ORIGINAL ARTICLE

A Marginal Structural Model to Estimate the Causal Effect of Antidepressant Medication Treatment on Viral Suppression Among Homeless and Marginally Housed Persons With HIV

Alexander C. Tsai, MD, PhD; Sheri D. Weiser, MD, MPH; Maya L. Petersen, MD, PhD; Kathleen Ragland, PhD; Margot B. Kushel, MD; David R. Bangsberg, MD, MPH

Context: Depression strongly predicts nonadherence to human immunodeficiency virus (HIV) antiretroviral therapy, and adherence is essential to maintaining viral suppression. This suggests that pharmacologic treatment of depression may improve virologic outcomes. However, previous longitudinal observational analyses have inadequately adjusted for time-varying confounding by depression severity, which could yield biased estimates of treatment effect. Application of marginal structural modeling to longitudinal observation data can, under certain assumptions, approximate the findings of a randomized controlled trial.

Objective: To determine whether antidepressant medication treatment increases the probability of HIV viral suppression.

Design: Community-based prospective cohort study with assessments conducted every 3 months.

Setting: Community-based research field site in San Francisco, California.

Participants: One hundred fifty-eight homeless and marginally housed persons with HIV who met baseline immunologic (CD4+ T-lymphocyte count, <350/μL) and psychiatric (Beck Depression Inventory II score, >13) inclusion criteria, observed from April 2002 through August 2007.

Main Outcome Measures: Probability of achieving viral suppression to less than 50 copies/mL. Secondary outcomes of interest were probability of being on an antiretroviral therapy regimen, 7-day self-reported percentage adherence to antiretroviral therapy, and probability of reporting complete (100%) adherence.

Results: Marginal structural models estimated a 2.03 greater odds of achieving viral suppression (95% confidence interval [CI], 1.15-3.58; $P=.02$) resulting from antidepressant medication treatment. In addition, antidepressant medication use increased the probability of antiretroviral uptake (weighted odds ratio, 3.87; 95% CI, 1.98-7.58; $P<.001$). Self-reported adherence to antiretroviral therapy increased by 25 percentage points (95% CI, 14-36; $P<.001$), and the odds of reporting complete adherence nearly doubled (weighted odds ratio, 1.94; 95% CI, 1.20-3.13; $P=.006$).

Conclusions: Antidepressant medication treatment increases viral suppression among persons with HIV. This effect is likely attributable to improved adherence to a continuum of HIV care, including increased uptake and adherence to antiretroviral therapy.

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Author Affiliations are listed at the end of this article.

Depression is common among people living with human immunodeficiency virus (HIV)/AIDS. In a nationally representative probability sample of adults receiving care for HIV in the United States, the 12-month prevalence of major depressive disorder according to the Composite International Diagnostic Interview Short Form was 36%.[1] This finding exceeds the 5% to 7% 12-month prevalence of major depressive disorder in the general population.[2-4]

Among persons living with HIV, depression has been associated with reduced uptake of[5,6] and adherence to[7-9] antiretroviral therapy (ART), as well as decline in CD4+ T-lymphocyte count[10] and progression to AIDS.[11] However, little research exists on whether pharmacologic treatment of depressed mood can improve HIV outcomes.[12] One analysis of electronic medical record data from persons with HIV enrolled in 2 large health maintenance organizations showed that depression was associated with reduced odds of achieving HIV-1 RNA suppression to less than 500 copies/mL and that treatment with selective serotonin reuptake inhibitor (SSRI) medications was as-

sociated with improved ART adherence and viral suppression.[8] This analysis, however, did not adjust for depression severity, which could have confounded the observed relationship between treatment and outcome. Specifically, patients with more severe symptoms of depression are more likely to be prescribed treatment with antidepressant medication, and antidepressant medication treatment may improve subsequent depression severity (**Figure**). Confounding arises because depression severity is associated with the outcome.

Although observational studies using conventional statistical methods can adjust for baseline confounding by indication (to the extent that confounders are measured without error), they are unable to adjust for time-dependent confounding that arises in longitudinal treatment settings. Conventional statistical adjustment, ie, including depression severity as a time-dependent variable in a regression model, may bias the estimated treatment effect by conditioning on part of the effect of interest. The statistical method of marginal structural models provides a means to account for this time-dependent confounding by indication. Under certain assumptions (the validity of which are examined in this article), marginal structural modeling aims to use observational data to approximate the findings of a randomized controlled trial.[13-16] Therefore, we fit a marginal structural model to data from a longitudinal cohort of homeless and marginally housed persons with HIV to estimate the effect of treatment with antidepressant medications on ART adherence and viral suppression.

