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MAJOR ARTICLE

HIV Treatment with Antiretroviral Therapy Mitigates the High Risk of Mental Health Disorders Associated with HIV Infection in US Population

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Introduction: Whether treatment of HIV with ART is associated with lower risk of MHD among people living with HIV (PLWH) remains unknown. We aim to determine the association between HIV and MHD and whether ART alters the risk of MHD among PLWH in the US adult population.

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Methods: We conducted a real-world study using the Merative™ MarketScan® claims database (2016-2020), identifying individuals with HIV diagnosed using the ICD-10 codes and those without HIV. A multivariable stratified Cox proportional hazards regression model was conducted to examine the association of HIV treatment status with MHD, adjusting for potential confounders. Additionally, we sought to determine the effect of modification of ART.

Results: A total, of 313,539 individuals, mean age ([SD] of 44.2 [11.4] years), predominantly males (81.2%), residing in the South region of the US (50.9%) were included in the present analysis. During 671,880 person-years of follow-up, 46,235 incident MHD cases occurred. In the multivariable Cox proportional hazard model, PLWH was associated with higher risk of incident MHD. Relative to those without HIV, the adjusted HR was 1.85 (95% CI, 1.79–1.92; *P*<0.001) for those with HIV on treatment, and 2.70 (95% CI, 2.59–2.82; *P*<0.001) for those with HIV without any treatment. Stronger associations between HIV and MHD were observed in men relative to women, among those aged 18-34 relative to those aged 55-63, and those with no overweight/obesity relative to obese individuals (*P*-interaction <0.001 for all).

Conclusions: HIV was associated with an increased risk of developing MHD. However, HIV treatment mitigated the risk.

Keywords: HIV; mental health; ART; real-world data; US; PLWH

INTRODUCTION

HIV remains a public health problem in the United States (US). According to the Centers for Disease Control and Prevention (CDC), an estimated 1.2 million people were living with HIV (PLWH) in the US at the end of 2019.[1] While much progress has been made, HIV remains incurable; however, antiretroviral therapy (ART) is effective in controlling disease progression, improving quality of life and achieving near-normal life expectancy. [2, 3] ART is a treatment regimen typically consisting of a combination of three or more antiretroviral drugs.[3] The US has made significant strides in HIV prevention, treatment, and care since the beginning of the epidemic 40 years ago[4] with a plan for ending the HIV Epidemic, which is a federal effort designed to reduce new HIV infection in the US by 90% by 2030.[5]

Mental health disorders (MHD), including major depression, are a significant public health problem and serious medical illness in the US.[6, 7] They are key contributing factor to the global burden of disease and associated with increased rates of chronic diseases, suicide attempts, medical costs, disability, and impaired function.[8-10] According to the National Institute of Mental Health, nearly one in five US adults lives with mental illness, representing an estimated 52 million individuals in 2019.[11] Every year, about 19 million American adults (9.5% of the adult population) suffer from a depressive illness.[12] According to a previous review, mental health illnesses are one of the most common comorbidities among PLWH.[13]

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There have been few reported epidemiological studies on the association between HIV and MHD.[14] However, these studies had several limitations such as a not assessing the impact of HIV treatment on the risk of MHD, or not including all categories of MHD. Furthermore, these studies did not examine whether PLWH who received ART treatment had modified risk of developing MHD. For example, a study conducted by Mirza et al. was limited to only US military personnel and had an almost exclusively male study population (97% of PLWH were men). The study reported that about 56% of service members living with HIV had higher risk of developing MHD compared to those without HIV.[15] Another study conducted in the US found that in men who have sex with men (MSM) living with HIV, sleep disturbance was associated with significant increases in depression compared to MSM without HIV.[16] A recent study conducted in the UK by Gooden et al. suggested that PLWH had higher risk of developing composite mental illness, depression, anxiety, and severe mental illness compared with persons without HIV.[17] To the best of our knowledge, no study has yet used a large insured US population to investigate whether ART mitigates the risk of MHD among PLWH. We aim to address this gap in the literature to examine the association between HIV and MHD and whether ART is associated with an altered risk of developing MHD among PLWH in the US adult population.

