

# Directly Observed Antidepressant Medication Treatment and HIV Outcomes Among Homeless and Marginally Housed HIV-Positive Adults: A Randomized Controlled Trial

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Depressive, pain, and substance use disorders are highly prevalent among persons living with HIV/AIDS<sup>1,2</sup> and among the homeless and marginally housed.<sup>3-5</sup> The triple diagnosis of depression, HIV, and substance use poses unique treatment challenges for clinicians: successful management of one condition is often dependent on successful management of the others, and the optimal sequencing of depression treatment, substance use treatment, and stabilization of psychosocial comorbidities remains unclear. Adherence to the entire continuum of HIV care is often hampered by depression<sup>6-8</sup> and substance use.<sup>9,10</sup> For homeless persons, the need to address subsistence concerns such as obtaining food and shelter may not only adversely affect mental well-being<sup>11</sup> but may also divert attention away from medication adherence and regular clinic attendance.<sup>12</sup> Timely and effective depression treatment is critical for HIV-positive persons, because depression has been associated with CD4<sup>+</sup> T-lymphocyte cell count decline,<sup>13</sup> progression to AIDS,<sup>14</sup> and AIDS-related mortality.<sup>15</sup> Yet depression remains pervasively underdiagnosed and undertreated among the homeless<sup>16-18</sup> and among HIV-positive persons.<sup>19,20</sup>

Depression treatment might be expected to improve virological or immunologic outcomes through improved adherence, but this has not been conclusively demonstrated.<sup>21-23</sup> We therefore sought to determine whether treatment with once-weekly fluoxetine reduced depression symptom severity among homeless and marginally housed persons with comorbid depression and HIV. Because this population faces many psychosocial barriers to successful medication adherence,<sup>12,24</sup> in addition to depression,<sup>25</sup> we employed a directly observed treatment strategy similar to that used for treatment and management of patients with

**Objectives.** We assessed whether directly observed fluoxetine treatment reduced depression symptom severity and improved HIV outcomes among homeless and marginally housed HIV-positive adults in San Francisco, California, from 2002 to 2008.

**Methods.** We conducted a nonblinded, randomized controlled trial of once-weekly fluoxetine, directly observed for 24 weeks, then self-administered for 12 weeks (n = 137 persons with major or minor depressive disorder or dysthymia). Hamilton Depression Rating Scale score was the primary outcome. Response was a 50% reduction from baseline and remission a score below 8. Secondary measures were Beck Depression Inventory-II (BDI-II) score, antiretroviral uptake, antiretroviral adherence (measured by unannounced pill count), and HIV-1 RNA viral suppression (< 50 copies/mL).

**Results.** The intervention reduced depression symptom severity (b = -1.97; 95% confidence interval [CI] = -0.85, -3.08; P < .001) and increased response (adjusted odds ratio [AOR] = 2.40; 95% CI = 1.86, 3.10; P < .001) and remission (AOR = 2.97; 95% CI = 1.29, 3.87; P < .001). BDI-II results were similar. We observed no statistically significant differences in secondary HIV outcomes.

**Conclusions.** Directly observed fluoxetine may be an effective depression treatment strategy for HIV-positive homeless and marginally housed adults, a vulnerable population with multiple barriers to adherence. (*Am J Public Health.* 2013;103:308-315. doi:10.2105/AJPH.2011.300422)

tuberculosis and HIV.<sup>26</sup> This strategy reduced the potential for incomplete adherence to reduce the effectiveness of antidepressant treatment. A secondary aim was to determine whether depression treatment improved antiretroviral therapy (ART) uptake among persons eligible for treatment and ART adherence and viral suppression among treated persons.

## METHODS

From July 2002 through February 2008, we recruited English-speaking adults with comorbid HIV and depression. We sought participants in homeless shelters, free lunch programs, low-income single-room-occupancy hotels, public HIV clinics, and social service agencies throughout the Tenderloin, South of Market, and Mission districts of San Francisco, California. We recruited a small

proportion of participants from Research in Access to Care for the Homeless, an observational, prospective cohort of homeless and marginally housed persons living with HIV (drawn from the same sampling frame).<sup>27,28</sup> Potential participants were screened in several sequential steps (Figure 1) before undergoing structured diagnostic assessment<sup>29</sup> to determine whether they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for major depressive disorder, minor depressive disorder, or dysthymia.<sup>30</sup> Experienced clinical raters certified to have high interrater reliability and procedural integrity administered all instruments and conducted structured assessments. All potential participants received confirmatory HIV testing to document their serostatus (Quest Diagnostics, Inc, Valencia, CA).