METHODS

THE COHORT

Data for this analysis were drawn from participants observed from April 2002 through August 2007 in the Research on Access to Care in the Homeless (REACH) study, which is an observational prospective cohort of homeless and marginally housed adults with HIV in San Francisco, California.[17,18] In brief, study participants in the parent cohort were recruited from homeless shelters, free-lunch programs, and low-income, single-room-occupancy hotels. Participants signed a written consent form on entry into the study and were reimbursed $10 to $15 per assessment, which occurred approximately every 3 months at the University of California at San Francisco (UCSF) Clinical and Translational Science Institute Tenderloin Clinical Research Center and included a structured interview and blood collection. This recruitment method yielded information updated quarterly on sociodemographics, depression severity, alcohol and other drug use, health services utilization, overall health status, and medications. Depression severity was measured with the Beck Depression Inventory II (BDI-II).[19] The Committee on Human Research at UCSF approved all study procedures.

Participants were eligible for inclusion in this analysis if they had (1) a CD4+ T-lymphocyte count less than 350/μL at baseline and (2) symptoms of depression at baseline, defined as a BDI-II score greater than 13. Our choice of a CD4+ count less than 350/μL was based on a threshold, widely used at the time of the study, for deciding when to initiate ART in asymptomatic HIV-infected patients.[20] The psychiatric inclusion criterion represents a reasonable clinical threshold at which many psychiatrists would choose to recommend starting psychopharmacologic or psychotherapeutic treatment for depressed mood. We decided not to limit the sample to participants with formal *DSM* diagnoses because subsyndromal symptoms are commonly experienced during the course of mood disorders and are associated with significant psychosocial impairment.[21-23]

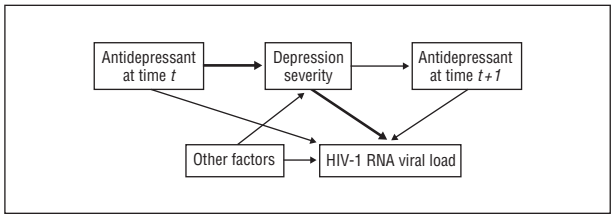

Figure. Model of the causal pathway between antidepressant medication use and suppression of human immunodeficiency virus (HIV), with time-varying confounding by indication. Depression severity confounds the observed relationship between antidepressant medication use and viral suppression because patients with more severe depression are more likely to be prescribed antidepressant medication and are also more likely to have worse virologic outcomes. During the course of longitudinal follow-up, depression severity may be improved by past treatment with antidepressant medication. It is therefore part of the causal pathway of interest (leading from antidepressant medication treatment to improved virologic outcome). Conventional statistical adjustment, ie, including depression severity as a time-dependent variable in a regression model, may bias the estimated treatment effect toward the null by conditioning on part of the effect of interest.

For this study, the primary outcome of interest was probability of HIV-1 RNA viral suppression to less than 50 copies/mL. Plasma was processed and stored at −40°C within 6 hours of collection. Determinations of HIV-1 viral load were made by means of an ultrasensitive assay (HIV-1 Amplicor Monitor, Version 1.5; Roche Molecular Systems, Alameda, California), with a lower detection limit of 20 copies/mL. Secondary outcomes of interest were (1) probability of being on an ART regimen; (2) self-reported ART adherence, defined as the percentage of prescribed ART doses taken within a 7-day recall period[24,25]; and (3) probability of reporting complete (ie, 100%) ART adherence. Zero adherence was assigned to participants who were eligible for but were not taking ART, consistent with an expanded concept of adherence to a continuum of HIV care including ART uptake, persistence, and dose-taking adherence (or execution)[26,27] that has been used in previous research.[28]