METHODS

Data source

This analysis was conducted using prospectively collected the Merative™ MarketScan® Commercial Claims and Encounters database from 2016 to 2020. The Merative™ MarketScan® Research Databases is one of the largest and longest nationwide longitudinal claims databases used for healthcare research that contains data on over 275 million unique deidentified patients.[18] The MarketScan® databases include covered employees and family members from large employers and health plans across the 50 states of the US and the District of Columbia.[19] Longitudinal tracking of detailed patient-level healthcare claims information provides comprehensive data, including demographic characteristics such as age, gender, geographic locations, inpatient and outpatient medical information, detailed prescription drug, and financial information.[20] The MarketScan® Research Databases fully comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).[20] The Marketscan® database has been widely used in large epidemiologic outcomes research and health economic studies.[21, 22] The protocol of this study was reviewed and received a determination of non-human subjects research by the Penn State Institutional Review Board. The individual informed consent requirement was waived for this secondary analysis of de-identified data.

Cohort derivation and assessment of exposure

We identified PLWH, aged 18-63 years using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), codes[23] (Supplemental Table 3) from January 1,

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2017, through December 31, 2019. We had a very large number of persons without HIV in the database (over 30 million); therefore, for each stratum of PLWH by birth year and sex, we randomly selected 10 times as many persons without HIV as PLWH. For these non-HIV patients, we randomly assigned a pseudo-index date from January 1, 2017, to December 31, 2019. Both PLWH and persons without HIV did not have ICD-10 diagnosis codes of MHD prior to the index date. PLWH and persons without HIV displayed a minimum of at least 12 months of continuous enrollment prior to the index date and at least 12 months of continuous enrollment after the index date. We identified a total of 37,329 PLWH and 373,290 persons without HIV before excluding those with prevalent MHD. After excluding individuals with prior diagnosis of MHD, a total of 26,410 PLWH and 287,129 without HIV diagnosis were included in the current analysis. We identified 17,830 PLWH with any prescription of ART-related medications prior to the onset of MHD (Supplemental Table 4), and 8,580 patients without treatment. We used the earliest date of receiving HIV treatment as the index date for PLWH with treatment and the earliest date when an HIV diagnosis code was observed for PLWH without treatment in the current analysis.

Participants were divided into 3 categories in our primary analysis, according to HIV and treatment status: persons without HIV, PLWH with treatment, and PLWH without treatment.

Assessment of outcomes

The primary outcome was the composite of any MHD, defined using ICD-10 codes for mental health diagnosis or substance use disorders as done in previous studies[24, 25] (Supplemental Table 3) that occurred after index dates during the follow-up period. As the secondary outcomes (psychotic disorder, major depression, other mood disorder, anxiety, and related disorder, and other mental health conditions; Table 3), the association of HIV with these individual MHD groups also was explored.

Assessment of potential covariates

Demographic data on age (years), sex (male/female), place of residence (urban/rural), and US census region (South, West, Midwest, Northeast) were extracted directly from the Marketscan® database. Based on a comprehensive literature review, the following potential confounding factors were identified at baseline (e.g., during the 12 months prior to the index date), using their corresponding ICD-10-CM codes (Supplemental Table 3): overweight/obese, non-alcoholic fatty liver disease (NFALD), ischemic heart disease, congestive heart failure, hypertension, diabetes, chronic kidney disease (CKD), dyslipidemia, stroke, with each categorized as (yes/no).

Statistical analysis

We calculated the person-time of follow-up for each participant following the index date to the first occurrence of an outcome of interest (MHD), end of enrollment, or end of the study period (December 31, 2020), whichever took place first. HIV status was deemed as the primary exposure. Descriptive statistics were calculated to summarize patient characteristics, stratified by HIV status,

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and were presented as age-adjusted percentages (for categorical variables) and means and standard deviations (for continuous variables), as applicable. An initial stratified Cox proportional hazards regression model adjusting for age and sex was applied to calculate the hazard ratio (HR) and 95% confidence interval (95% CI). We then ran a parsimonious multivariable stratified Cox regression model to adjust for all potential confounding factors.

We conducted subgroup analyses by calculating the unadjusted incidence rates and corresponding 95% CI per 1000 person-years of follow-up for the two cohorts within each subgroup.