We excluded potential participants if they did not live in San Francisco; were unwilling to take fluoxetine; had a CD4<sup>+</sup> T-lymphocyte cell count nadir of 350 cells per milliliter or lower and were not currently taking ART; were unable to commit to the required study visits; reported taking antidepressant medications, mood stabilizers, or other neuroleptics within 3 months prior to study entry; reported being under psychiatric care within 6 months prior to study entry; reported a previous diagnosis of bipolar disorder or schizophrenia; exhibited signs and symptoms consistent with a *DSM-IV* diagnosis of dementia, any psychotic disorder, or bipolar disorder; were deemed to have a current substance use disorder of a severity requiring immediate residential or inpatient treatment; were at imminent risk of completed suicide; were pregnant; were prescribed a medication or had a history of a medical condition that could harmfully interact with fluoxetine; or were already participating in an ongoing adherence study.

### Study Design

Participants who remained eligible at the end of the screening process were randomly assigned to receive fluoxetine treatment or referral to the community for psychiatric care (Figure 1). We employed blocked randomization within categories of *DSM-IV* diagnosis, substance use, ART use, and CD4 count, with a random choice of 8, 10, or 12 participants in each block. We generated the randomized treatment assignment list prior to study enrollment. Participants were enrolled and assigned to a treatment arm by research staff who obtained the assignment from a password-protected database maintained by the study programmer. Only the study programmer and senior epidemiologist had access to the randomization list (K. R. and E. D. C.).

Participants assigned to the intervention arm received an explanation of their psychiatric diagnosis and were told that they would be treated with fluoxetine. Treatment was directly observed for 24 weeks, introduced in 3 phases of gradually increasing independence from the study provider: (1) 20 milligrams fluoxetine directly observed each weekday and self-administered on weekends, for 2 weeks; (2) 90 milligrams fluoxetine directly observed weekly, for 22 weeks; and (3) 90 milligrams fluoxetine

self-administered weekly, for 12 weeks. In 2005, midway through the study, the manufacturer (Eli Lilly & Co, Indianapolis, IN) ceased donating samples of Prozac Weekly. Therefore, we switched participants from that medication to 90 milligrams generic fluoxetine, also taken weekly. All directly observed doses were delivered in the Tenderloin District at the study research site, a system previously shown to be effective for isoniazid distribution in a similar population.<sup>31</sup>

A study psychiatrist met with intervention arm participants weekly for the first month, every 2 weeks for the second month, and monthly thereafter. At each visit, the psychiatrist conducted a thorough psychiatric interview and mental status exam and inquired about treatment response and possible adverse side effects. Study psychiatrists also used the 17-item Hamilton Rating Scale for Depression (Ham-D)<sup>32</sup> and the Clinical Global Impression Severity and Improvement scales<sup>33</sup> to guide assessment of treatment response. These instruments were administered without blinding, because the clinical assessments were separate from the blinded study assessments. The dose of fluoxetine was increased to 180 milligrams once weekly for partial responders and non-responders. If deemed necessary by study psychiatrists, augmenting medications were added to treat symptoms to remission. We reimbursed intervention arm participants \$25 per week for completion of all scheduled directly observed doses and \$25 per week for the final 12 weeks of self-administered treatment.

Participants randomized to the referral arm received an explanation of their diagnosis and were advised to seek treatment at a public mental health clinic that specialized in the care of HIV-positive persons, located 0.5 mile away along a major public transportation corridor. Referral arm participants received a \$25 weekly incentive to come to the research study site to update contact information and undergo data collection procedures.

### Outcome Measures and Covariates

Research visits occurred monthly and coincided with psychiatric treatment visits when possible. Structured interviews were used to collect information about participants' sociodemographic characteristics, health behaviors, and HIV care at baseline, as well as their experience