STATISTICAL ANALYSIS

We used weighted regression modeling to estimate the parameters of a marginal structural model.[13-16] That is, rather than adjust for time-dependent confounding by including depression severity as a covariate in the regression model, each patient received a weight inversely proportional to the estimated probability of having his or her own observed antidepressant medication treatment history. Intuitively, this approach corrects for the nonrandom assignment of antidepressant medication treatment by up-weighting individuals whose treatment and covariate histories are underrepresented compared with what would have been observed if treatment had been randomized. This approach accounts for confounding without stratifying or conditioning on factors in the postulated causal pathway and has been successfully applied in the field of HIV medicine, yielding results that have more closely approximated the findings from randomized controlled trials than have other statistical adjustment methods.[13,15] Marginal structural modeling has also been used to estimate the effects of other time-varying exposures, such as methotrexate in patients with rheumatoid arthritis[29] and aspirin among middle-aged men.[30]

The model used to estimate the denominator of the weights was a pooled logistic regression model[31] for the probability of receipt of antidepressant medication at a given visit. Included in this logistic model were variables, measured at baseline, that

have been previously studied as potential correlates of psychotropic medication use among persons with HIV[32,33]: age (years), sex, education (high school graduate and some college vs no diploma), self-identified race (white, black, or other), presence of 1 of 5 chronic medical conditions (heart disease, hypertension, diabetes, emphysema, and asthma), CD4+ count nadir, substance use (alcohol, crack cocaine, methamphetamines, heroin, or any injection drug) in the 30 days before baseline, and BDI-II score. We also included time-varying BDI-II score, measured at the previous visit, and cumulative number of days of follow-up, modeled as a restricted cubic spline with knots at the 5th, 25th, 50th, 75th, and 95th percentiles. The model used to estimate the numerator of the weights was similar except that terms depending on the time-varying covariates were eliminated.

Each person-visit was treated as an observation, and the model was fit on the subsample of person-visits for which no exposure to antidepressant medication had yet occurred through the previous visit. We conducted the analysis using a conservative "intention-to-treat" assumption,[15,34] which is necessary to avoid generating overinflated estimates of treatment effect.[35,36] In the context of our study, the observational analog of this assumption meant that once participants started on an antidepressant medication regimen, they were assumed to remain on it thereafter (ie, probability weights were unaffected by subsequent depression severity scores or weights). To adjust for potential selection bias by measured factors due to loss to follow-up, a second set of censoring weights was obtained by a similar procedure, whereby participants who died were designated treatment failures and censoring was defined as loss to follow-up for any other reason.[13,14] The overall inverse probability of treatment and censoring (IPTC) weights were computed as the product of the treatment and censoring weights and then stabilized to increase efficiency.[13,14]

To estimate the effect of antidepressant medication treatment on viral suppression, the IPTC weights were used in a weighted pooled logistic regression model with viral suppression to less than 50 copies/mL as the outcome. We reassessed the statistical significance of the treatment estimate when self-reported ART adherence was included in the regression model. We interpreted an attenuated treatment estimate as suggestive that the effect was mediated by adherence, although additional assumptions would be necessary to make a definitive conclusion. For the secondary outcomes, we estimated the effect of antidepressant medication treatment on self-reported adherence by using the same IPTC weights in a weighted pooled linear regression model with self-reported adherence as the outcome and in weighted pooled logistic regression models with being on an ART regimen and complete adherence as the outcomes. These regression models included the same baseline covariates as were used in estimation of the weights but did not include the time-varying covariate. The primary regressor of interest was receipt of antidepressant medication treatment at or before the previous (quarterly) visit. We used a 12-week lag period because this has been considered a duration of antidepressant medication treatment sufficient to produce a robust therapeutic effect.[37,38] All analyses were censored at the last time the participant remained under follow-up. Standard errors were based on robust variance estimates to account for clustering of observations within participants over time.[39-42]

