PLWHIV = people who are living with human immunodeficiency virus infection.

Keywords: CD4 lymphocyte count, depression disorder, disease progression, HIV/AIDS, latent class, major

1. Introduction

It is estimated that about 955,081 people are living with human immunodeficiency virus infection (PLWHIV) in the United States; 55% of these cases have received a stage 3 (acquired immunodeficiency syndrome [AIDS]) classification at some point during follow-up.[1] Recent estimates from Oklahoma, a state in the South Central United States, show there were 5756 PLWHIV (0.13%) at the end of 2015; 6% of these cases were newly diagnosed and 47% had an AIDS diagnosis.[2] Males accounted for majority (83%) of the 5756 cases, 70% were 20 to 39 years old, 56% were African Americans, and 55% were self-reported men who have sex with men. About 84% of the PLWHIV were linked to care at some point following their initial diagnosis. It is important to note, however, that these estimates are probably an underestimate of the true incidence and prevalence since 1 in 7 persons living with human immunodeficiency virus (HIV) are unaware of their status.[1]

Between 22% and 36% of PLWHIV are diagnosed with major depression disorder (MDD) in the US annually.[3,4] Although it may seem like an unavoidable response to an HIV/AIDS diagnosis, if untreated, it could adversely affect a patient's prognosis. Among PLWHIV, MDD has been shown to be associated with poor adherence to antiretroviral therapy (ART),[5] increased likelihood of HIV transmission,[6] virologic failure,[7] and disease progression to AIDS.[8] Retention in care following initial diagnosis is a considerable challenge among

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PLWHIV and is differentially influenced by MDD.[9–11] It is therefore critical to determine the risk and burden of MDD among PLWHIV in order to optimize allocation of scarce resources and facilitate appropriate MDD prevention intervention planning.

Moreover, MDD prevention efforts are complicated by the uncertainty in existing literature regarding whether MDD leads to HIV disease progression and vice versa. Some studies hypothesize that the association between MDD and HIV disease progression may be mediated by ART nonadherence.[5,6] On the other hand, others suggest the relationship between HIV disease progression and MDD is driven by immunologic mechanisms that are independent of ART adherence.[7,8] It is also unknown whether the pattern of MDD illness (vs incidence) differentially affects HIV disease progression.

Therefore, the objective of this study was to identify MDD trajectories, examine their association to known risk factors and HIV disease progression during a 6-year follow-up among PLWHIV receiving medical care at an outpatient HIV clinic in South Central United States.

2. Methods

2.1. Study design

An open dynamic (ie, participants can leave or be added over time) retrospective cohort study design was used to address the above study objectives. The Oklahoma University Health Sciences Center Institutional Review Board approved this study's protocol, procedures, and activities.

2.2. Study site and participants

Study participants were PLWHIV who sought treatment at an outpatient HIV clinic in South Central United States. The clinic receives about 200 new admissions annually, with an average follow-up of 2 to 4 years. Patient care services are delivered by board-certified infectious disease physicians, nurse practitioners, and support staff. The clinic also provides in-house case management and psychiatric counseling services. PLWHIV treated at the clinic are referred from a variety of sources: regional hospitals and medical centers, self-referrals, State and County Health Departments, and statewide HIV/sexually transmitted disease testing and counseling programs and clinics.

2.3. Data sources

Demographic and medical data, including HIV and MDD diagnosis, treatment and monitoring were abstracted from electronic medical records (EMRs) system (Centricity). Data from the all patients served by the clinic between 2009 and 2014 were included in our analyses, yielding an approximate sample size of 2260 patients. Additional patient medical information was obtained from the HIV Drug Assistance Program, case management, and psychiatric counseling service databases. A sequential linking strategy was used to merge datasets across databases using unique patient identifiers (eg, names, social security numbers, and case numbers). After the retrieved dataset were checked and cleaned, they were converted into a limited dataset for analysis, purging social security numbers, names, and other individual patient identifiers to limit the potential for unnecessary disclosure of protected health information.

2.4. Inclusion/exclusion criteria

HIV infected patients who self-reported no history of past HIV-related treatment at their first clinic visit and who received their first HIV-related treatment through the HIV clinic during the study period were included in our analyses. The 9th and 10th Revisions of the International Classification of Diseases (ICD-9/10) diagnosis codes were used to confirm patients with HIV infection (042*, V08*, or 795.71 and B20*, respectively, including diagnostic-related group codes: 488-490). Patients with a clinic visit prior to the study period (<2009) were excluded.