Considering that several comorbid diseases frequently are associated with HIV, we conducted several sensitivity analyses to test the robustness of our results and to address the possibility of residual confounding. First, we performed an analysis based on propensity score strata (propensity score stratification method). Propensity scores were estimated from a logistic regression model using the covariates in the full model, to balance baseline data between PLWH and without HIV. Second, we further excluded those taking antipsychotics, antidepressants, and antianxiety drugs. Third, we reran the analyses for individuals without any apparent comorbidities after excluding those with overweight/obesity, NFALD, ischemic heart disease, congestive heart failure, hypertension, diabetes, CKD, dyslipidemia, and stroke. Fourth, models including interactions with HIV, specifically age (years) and sex (the 2 most important determinants for risk of HIV and MHD), and obesity in relation to MHD risk were assessed by the -2-log likelihood ratio (-2 LL) controlling for the same covariates above. Subgroup analyses were further conducted when a significant interaction was observed. The proportional hazard (PH) assumption was checked by log-log survival curve. Data were analyzed in SAS Software version 9.4 (SAS Institute Inc; Cary, NC) and R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) using a two-tailed alpha level of 0.05.

RESULTS

In total, 313,539 individuals (mean [SD] age 44.2 [11.4] years), predominantly males (81.2%), residing in the South region of the US (50.9%) were included in the present analysis. During 671,880 person-years of follow-up, we identified 46,235 incident MHD cases. PLWH, particularly those without treatment, had higher likelihood of having chronic conditions, such as overweight/obesity, diabetes, stroke, ischemic heart disease, and congestive heart failure relative to persons without HIV (Table 1). Supplemental **Figure 1**, log-log survival curves for checking the PH assumption for three groups were almost completely parallel and PH assumption was satisfied.

Among men, the unadjusted incidence rates of MHD were higher among PLWH without treatment (180.4 per 1000-PY) as compared to those without any diagnosis of HIV (59.0 per 1000 PY), though there was not a statistically significant difference in unadjusted rates among women. PLWH without treatment in the age group of 18-34 years had the highest unadjusted incidence

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rate of MHD (209.3 per 1000-PY) as compared to those without HIV (69.5 per 1000-PY) (Supplemental Table 1). PLWH without treatment residing in the South region had higher incidence rates of MHD (187.7 per 1000-PY) compared to those without HIV (65.0 per 1000-PY). We next examined multiple canonical risk factors for MHD in these three cohorts (Supplemental Table 1). Among individuals with overweight/obesity, NAFLD, hypertension, diabetes, ischemic heart disease, congestive heart failure, and CKD, the unadjusted incidence rates of MHD were consistently higher among PLWH without treatment as compared to persons without HIV. The overall unadjusted incidence rate of MHD was higher among PLWH not on treatment (168.9 per 1000 persons-years [PY])) compared to those without HIV (63.5 per 1000-PY) (Table 2, Figure 1).

After controlling for potential confounders in our fully stratified Cox model, PLWH was associated with higher risk of developing MHD (Table 2). Relative to those persons without HIV, the adjusted HR was 1.85 (95% CI, 1.79–1.92; $P<0.001$) for PLWH with treatment, and 2.70 (95% CI, 2.59–2.82; $P<0.001$) for PLWH without any treatment (Table 3). The analysis using the propensity score strata and excluding those taking antipsychotics, antidepressants, and antianxiety use yielded similar observed results (Table 2). Excluding participants with other common chronic conditions (overweight/obesity, NFALD, hypertension, diabetes, dyslipidemia, stroke, ischemic heart disease, congestive heart failure, CKD) also generated similar results (Table 2). A similar pattern was observed when each individual category of MHD was examined as an outcome (Table 3). Stronger associations between HIV and MHD were observed in men relative to women, among those aged 18-34 relative to those aged 55-63, and those with no overweight/obesity relative to obese individuals (P-interaction <0.001 for all) (supplemental Table 2).

DISCUSSION

In this large-scale study of 313,539 individuals using the MarketScan® claims database, we found that PLWH have an increased risk for developing composite MHD compared with persons without HIV. A similar pattern was observed when individual MHD diagnosis was examined as outcomes. These associations were independent of demographics and major chronic medical conditions. Treating HIV with ART was associated with lower risk of MHD compared to those without treatment. To our knowledge, our study represents the first attempt to determine if treatment of HIV with ART is associated with lower risk of MHD using large real-world data of insured population in the US. HIV treatment was significantly associated with lowered MHD but not to the level of subjects without HIV. The risk differed across sex, age groups, and overweight/obesity.