SENSITIVITY ANALYSIS

We undertook a number of sensitivity analyses to assess the robustness of our findings.[43] First, in light of previous research showing that the efficacy of antidepressant medication in improving mood is greater among those with more severe depression,[44-46] we stratified our analyses by baseline depression severity. We compared the effect of antidepressant medication treatment on viral suppression among those with minimal or mild depression at baseline (BDI-II score, <20) vs moderate to severe depression at baseline (BDI-II score, ≥ 20). Second, we examined the sensitivity of our estimates to different model specifications. We included different configurations of additional baseline and time-varying covariates, including alcohol and other substance use (previous 30 days), 36-Item Short Form Health Survey mental component summary and physical component summary scores, self-reported overall health, emergency department and hospital utilization (previous 90 days), homelessness status (previous 90 days), and representative payeeship (previous 90 days). Third, to explore bias-variance tradeoffs, we progressively trimmed[47] the IPTC weights at the 1st and 99th percentiles, the 5th and 95th percentiles, and the 10th and 90th percentiles. Fourth, we refit all models using treatment with SSRI medication (vs no SSRI) as the exposure. We examined the effect of this specific class of antidepressant medication because SSRIs are generally regarded, owing to safety and tolerability considerations,[48] as first-line agents for pharmacologic treatment of depression in patients with a substance abuse comorbidity profile similar to that of the participants in the REACH cohort. Furthermore, SSRIs are the class of antidepressant medication most commonly prescribed to HIV-infected persons with mood disorders.[33]

RESULTS

CHARACTERISTICS OF THE SAMPLE

A total of 158 participants (of 551 in the parent cohort) met inclusion criteria and contributed a total of 1782 person-quarters of observation. The average length of follow-up was 2.9 years (median, 3.0 years; range, 0.2-5.3 years). During the follow-up period, 38 participants died (24.1%) and 17 were lost to follow-up (10.8%). An additional 8 completed 12 months of follow-up according to a prespecified protocol for a related randomized controlled trial (but then exited the cohort) (5.1%), and 1 left the study because of incarceration (0.6%).

At baseline, 92 participants (58.2%) were on an ART regimen. There were 750 person-quarters of observation contributed before antidepressant medication initiation, with SSRI medications being the most frequently prescribed type of antidepressant medication (84.3%). Among the 119 participants who ultimately received antidepressant medication treatment at some point during follow-up, the average percentage of the time that subjects were actually taking antidepressant medication after initiation was 67% (median, 73%; interquartile range, 42%-100%). In terms of total treatment time, 763 of 1259 (60.6%) person-quarters of observation after antidepressant medication initiation were spent on treatment. Many subjects experienced 1 or more subsequent interruptions of antidepressant medication treatment, suggesting that our intention-to-treat assumption would yield conservative estimates of treatment effect.[35,36] The median duration of uninterrupted antidepressant medication treatment was 251 days (interquartile range, 85-432 days).

Baseline summary statistics for the sample are displayed in **Table 1**. One-third to one-half of the sample reported alcohol or other drug use. Participants who had ever been treated with antidepressant medications ap-

Table 1. Baseline Characteristics of Study Participants

	No. (%)		
	Ever Taken Antidepressant Medication (n=119)	Never Taken Antidepressant Medication (n=39)	*P* Value[a]
Beck Depression Inventory II score, mean (SD)	23.9 (11.3)	20.2 (8.2)	.06
Age, mean (SD), y	41.9 (8.2)	41.6 (7.3)	.82
Female sex	85 (71.4)	32 (82.1)	.19
Race			
White	53 (44.5)	15 (38.5)	.48
Black	38 (31.9)	15 (38.5)	.47
Other	28 (23.5)	9 (23.1)	.98
Education			
No diploma	34/116 (29.3)	9 (23.1)	.45
High school graduate	44/116 (37.9)	16 (41.0)	.73
Some college or more	38/116 (32.8)	14 (35.9)	.72
Homeless (previous 90 d)	19 (16.0)	9 (23.1)	.31
Representative payeeship (previous 90 d)	55 (46.2)	15 (38.5)	.40
Any chronic medical condition	42/115 (36.5)	4 (10.3)	.002
SF-36 PCS score, mean (SD)	38.7 (11.5)	39.1 (10.6)	.86
SF-36 MCS score, mean (SD)	35.1 (12.0)	44.3 (11.2)	<.001
Good or better self-reported health	103 (86.6)	34 (87.2)	.92
CD4+ T-lymphocyte count/μL, mean (SD)	189 (100)	194 (101)	.78
Log viral load, mean (SD)	8.5 (3.2)	8.6 (3.7)	.94
Viral load <50 copies/mL	12 (10.1)	7 (17.9)	.19
Receiving antiretroviral therapy at baseline	74 (62.2)	18 (46.2)	.08
No. of antiretroviral medications, mean (SD)	3.7 (0.85)	3.4 (0.92)	.22
Covered by any health insurance	106 (89.1)	31 (79.5)	.13
Alcohol use (previous 30 d)	45 (37.8)	15 (38.5)	.94
Any illicit drug use (previous 30 d)	56 (47.1)	22 (56.4)	.31
Crack cocaine use	35 (29.4)	13 (33.3)	.64
Powder cocaine use	4 (3.4)	1 (2.6)	.81
Methamphetamine use	30 (25.2)	9 (23.1)	.79
Heroin use	11 (9.2)	8 (20.5)	.06
Injection drug use	33 (27.7)	15 (38.5)	.21
Any emergency department visit (previous 90 d)	28 (23.5)	7 (17.9)	.47
Any hospitalization (previous 90 d)	21 (17.6)	4 (10.3)	.27