2.5. Doctor diagnosed MDD

The operational definition of MDD was a documented billing code indicating a diagnosis of depression (minor or major) and a psychiatric narrative note detailing the criteria used to determine the diagnosis based on the ICD-9 diagnosis codes (296.2, 296.3). A random sample of 10% of the patients identified with and without an MDD diagnosis was reexamined using patient medical chart histories to determine the reliability of the data abstraction and mining processes revealing 100% percent agreement. In our analyses, MDD status was tracked in 12-month intervals (starting on the date of the first clinic visit). If a patient did not visit the clinic during any referenced 12-month period, the MDD outcome was classified as missing data.

2.6. HIV disease progression (measured by cluster of differentiation 4 [CD4]+ T-lymphocyte count of cells/μL)

Patient CD4 counts measurements were aggregated as 12-month interval mean values using data from the EMR (with follow-up starting on the date of the first clinic visit). That is, for every 12-month period, each patient's assessments of CD4 count were summarized using the mean statistic. If a patient did not visit the clinic during any referenced 12-month period, their CD4 count measure for that period was classified as missing data. The mean CD4 count values were further dichotomized with a low threshold set at <200 cells/μL for our analyses.

2.7. Baseline socio-demographic data

Information on patient age, gender, race/ethnicity, and marital status was determined from the EMR records documented at the patient's first clinic visit. Information from the HIV Drug Assistance Program and the psychiatric counseling service databases were used to cross-validate all socio-demographic data.

2.8. Statistical analysis

The prevalence of doctor diagnosed MDD and low CD4 count were summarized by patient socio-demographic characteristics. Chi-square (or Fisher exact) tests were used to examine the relationship between subgroup categories of socio-demographic characteristics, MDD diagnosis, and CD4 count status.

Latent class growth analysis (LCGA)[12] was used to identify groups of patients that follow a similar progression of MDD diagnoses during the 6-year follow-up period (2009–2014) and estimate the effect of time-independent/stable covariates (ie, risk factors – sex, race/ethnicity, age, marital status, and baseline CD4 count) on emergent trajectory groups' shape and membership.

The likelihood equation of an individual patient's observed MDD diagnoses over time includes 2 components – probability of group membership and probability of observed data given group membership. The probability of group membership is modeled using a generalized (multinomial) logit model; time-independent variables are added to this model to predict group membership.

In LCGA, the underlying trajectory groups are not directly observable, but are estimated as a continuous function of time (eg, years) from the start of follow-up. Final model selection involved an iterative estimation of the number of trajectory groups, and the shape of each trajectory group using both statistical[13] and nonstatistical considerations.[14] Statistical considerations[15,16] included the use of Bayesian information criteria (BIC), Akaike information criteria (AIC) to determine the best fitting model; smaller BIC and AIC values denoted better models. Entropy was used as an index of classification accuracy based on posterior probabilities; better classification was denoted by higher entropy values. The non-statistical considerations included reasonable sample sizes in each identified trajectory group and nonoverlapping confidence intervals (CIs) of trajectory group posterior probabilities.[14]

Generalized linear mixed models (GLMMs)[17] were used to examine whether group membership predicted future low CD4 counts. Each patient was modeled as a random intercept. Trajectory group and patient characteristic fixed effects (including interaction terms) were estimated by holding other factors constant. In the absence of significant interaction terms, potential confounding effects were examined and controlled for in our final models. A variable was considered a confounder if its inclusion or deletion from the model resulted in more than a 10% difference in the regression parameter of the variable of interest (ie, main effect). The GLMM approach accounts (adjusts) for correlation due to the repeated CD4 count measurements nested within each patient.