These findings reinforce the importance of integrating mental health screening and services in the treatment of PLWH.[26, 27] Improved screening for MHD among PLWH, both in the context of HIV treatment and among those not on treatment, can provide opportunities for linkage to mental health care. Numerous models for HIV and mental health care integration exist, but fragmented care frequently leads to difficulties in implementation.[28] As the HIV epidemic in the United

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States continues to age, MHD burden among those living with HIV is likely to continue to grow[29] and yet MHD in this population increases the risk of suicide deaths by nearly 100 fold.[30]

Substantial evidence suggests that intersecting factors put individuals at risk of both HIV and MHD.[26] Structural factors, such as poor housing and inadequate neighborhoods, are tied to both to HIV acquisition[31] and adverse mental health outcomes.[32] Additionally, it is plausible there is a direct pathophysiological effect of HIV on the neurons since HIV is neurotropic which may potentiate brain disorders including those of mental health.[33] Further, MSM bear the highest burden of HIV in the US, with nearly 3 in 4 new HIV diagnoses among MSM,[34] while simultaneously experiencing same-sex sexual stigma and discrimination that may lead to worsened mental health.[35] HIV-related stigma and the chronic stress of living with HIV may further exacerbate these vulnerabilities. HIV-associated stigma and loneliness partially explain depression among older HIV-positive adults, suggesting that interventions to reduce stigma and increase social support may help to combat increases in depression among PLWH.[36] Work has shown that receipt of positive emotional and social support was inversely associated with mental health burdens among PLWH.[37] Further, among PLWH, there are plausible biological mechanisms to suggest that chronic immune activation may lead to poorer mental health outcomes, particularly depression, among PLWH.[26] Our findings suggest that this effect may be moderated by HIV treatment.

Previous work has shown that those with MHD are less likely to engage in HIV care[38, 39] and have poorer adherence to treatment.[40] Our findings suggest that the reverse is true as well, those on HIV treatment are less likely to develop MHD than those who are not on HIV treatment. These findings suggest that beyond integrating MHD treatment with HIV treatment, providing opportunities for linkage to HIV care among those seeking treatment for MHD can help decrease HIV-related morbidity due to unsuppressed HIV.[41]

Study strengths and limitations

Strengths of our study include an analysis based on longitudinal data of a large sample of PLWH and controls without HIV. To the best of our knowledge, it also is the first study to examine the association between HIV treatment and MHD among a large sample of commercially insured patients using national real-world data. Notwithstanding, our study has several limitations that should be noted when interpreting the results. This is an observational study that used US medical claims data and therefore causality cannot be inferred. Our current study design included those who had continuous enrollment in their private insurance plan from 1 year before to 1 years after index date thus creating some selection bias, but this continuous enrollment has enabled us to establish some boundaries for health history. Moreover, because of the complexity and lack of additional information from the database, we could not conduct analyses of specific ART regimens on the risk of developing MHD for the present study. While all data were collected retrospectively, individuals were prospectively followed forward in time to determine the outcome of interest. We

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are unable to account for individuals with undiagnosed mental health disorders being potentially less likely to initiate ART, thus our findings that PLWHIV on ART were less likely to develop MHD than those not on ART could be confounded by this unmeasured factor. We acknowledge that claims-based databases can misclassify patients based on misreporting or underreporting of diagnoses or medications. Moreover, the MarketScan® database does not capture data on race or ethnicity, thus precluding any analysis to assess for confounding of the relationship between MHD and HIV or HIV treatment status by race/ethnicity.

Despite these limitations, we believe this study provides new real-world evidence regarding the association between HIV treatment and MHD using large real-world data of the US population.

CONCLUSIONS:

Findings from this large real-world study indicate that HIV is associated with increased MHD risk, consistent with the previous studies. Our study shows that among PLWH, treatment with ART was associated with lower risk of MHD compared to those without treatment. Our findings highlight the importance of ART among PLWH to reduce their risk of adverse health outcomes including MHD and improve quality of life.