Abbreviations: MCS, mental component summary; PCS, physical component summary; SF-36, 36-Item Short Form Health Survey.
[a] Statistical significance of between-group comparisons was assessed by unpaired, 2-tailed *t* tests and χ^2 tests.

peared to have greater severity of illness at baseline. The ever-treated group had a lower mean baseline 36-Item Short Form Health Survey mental component summary score, and a higher proportion had a chronic medical condition. The ever-treated and never-treated groups were relatively balanced with regard to other baseline characteristics, such as CD4+ count, log viral load, self-reported overall health, alcohol use, and socioeconomic indicators.

Mean depression severity as measured by the BDI-II was greater among those who had ever initiated treatment with antidepressant medications (23.9 vs 20.2; *P*=.06). This finding was consistent with what was observed in the multivariable probability-of-treatment model used to construct the weights (**Table 2**): each 1-point increase in the BDI-II at the previous visit was associated with a 4% increased odds of initiating treatment with antidepressant medication (adjusted odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01-1.08; *P*=.02), even after adjusting for baseline severity of depression. Participants were also more likely to start antidepressant medication treatment if they were male or chronically ill. Stabilized IPTC weights based on the resulting model fit had a mean (SD) of 1.001 (0.12). Further details on the distribution of both stabilized and unstabilized weights are shown in the eFigure (http://www.archgenpsychiatry.com).

Table 2. Factors Associated With Starting Antidepressant Medication Treatment

	Adjusted OR (95% CI)[a]	Wald *P* Value
Baseline age, y	1.01 (0.96-1.07)	.64
Female sex	0.29 (0.10-0.86)	.03
Education		
No diploma	1.00 [Reference]	
High school graduate	0.91 (0.31-2.66)	.87
Some college or more	2.21 (0.66-7.45)	.20
Race		
Other	1.00 [Reference]	
White	0.29 (0.10-0.84)	.02
Black	0.34 (0.12-0.97)	.04
Any chronic illness	7.35 (2.71-19.9)	<.001
CD4+ T-lymphocyte count nadir	0.99 (0.99-1.00)	.12
BDI-II score at baseline	1.02 (0.99-1.06)	.24
BDI-II score at previous visit	1.04 (1.01-1.08)	.02
Cumulative days of follow-up	0.99 (0.99-1.00)	.73

Abbreviations: BDI-II, Beck Depression Inventory II; CI, confidence interval; OR, odds ratio.
[a] Odds ratios are derived from a pooled unweighted logistic regression model fit on the subsample of person-visits for which no exposure to antidepressant medication had yet occurred through the previous visit.

EFFECT OF ANTIDEPRESSANT MEDICATION TREATMENT

Without any adjustment for confounding, antidepressant medication treatment was associated with a 1.55 greater odds (95% CI, 1.03-2.31; *P*=.03) of achieving viral suppression (**Table 3**). By means of a conventional multivariable logistic regression adjustment strategy for confounding, antidepressant medication treatment was associated with a 1.58 greater odds (95% CI, 1.07-2.31; *P*=.02) of achieving viral suppression. However, because depression severity is affected by past treatment with antidepressant medication, these estimates may not carry a causal interpretation as the overall effect of antidepressant medication treatment. Marginal structural models estimated a 2.03 greater odds (95% CI, 1.15-3.58; *P*=.02) of achieving viral suppression. When self-reported ART adherence was included in the regression model, the estimated effect declined in magnitude and statistical significance (weighted OR, 1.32; 95% CI, 0.73-2.40; *P*=.36).