All statistical models adjusted for missing data bias under the assumption that data were missing at random[18] using a full information maximum likelihood-based approach.[19] All statistical analyses were implemented using SAS 9.4 (SAS Institute Inc., Cary, NC); the TRAJ procedure was used for LCGA.[12]

3. Results

3.1. Baseline and follow-up summary characteristics

Overall, 2260 unique patient records were abstracted from the EMR databases during the 6-year follow-up period (2009–2014). Majority (79%) of the patients were male, 55% were Caucasian, 70% were between 21 and 50 years old, 79% were single, and 17% had a low CD4 count at baseline. The overall 6-year prevalence of doctor diagnosed MDD and low CD4 count was 24% and 21%, respectively. Table 1 summarizes the distribution of patient characteristics by MDD and CD4 count status. Briefly, the prevalence of MDD diagnoses was higher among female than male (29% vs 23%; $P<.01$) and non-Hispanic than Hispanic (26% vs 17%; $P=.02$) patients. The prevalence of low CD4 count differed by race ($P=0.01$) and age ($P<.01$); low CD4 counts were most prevalent among American Indian/Alaska Native (30%), followed by African Americans (24%) and lowest among Whites (18%). Patients between 41 and 50 years old had the highest prevalence of low CD4 count (24%) while 21 to 30 year olds had the lowest prevalence at 13%.

Service attrition (ie, 2 consecutive years with no clinic visit) at the 2nd, 3rd, 4th, 5th, and 6th year of follow-up was 22%, 43%, 58%, 71%, and 94%, respectively. Among the patients seen at the clinic during the 6-year follow-up (2260), 1494 (66%) had at least 1 clinic visit (during which MDD and CD4 count assessments were conducted) each year during their first 4 years of follow-up. For those patients whose follow-up began in 2009 (n=268), service attrition was 21% at the 3rd year and 45% at the 6th year of follow-up. Having an MDD diagnosis ($P=.21$) or low CD4 count ($P=.33$) diagnosis was not associated with service attrition/retention even after controlling for maximum possible years of follow-up.

3.2. Doctor diagnosed MDD trajectory groups

Using data from 1494 patients with at least 1 follow-up assessment of MDD and CD4 count each year for at least 4 years, LCGA analyses showed that a 4-trajectory group solution was the most parsimonious model (Fig. 1). This model had the lowest (best) BIC (2915.8), AIC (2873.2), and entropy (0.96) based on the sequential estimation of 1 to 5 trajectory models. The 3-trajectory model had higher BIC (3015.6) and AIC (2978.4) and entropy (0.86) values indicating poorer model fit while the 5-trajectory model duplicated an already existing group (low-chronic) in the 4-trajectory model without improvement in BIC (2934.7), AIC (2874.6), or entropy (0.89) values.

The identified 4 distinct trajectories were described as low-chronic (n=1112, 74%), moderate-ascending (n=50, 3%), high-episodic (n=85, 6%), and high-chronic (n=247, 17%). In the low-chronic group, the probability of a MDD diagnosis was negligible from baseline through to the 6th year follow-up; 97% of patients in this group never had a MDD diagnosis during follow-up. The moderate-ascending group had a steadily increasing probability of MDD diagnosis from baseline (50%) through to the 6th year follow-up (88%). The high-episodic group had a 28% probability of MDD diagnoses at baseline that rapidly increased to 80% by the 3rd year of follow-up; however, the probability of illness decreased at subsequent follow-up with a negligible probability of MDD diagnosis at the 6th year. For the high-chronic group, the probability of MDD diagnosis rose from 28% (at baseline) to 90% in the 2nd year and remained close to 100% at subsequent follow-up years.

3.3. Predictors of doctor diagnosed MDD trajectory group membership

Multivariable multinomial logistic regression results (Table 2) showed that male patients had lower odds of high-chronic and moderate-ascending than the low-chronic group membership. Caucasian patients had higher odds of high-chronic and moderate-ascending than the low-chronic group membership. Patients with a low baseline CD4 count had lower odds of high-chronic but higher odds of high-episodic than low-chronic group membership. The odds of high-chronic (vs low-chronic) group membership increased with older age; however, marital status and ethnicity did not predict MDD diagnosis trajectory group membership.

3.4. Doctor diagnosed MDD trajectory groups and low CD4 counts

Overall, GLMM results showed that the odds of having a low CD4 count did not change between trajectory groups over time (trajectory group × follow-up year: $P=.93$; Table 3). However, there was a significant trajectory group and follow-up year effect

Table 1

Prevalence of doctor diagnosed MDD and low CD4 count by patient characteristics in an out-patient HIV clinic, 2009–2014.