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Conflicts of interest disclosure: The authors have no conflicts of interest to disclose.

Authors' contributions: Designed research (project conception, development of overall research plan, and study oversight): DMB and VMC. Data extraction: DMB. Analyzed data: DMB. Performed statistical analysis: DMB. Wrote the first draft of the manuscript: KR and DMB. Review and editing: All authors. All authors have read and approved the final manuscript.

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Figure 1**. Cumulative incidence of MHD among HIV population: The incidence is higher in PLWHIV not on treatment, followed by PLWHIV on treatment and lower in persons without HIV.**

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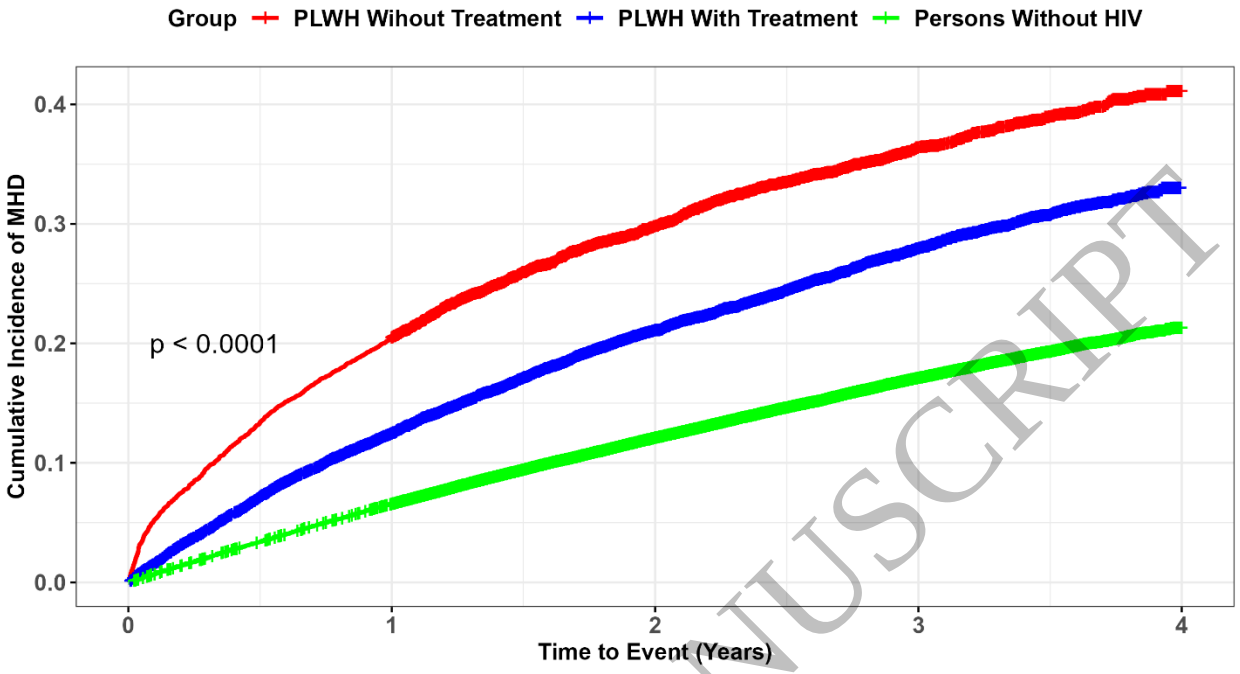

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Table 1| Age-standardized characteristics of the study population at baseline by HIV status