Table 3. Estimates of Effect of Antidepressant Medication Treatment on Viral Suppression[a]

	OR (95% CI)	*P* Value
Unweighted, crude	1.55 (1.03-2.31)	.03
Unweighted, adjusted	1.58 (1.07-2.31)	.02
Weighted	2.03 (1.15-3.58)	.02

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Estimates were made by conventional statistical adjustment vs inverse probability of treatment and censoring weighting. The naive (unweighted) estimates do not have a causal interpretation and are shown here for comparison purposes only. The estimates from the marginal structural models have the following interpretation: if, contrary to fact, participants are exposed to antidepressant medication at or before the previous visit, then their average odds of achieving viral suppression would be the OR given.

Antidepressant medication treatment seemed to have larger effects among participants with more severely depressed mood. Among those with minimal or mild depression severity at baseline (BDI-II score, <20), antidepressant medication treatment did not result in a statistically significantly increased odds of achieving viral suppression (weighted OR, 1.75; 95% CI, 0.71-4.33; *P* = .23). However, the CI does not rule out the possibility of a reasonably large benefit in this subgroup. Among those with moderate to severe depression at baseline (BDI-II score, ≥20), the effect on viral suppression was statistically significant (weighted OR, 2.77; 95% CI, 1.26-6.09; *P* = .01).

In supplemental analyses, we sought to determine whether the effect of antidepressant medication treatment on viral suppression could be attributable to its effects on adherence to a continuum of HIV care. Weighted regression showed that antidepressant medication use resulted in a 3.87 greater odds of being on an ART regimen (95% CI, 1.98-7.58; *P* < .001). In addition, antidepressant medication treatment increased self-reported adherence by 25% (95% CI, 14%-36%; *P* < .001) and nearly doubled the odds of achieving complete adherence (weighted OR, 1.94; 95% CI, 1.20-3.13; *P* = .006).

SENSITIVITY ANALYSIS

To explore the sensitivity of our estimates to alternative model specifications, we added more baseline and time-varying covariates to the regression models in different configurations (eTable 1). Under these alternate specifications, the estimated OR for achieving viral suppression ranged from 1.52 to 2.19 (with *P* values from .19 to .01). Because these alternate specifications did not produce qualitatively dissimilar estimates, we reported the results of the original model as our primary findings. Next, we progressively truncated the IPTC weights at the 1st and 99th, 5th and 95th, and 10th and 90th percentiles (eTable 2). The estimated ORs were qualitatively similar to (ie, within ±2% of) the original estimates, indicating that, despite relatively larger weights, outlier participants did not exert overt influence on the results. Finally, we refit all models to determine the effect of SSRI medication treatment on viral suppression. Marginal structural models estimated qualitatively similar effects of SSRIs on probability of achieving viral suppression (weighted OR, 1.73; 95% CI, 0.84-3.55; *P* = .14).

COMMENT

Using a marginal structural model to account for time-varying confounding by depression severity, we found that antidepressant medication treatment increased the probability of achieving viral suppression among a cohort of homeless and marginally housed persons with HIV. In supplemental analyses, we found evidence of improved adherence along a continuum of HIV care: antidepressant medication treatment increased the probability of ART uptake nearly 4-fold and also resulted in a 25–percentage point increase in self-reported ART adherence and a nearly 2-fold–increased probability of achieving complete adherence. These results are consistent with previous studies linking depressive symptoms to reduced uptake[5,6] and adherence[7-9] to ART.

Although changes in behavior are the most plausible explanation for our findings,[49,50] some researchers have hypothesized that biological pathways may directly link depression to poorer HIV outcomes.[51] This hypothesis is consistent with previous studies showing that, even after adjusting for ART adherence, depression is associated with worsened HIV outcomes, including CD4+ count decline,[52] incident AIDS-defining illness,[53] and AIDS-related mortality.[54] One study showed that resolution of a major depressive episode was associated with increased natural killer cell activity.[55] More recently, a cross-sectional analysis of data from 658 HIV-positive men and women showed that participants taking SSRIs were less likely to have detectable cerebrospinal fluid HIV-1 RNA levels.[56] This relationship held even among those not concurrently taking ART, suggestive of a biological effect and leading some to suggest that psychotropic medications could be useful as adjunctive treatment for persons with HIV.[57] In our marginal structural model analysis, the estimated effect of antidepressant medication treatment became statistically nonsignificant when adjusted for ART adherence, suggesting that the effect of antidepressants on HIV treatment response is at least partially mediated by adherence. However, the attenuation of the treatment effect once adherence was added to the model could also have been due to the limitations of our relatively small sample size. Additional assumptions would be required to fully interpret the adjusted effect as a direct (nonmediated) effect of antidepressant medication treatment.[58,59] In particular, we would need to assume that the baseline covariates alone capture all the confounding from the effect of adherence on viral suppression, which is unlikely to be the case. Distinguishing the relative contributions of the 2 mechanisms, direct vs indirect (biological vs behavioral), through which antidepressant medication treatment could affect virologic outcomes was beyond the scope of our study and remains an important area for future work.