Characteristic (n; %)	MDD prevalence, %	*P*	Low CD4 count prevalence, %	*P*
Sex				
Female (470; 21%)	29	**<.01**	19	.20
Male (1790; 79%)	23		21	
Race				
American Indian/Alaska Native (121; 5%)	23	**<.01**	30	**.01**
Asian (96; 4%)	12		20	
Black/African American (647; 29%)	21		24	
Native Hawaiian/Pacific Islander (25; 1%)	36		20	
White (1240; 55%)	28		18	
Unspecified (131; 6%)	13		22	
Ethnicity				
Hispanic/Latino (141; 6%)	17	**.02**	24	.53
Non-Hispanic/Latino (1712; 76%)	26		21	
Unspecified (407; 18%)	21		20	
Baseline age (in years)				
≤20 (20; <1%)	15	.09	0	**<.01**
21–30 (355; 16%)	19		13	
31–40 (515; 23%)	23		21	
41–50 (693; 31%)	26		24	
51–60 (565; 25%)	27		23	
61–70 (99; 4%)	23		19	
≥71 (13; <1%)	15		23	
Marital status				
Married (219; 10%)	21	.06	22	.22
Single (1789; 79%)	24		20	
Divorced/separated (149; 7%)	32		26	
Widowed (22; 1%)	32		32	
Unspecified (81; 4%)	16		23	
Baseline year				
2009 (268; 12%)	28	**<.01**	18	**<.01**
2010 (974; 43%	27		17	
2011 (252; 11%)	24		30	
2012 (255; 11%)	23		24	
2013 (313; 14%)	20		25	
2014 (198; 9%)	14		21	
Baseline CD4 count <200 cells/μL				
Yes (377; 17%)	22	0.35	100	**<.01**
No (1883; 83%)	25		5	
Baseline MDD diagnosis				
Yes (110; 5%)	100	**<.01**	15	0.15
No (2150; 95%)	20		21	

CD4 = cluster of differentiation 4, HIV = human immunodeficiency virus, MDD = major depression disorder.

on CD4 count status ($P < .01$); patients in the high-chronic had 37% (adjusted odds ratio [aOR]: 0.63; 95% CI: 0.49–0.81) lower odds of low CD4 counts than patients in the low-chronic group. In contrast, the odds of low CD4 counts were 53% (aOR: 1.53; 95%CI: 1.08–2.19) higher among patients in the moderate-ascending than the low-chronic group, but were not different between the high-episodic versus low-chronic groups (aOR: 1.11; 95%CI: 0.74–1.67). Overall, the odds of low CD4 counts decreased over time ($P < .01$).

After adjusting for trajectory group membership (Table 4), male (vs female) patients had 25% higher odds of low CD4 counts during follow-up. American Indians and African Americans had 85% and 58% higher odds of low CD4 counts compared to Caucasian patients. Additionally, Hispanic ethnicity was associated with 52% higher odds of low CD4 counts than non-Hispanic ethnicity. The odds of low CD4 counts increased with older age among patients between 31 and 60 years old; this trend was reversed among older (>60 years) patients. Patients who were divorced or separated at baseline had 62% higher odds of low CD4 counts than their married counterparts did.

4. Discussion

Our analysis of medical records data from PLWHIV seeking medical care at an outpatient HIV clinic identified 4 distinct but generalizable doctor diagnosed MDD trajectory groups: low-chronic, moderate-ascending, high-episodic, and high-chronic. Male sex, minority race (American Indian and African-Americans), older age (>30 years), and low baseline CD4 count predicted trajectory group membership while marital status and ethnicity did not. The relationship between MDD trajectory group membership and CD4 count status did not change over time. Contrary to our expectation, patients in high-chronic group had lower odds of having low CD4 counts than the low-chronic group while those in the moderate-ascending group had higher