	HIV Status		
	No HIV (n=287129)	HIV with treatment (n=17830)	HIV without treatment (n=8580)
Age of Patient*	44.0 (11.4)	46.9 (10.7)	43.8 (11.9)
Men, %(n)	81.4 (233697)	82.2 (14661)	73.9 (6338)
Urban, %(n)	85.1 (244477)	84.3 (15036)	85.2 (7312)
Region of US			
- Northeast, %(n)	14.1 (40347)	17.6 (3139)	28.8 (2472)
- Midwest, %(n)	25.5 (73278)	10.2 (1812)	10.1 (868)
- South, %(n)	50.5 (145053)	58.5 (10436)	51.8 (4448)
- West, %(n)	9.9 (28451)	13.7 (2443)	9.2 (792)
Comorbidities			
Overweight/obesity, %(n)	7.3 (21021)	6.4 (1144)	8.3 (716)
Non-alcoholic fatty liver, %(n)	1.1 (3041)	1.6 (278)	1.6 (134)
Hypertension, %(n)	20.4 (58622)	19.9 (3544)	20.0 (1718)
diabetes, %(n)	8.9 (25677)	9.1 (1625)	9.8 (839)
Dyslipidemia, %(n)	21.6 (62117)	24.1 (4288)	23.3 (1998)
Stroke, %(n)	0.6 (1793)	0.8 (143)	1.0 (85)
Ischemic heart diseases, %(n)	2.3 (6542)	2.3 (414)	2.4 (210)
Congestive heart failure, %(n)	0.7 (2025)	0.9 (162)	1.1 (98)
Chronic Kidney Disease, %(n)	0.9 (2469)	3.2 (572)	2.2 (189)

Values are means (SD) for continuous variables; percentages or ns or both for categorical variables, and are standardized to the age distribution of the study population.

* Value is not age-adjusted

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Table 2| Incidence rates and stratified Cox proportional hazard models hazard ratio (95% CI) for the association between HIV and mental health disorders in the MarketScan® database from 2016-2020.

Variable	No HIV	HIV with Treatment	HIV without Treatment
Person-years	618,605	36,782	16,493
Mental health disorders cases, n	39,275	4,174	2,786
Incidence rate, 95% CI per 1000 person-years*	63.5 (62.8, 64.1)	113.5 (110.1, 117.0)	168.9 (163.0, 175.3)
Model 1	(reference)	1.82 (1.76, 1.88)	2.57 (2.47, 2.67)
Model 2	(reference)	1.85 (1.79, 1.92)	2.70 (2.59, 2.82)
Sensitivity analyses‡			
Analysis based on propensity score strata	(reference)	1.82 (1.77, 1.88)	2.71 (2.61, 2.82)
Excluding those taking antipsychotics antidepressants, and antianxiety use	(reference)	1.82 (1.75, 1.90)	2.71 (2.58, 2.84)
Excluding individuals with common chronic conditions$	(reference)	2.06 (1.97, 2.15)	2.91 (2.76, 3.06)

*Unadjusted incidence rate per 1000-person-years

Model 1: stratified by age (years) and sex (men/women)

Model 2: Model 1 + further stratified by US region (Northeast, Midwest, South, West), place of residence (urban/rural), overweight/obesity, NFALD, hypertension, diabetes, dyslipidemia, stroke, ischemic heart disease, congestive heart failure, chronic kidney disease (each yes vs. no).

‡Based on the full stratified model 2.

$Chronic conditions include obesity, NFALD, hypertension, diabetes, dyslipidemia, stroke, ischemic heart disease, congestive heart failure, chronic kidney disease

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Table 3| Stratified Cox proportional hazard models hazard ratio (95% CI) for the association between HIV and type of mental health disorders in the MarketScan® database from 2016-2020 (n=313,649).

Type of Mental Health disorders	No HIV	HIV with treatment	HIV without treatment
Anxiety and Related Disorder	(reference)	1.46 (1.38, 1.54)	2.11 (1.97, 2.25)
Major Depression	(reference)	2.62 (2.44, 2.82)	3.50 (3.20, 3.83)
Psychotic Disorder	(reference)	2.24 (1.38, 3.62)	4.07 (2.48, 6.70)
Other Mood Disorder	(reference)	2.38 (2.00, 2.84)	3.71 (3.03, 4.56)
Other Mental Health Conditions	(reference)	1.94 (1.84, 2.06)	3.04 (2.84, 3.25)

Psychotic disorder (F20-F29), major depression (F32, F33); other mood disorder (F30, F31, F34-F39), anxiety and related disorder (F40-F48), and other mental health condition (F17-F19, F49-F69, F80-F89, F90-F99).

Based on the full Stratified Cox proportional Model: stratified by age (years) and sex (men/women), US region (Northeast, Midwest, South, West), place of residence (urban/rural), overweight/obesity, NFALD, hypertension, diabetes, dyslipidemia, stroke, ischemic heart disease, congestive heart failure, chronic kidney disease (each yes vs. no).

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