We observed greater effects of antidepressant medication on viral suppression among participants with more severe depressive symptoms at baseline. This finding is potentially analogous to results from recently published meta-analyses of randomized controlled trials showing that the efficacy of antidepressant medication on mood is greater among those with more severe depressive symp-

toms at baseline.[44-46] In other clinical contexts, marginal structural models have also estimated treatment effects that closely approximate the findings from randomized controlled trials.[16,60-62] Even though our estimates have a causal interpretation under certain assumptions, randomized controlled trial evidence is needed to definitively conclude that pharmacologic treatment of depression has beneficial effects on HIV treatment adherence and HIV treatment outcomes.

Despite these caveats, our study contributes to a sparse literature on how treatment of depression can result in improved HIV outcomes. To our knowledge, no randomized controlled trials of antidepressant medication treatment alone have shown improvements in virologic outcomes. Safren et al[63] studied the effect of individual cognitive behavioral therapy among persons living with HIV who were also diagnosed as having a depressive mood disorder. The cognitive behavioral therapy intervention explicitly incorporated adherence training and improved ART adherence by more than 20 percentage points at 12-month follow-up, but the small sample size limited the investigators' ability to detect differences in viral load. Two randomized studies of group-based cognitive behavioral stress management for persons with HIV have yielded mixed results, one positive[64] and one negative,[65] but those studies enrolled participants with minimal depressive symptoms (ie, mean BDI of <14 at baseline). Our study is notable in that it suggests that antidepressant medication treatment can improve HIV care and HIV treatment outcomes among persons with significant depressive symptoms.

Also in contrast to these studies, the participants in the REACH cohort are drawn from a population whose frequently changing living situations and medical and psychiatric comorbidities can make controlled study difficult. All REACH participants were either homeless or marginally housed, approximately one-half reported alcohol or illicit drug use, and more than one-third had been assigned to representative payeeship. Because of these complex comorbidities, many of our study participants would have been excluded from most randomized controlled trials of antidepressant efficacy.[66,67] The clinical and public health importance of our work is further underscored by nationally representative evidence of underdiagnosis[68] and undertreatment[32] of depression among persons living with HIV/AIDS, as well as the fact that even incremental (eg, 10%) increases in ART adherence can improve virologic[69,70] and immunologic[71] outcomes in this population.

Despite these strengths, interpretation of our findings is subject to a number of limitations. Most participants in our study were female, which limits generalizability to the HIV epidemic in the United States.[68,72] However, while not formally a random sample of HIV-infected homeless and marginally housed persons, the parent cohort (REACH) was drawn from a systematic and reproducible venue-based sample[73] of homeless and marginally housed persons with HIV. The REACH cohort was composed of mostly men with a high prevalence of drug use, alcohol use, and mental illness and is roughly generalizable to the HIV-infected urban poor.[17,18] The preponderance of females in our analytic sample may reflect the overall epidemiology of major depressive disorder in the general population.[3,74] Although our sample may not represent patients seen in most clinical settings, it does reflect a population that has variable access to medical and mental health care services and that remains an important part of the national HIV epidemic.[75,76]

A second limitation is that our statistical analyses group antidepressant medications together into a single category, implicitly assuming equivalent treatment effects across medication classes. However, there is recent meta-analytic evidence to support this simplifying assumption.[77-79] Lack of power prevented us from studying individual drugs, but we conducted a sensitivity analysis for the most frequently prescribed medication class in our study (SSRIs) and observed qualitatively similar effects on viral suppression.

Finally, our data did not permit us to account for dose escalation. Drug metabolism and clearance vary widely between individuals, and psychiatrists frequently compensate for this pharmacokinetic variability by tailoring antidepressant medication dosage on their patients' responses. Our marginal structural model analysis can be conceptualized as analogous to a flexible randomized controlled trial in which subjects are randomized to receive antidepressant medication treatment (or not), but the drug and dose are left up to physician and patient discretion.