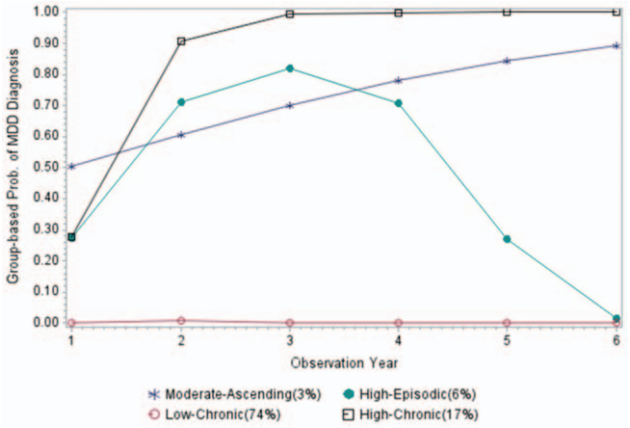

Figure 1. Doctor diagnosed MDD trajectories identified from an HIV clinic cohort using latent group-based trajectory modeling (N = 1494). The proportion of doctor diagnosed MDD at each observation year was estimated as a linear (low chronic and moderate-ascending), quadratic (high chronic), and cubic (high episodic) function of follow-up year. Solid lines represent the predicted probability of doctor-diagnosed MDD at each observation year for each trajectory group. HIV = human immunodeficiency virus, MDD = major depression disorder.

odds. Independent of trajectory group membership, the odds of having a low CD4 count decreased over time but was higher among male, American Indians, African-American, older (>30 years), and divorced/separated patients than their counterparts.

The LCGA approach provides a unique perspective of the dynamic nature of the relationship between longitudinal patterns of doctor diagnosed MDD and HIV disease progression. Specifically, our findings suggest that we can define groups of HIV patients that are homogenous with respect to their presentation of depressive symptoms whose threshold meets the criteria for an MDD diagnosis. These "latent" trajectory groups are associated with some but not all known risk factors of progressing to AIDS. In the absence of "gold standard" prognostic markers of HIV disease progression, our findings raise the question of whether the patterning of MDD diagnoses "trajectory groups" can aid early identification of patients at risk of HIV disease progression (ie, low CD4 count) in out-patient clinic settings.

Our findings support but also challenge some of the existing literature from previous longitudinal studies of MDD illness among PLWHIV. For instance, in attempting to address the causal relation between MDD and HIV disease progression, a 9-year longitudinal study among 96 HIV-infected men found that having depressive symptoms (measured using a Hamilton Depression Rating Scale case-finding tool) predicted increased risk of developing AIDS[20] or an AIDS clinical condition.[21] This finding is consistent with our results that show a higher risk of low CD4 counts over time among patients in the moderate-ascending (vs low-chronic) MDD trajectory group. However, our findings also show that patients in the high-chronic had lower odds of low CD4 count over time than those in the low-chronic group. This suggests that the longitudinal pattern of illness and not MDD status at any single time-point is associated with HIV disease progression. This distinction is obscured in previous studies that examine the effect of MDD status on HIV disease progression as a time invariant factor[22–24] instead of an illness that changes over time in unique patterns among different patients. This is underscored by the lack of an association between baseline MDD status and the 6-year prevalence of low CD4 counts, and change in CD4 count status between MDD trajectory groups over time.

Study findings also shed some light on "reverse causality of the MDD-HIV disease progression relationship" an area with contradictory findings.[24] The observed association between MDD trajectory groups and future CD4 counts may explain the mixed results regarding the effects of MDD on HIV disease progression. Specifically, study results suggest that HIV patients with increasing propensity for MDD illness over time "Moderate-Ascending" are more prone to HIV disease progression than other trajectory groups. Indeed, although having a low CD4 count at baseline was associated with higher odds of belonging to high-chronic MDD trajectory group, this group had lower odds of having low CD4 counts during follow-up. These results support the MDD to HIV progression hypothesis but underscore the role MDD pattern of illness on decreasing CD4 counts.

Table 2

Multivariable multinomial logistic regression results showing factors associated with MDD diagnosis trajectory group membership in the clinic cohort (N = 1494).

	MDD diagnosis trajectory group			
Exposure/risk factor	**Low chronic OR (95% CI)**	**High chronic OR (95% CI)**	**Moderate ascending OR (95% CI)**	**High episodic OR (95% CI)**
Male (reference = female)	1	**0.61*** **(0.44; 0.82)**	**0.56 (0.38; 0.83)**	1.03 (0.60; 1.77)
Race (reference = White)				
American Indian/Alaska native	1	0.63* (0.34; 1.19)	0.71 (0.32; 1.59)	0.70 (0.25; 1.99)
Asian	1	**0.29*** **(0.10; 0.80)**	0.25 (0.06; 1.06)	0.76 (0.26; 2.17)
Black/African American	1	**0.60*** **(0.43; 0.83)**	0.75 (0.50; 1.13)	0.88 (0.54; 1.43)
Native Hawaiian/Pacific Islander	1	**3.29*** **(1.25; 8.71)**	0.74 (0.09; 5.94)	0.98 (0.12; 8.13)
Hispanic (reference = non-Hispanic)	1	0.82* (0.43; 1.56)	0.92 (0.36; 2.35)	1.33 (0.46; 3.83)
Baseline age (reference ≤ 30)				
31–40 y	1	1.57* (0.92; 2.67)	1.35 (0.75; 2.46)	0.88 (0.46; 1.66)
41–50 y	1	**2.35*** **(1.43; 3.84)**	1.54 (0.87; 2.70)	0.74 (0.40; 1.38)
51–60 y	1	**2.51*** **(1.51; 4.15)**	1.16 (0.63; 2.15)	0.86 (0.46; 1.62)
>60 y	1	1.99* (0.96; 4.16)	1.49 (0.62; 3.58)	0.56 (0.16; 1.93)
Married (reference = not married)	1	0.80* (0.50; 1.27)	0.99 (0.57; 1.74)	0.41 (0.15; 1.15)
Baseline CD4 count <200 cells/μL	1	**0.64*** **(0.42; 0.96)**	0.83 (0.51; 1.37)	**1.77 (1.09; 2.88)**

Significant adjusted ORs are in bold. CD4 = cluster of differentiation 4, CI = confidence interval, MDD = major depression disorder, OR = odds ratio.
* Adjusted odds ratio: adjusted for sex, race, ethnicity, age, and marital status.

Table 3

Percent distribution of low CD4 count (<200 cells/μL) by trajectory group membership in the HIV clinic cohort (N = 1,494), 2009–2014.

		Follow-up year			
MDD trajectory (N)	Low CD4 count	1st year n, %	2nd year n, %	3rd year n, %	4th year n, %
Low-chronic (1112)	No	952 (86)	821 (87)	710 (89)	595 (91)
	Yes	160 (14)	121 (13)	87 (11)	57 (9)
High-chronic (247)	No	219 (89)	226 (92)	229 (93)	232 (95)
	Yes	28 (11)	21 (8)	18 (7)	11 (5)
Moderate-increasing (50)	No	46 (92)	44 (86)	42 (90)	34 (92)
	Yes	4 (14)	6 (12)	5 (10)	3 (8)
High-episodic (85)	No	72 (85)	67 (88)	40 (89)	15 (83)
	Yes	13 (15)	9 (12)	5 (11)	3 (17)

Percent distribution of patients with a CD4 count below 200 cells/μL did not differ between doctor-diagnosed MDD trajectories over time (GLMM: group × follow-up year interaction: $P = .93$). CD4 = cluster of differentiation 4, GLMM = generalized linear mixed model, MDD = major depression disorder.

Furthermore, study findings show that the pattern of MDD illness is associated with race, age, and marital status among PLHIV; this is consistent with previous studies.[25] For example, the finding that African-Americans are less prone to high-chronic MDD illness than Caucasians may be explained by the fact that they are less likely to seek depression treatment than Caucasians.[26] Similarly, the lower prevalence of depression symptom expression and consequently subdued treatment seeking behavior among Asians[27] may explain their low odds of membership in high-chronic group. On the other hand, the higher odds of MDD chronicity (ie, higher odds of membership in the high-chronic than low-chronic group) among native Hawaiian/Pacific Islander is contrary to existing research that show this group underutilizes traditional mental health services due to differing conceptualizations of distress, and limited access to culturally competent services.[28] Although, the detection of MDD illness among this hard-to-reach native Hawaiian/Pacific Islander patient population is a positive finding; it may be indicative of the severity of MDD illness (or treatment-resistant MDD) necessitating increased healthcare contact. More research is needed to understand why this group may have a more chronic MDD trajectory than Caucasians including differences in medical care seeking behavior. The higher odds of having a high-chronic pattern of MDD with older age could be attributed to increased HIV-associated stigma, increased loneliness, decreased cognitive functioning, and reduced levels of energy.[29] Consistent with existing research that shows older age is correlated with higher levels of HIV-treatment adherence,[30] our results show that older age is not associated with HIV disease progression.