As noted previously, marginal structural models require several assumptions. First, consistency implies that each participant's potential outcome under his or her observed antidepressant medication exposure history is precisely his or her observed outcome.[80] Although consistency may be problematic when the exposure is a feature such as obesity, it is plausible (although not empirically verifiable) in observational studies of medical treatments. Second, with regard to positivity, or the experimental treatment assumption,[14] there were no structural zeroes[43] in the setting of our data, ie, factors that would be deterministic of either treatment or nontreatment with antidepressant medication. We were able to identify exposed and unexposed participants at each level of depressive severity as measured by the BDI-II, thereby ruling out the presence of potential random zeroes. In addition, we fitted a regression model using all the baseline covariates and the time-varying covariate to compute predicted probabilities of treatment. We then visually inspected a plot of the log odds of treatment against both the observed treatment and predicted probabilities of treatment to ensure that there was an acceptable degree of variation of observed values across all levels of the predicted.[81,82] Third, we assumed that conditioning on several baseline covariates and recent values of depression severity was sufficient to achieve exchangeability between those who did and did not initiate treatment with antidepressant medication during the follow-up period.[83,84] This is not an empirically verifiable assumption, but we relied on previous studies to guide our inclusion of the most important confounders. Furthermore, we included a broad range of other covariates in an exhaustive sensitivity analysis, and our findings remained robust to these alternate specifications. Nonetheless, some unmeasured confounding could remain, eg, receipt of adherence counseling. Subjects who received adherence

counseling may be more likely to initiate antidepressant medication treatment because of greater interaction with the care team and greater awareness of depression severity, and they may also be more likely to adhere to ART. Fourth, we made the conservative intent-to-treat assumption, long recognized as the preferred approach to analysis of data from randomized controlled trials.[35,36,85] Thus, we anticipate some bias toward the null in our treatment estimates. Participants in the study cohort remained on antidepressant medication regimens an average of 67% (median, 73%) of the time after treatment initiation, which compares favorably with completion rates observed in long-term (ie, 6-8 months in duration) randomized controlled trials of SSRIs[86] and is similar to completion rates observed in short-term trials of both SSRIs[87] and tricyclic antidepressant medications.[88]

In summary, we introduced the method of marginal structural modeling to the psychiatric literature to estimate the causal effect of antidepressant medication treatment on viral suppression among a longitudinal cohort of homeless and marginally housed persons with HIV. Antidepressant medication treatment resulted in a 2-fold greater probability of achieving viral suppression, and this effect was likely due to improved adherence along a continuum of HIV care. The estimated effects are clinically meaningful and (under certain assumptions) have a causal interpretation, yet randomized controlled trials are needed to conclude definitively that antidepressant medication increases viral suppression in this population. Given the relatively high prevalence of underdiagnosed and undertreated depressive mood disorders among persons with HIV, our findings suggest that improved diagnosis and treatment of depression may have an important contribution to improving HIV treatment outcomes.

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Author Affiliations: Langley Porter Psychiatric Institute, University of California at San Francisco (Dr Tsai); Divisions of HIV/AIDS (Dr Weiser) and General Internal Medicine (Drs Ragland and Kushel), San Francisco General Hospital, University of California at San Francisco; Center for AIDS Prevention Studies (Dr Weiser), University of California at San Francisco; Division of Biostatistics, School of Public Health, University of California at Berkeley (Dr Petersen); Harvard Medical School, Boston, Massachusetts (Dr Bangsberg); Harvard Initiative for Global Health, Cambridge, Massachusetts (Dr Bangsberg); Center for Global Health, Massachusetts General Hospital, Boston (Dr Bangsberg); Mbarara University of Science and Technology, Mbarara, Uganda (Dr Bangsberg); and Phillip T. and Susan M. Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Charlestown, Massachusetts (Dr Bangsberg). Dr Tsai is now with the Robert Wood Johnson Health and Society Scholars Program at Harvard University.
Correspondence: David R. Bangsberg, MD, MPH, Harvard Initiative for Global Health, 104 Mt Auburn St, Cambridge, MA 02138 (dbangsberg@partners.org).
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