Table 4

Generalized linear mixed model regression results showing factors associated with low CD4 count (<200 cells/μL) in the HIV clinic cohort (N = 1494).

Characteristic	Crude OR (95% CI)	Adjusted OR (95% CI)
MDD trajectory group		
Low-chronic	1.0 (reference)	**1.0 (reference)**
Moderate-increasing	**1.52 (1.07–2.15)**	**1.53 (1.08–2.19)**
High-episodic	1.12 (0.75–1.67)	1.11 (0.74–1.67)
High-chronic	**0.62 (0.48–0.80)**	**0.63 (0.49–0.81)**
Follow-up year		
Baseline	1.0 (reference)	1.0 (reference)
2nd year	0.85 (0.68–1.07)	0.86 (0.69–1.07)
3rd year	**0.71 (0.56–0.90)**	**0.72 (0.56–0.92)**
4th year	**0.53 (0.40–0.70)**	**0.54 (0.41–0.72)**
Sex		
Female	1.0 (reference)	1.0 (reference)
Male	1.18 (0.99–1.41)	**1.25 (1.03–1.52)**
Race		
White	1.0 (reference)	1.0 (reference)
American Indian/Alaska native	**1.80 (1.34–2.40)**	**1.85 (1.38–2.49)**
Asian	1.06 (0.70–1.60)	0.95 (0.62–1.46)
Black/African American	**1.45 (1.23–1.71)**	**1.58 (1.33–1.87)**
Native Hawaiian/Pacific Islander	0.84 (0.44–1.63)	0.93 (0.47–1.86)
Ethnicity		
Non-Hispanic/Latino	1.0 (reference)	1.0 (reference)
Hispanic/Latino	1.22 (0.93–1.60)	**1.52 (1.06–2.18)**
Baseline age		
≤30	1.0 (reference)	1.0 (reference)
31–40	**1.83 (1.36–2.46)**	**2.13 (1.58–2.88)**
41–50	**2.10 (1.59–2.77)**	**2.55 (1.91–3.39)**
51–60	**2.05 (1.55–2.72)**	**2.53 (1.89–3.38)**
>60	**1.81 (1.22–2.69)**	**2.21 (1.47–3.33)**
Marital status		
Married	1.0 (reference)	1.0 (reference)
Single	0.98 (0.77–1.26)	0.96 (0.74–1.24)
Divorced/separated	**1.67 (1.20–2.31)**	**1.62 (1.16–2.28)**
Widowed	1.22 (0.65–2.28)	1.40 (0.73–2.67)

Adjusted odds ratio: final model adjusted for trajectory group, follow-up year, sex, race, ethnicity, age, and marital status. CD4 = cluster of differentiation 4, CI = confidence interval, HIV = human immunodeficiency virus, MDD = major depression disorder, OR = odds ratio.

Some limitations of this study need to be considered. MDD trajectories and CD4 counts were determined based on secondary data abstracted from EMRs; these data are prone to misclassification bias due to missing data. Moreover, if we assume nondifferential misclassification among identified trajectory groups, the direction of bias on MDD trajectory – CD4 count associations is not predictable since more than 2 trajectory groups are involved.[31]

Also, because the data collection activities did not encompass a research focus, study analyses were limited to available covariate information. Potentially relevant time-varying covariates that were not available include – receipt and adherence to MDD and/or HIV treatment, HIV treatment regimen, and socio-behavioral information (eg, substance or alcohol use). These factors may have influenced the shapes of emergent trajectory groups identified; however, how and to what extent trajectory shapes were modified remains unknown. Future research should examine the longitudinal effects of these time-varying factors on both MDD trajectories and HIV disease progression. In light of the utility of baseline CD4 count (time-invariant variable) as a

predictor of trajectory group membership, the effects of duration of HIV infection and viral subtype should also be examined.

In summary, despite these limitations, the use of medical record data representative of PLWHIV linked to care at some point following their initial diagnosis provides a unique opportunity to elucidate important epidemiologic relations between prevalently comorbid illnesses, MDD and HIV, in out-patient clinical settings. Study findings uniquely reveal that the pattern of MDD illness (specifically, "Moderate-Ascending") and not MDD status is a strong risk factor for HIV disease progression – a clinically important distinction with intervention potential in preventing HIV disease progression, a long-term sought goal of HIV treatment.

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Author contributions

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