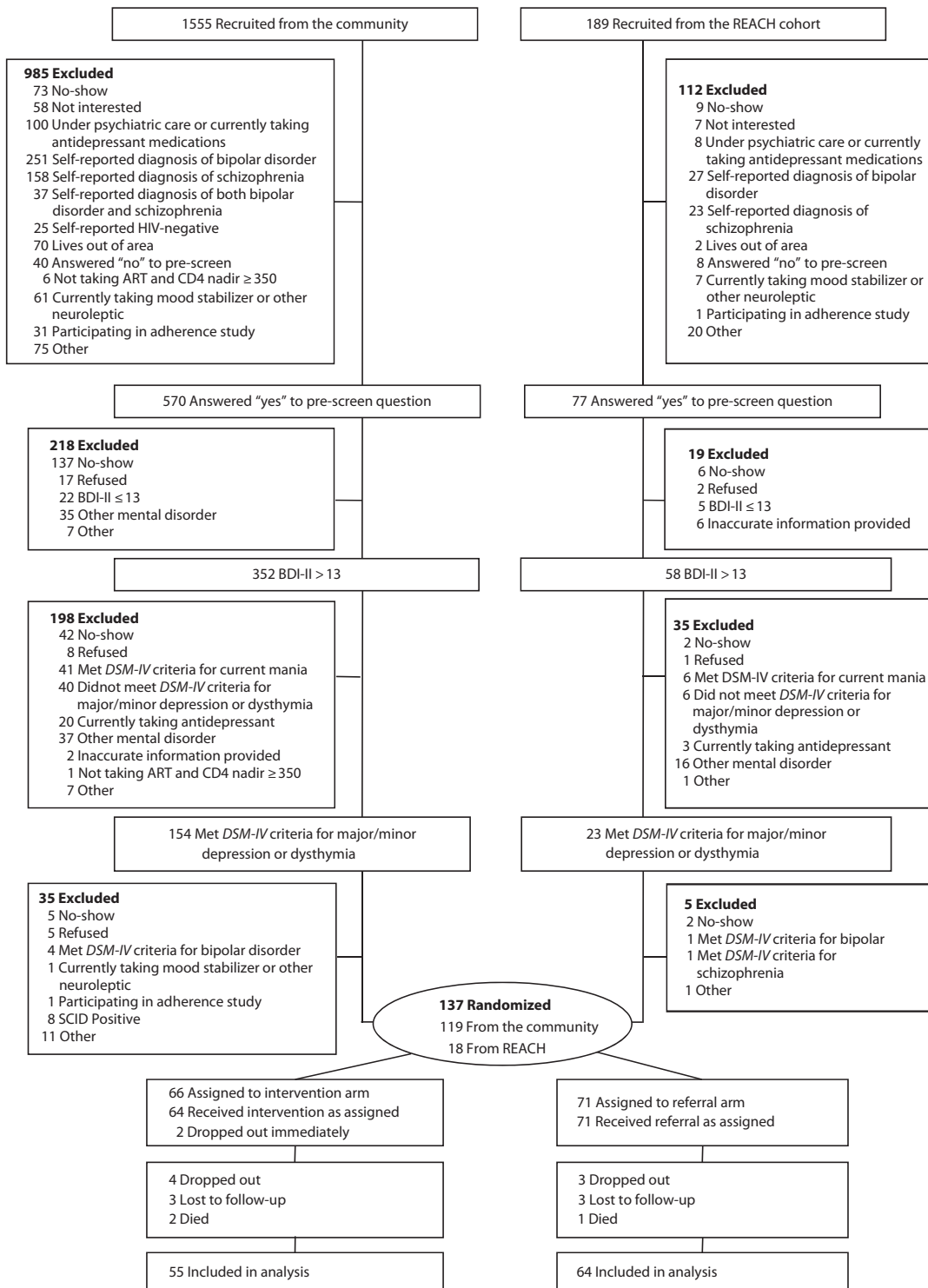
of gastrointestinal, neuropsychiatric, constitutional, and sexual symptoms every 3 months. We determined CD4<sup>+</sup> T-lymphocyte cell count through standard techniques (Unilab, San Jose, CA).

The primary outcome of interest was depression symptom severity, assessed with the Ham-D and administered by experienced clinical raters who were blinded to treatment assignment. We defined remission as a virtual absence of depressive symptoms (Ham-D ≤ 7) and response as a clinically meaningful degree of symptom reduction (≥ 50% reduction in symptom severity from baseline).<sup>34</sup> Our secondary depression outcome measure was the 21-item Beck Depression Inventory-II (BDI-II)<sup>35</sup> with remission (BDI-II ≤ 8) and response defined similarly.

Among study participants who were eligible for ART at baseline (i.e., CD4<sup>+</sup> T-lymphocyte cell count nadir < 350 cells/mL), we defined uptake of ART as the patient being on ART as of a given visit. Among study participants on ART at baseline, we measured ART adherence with unannounced pill counts conducted at the participant's usual place of residence.<sup>36</sup> We defined viral suppression as HIV-1 RNA less than 50 copies per milliliter. Plasma was processed and stored at -40°C within 6 hours of collection. We determined HIV-1 viral load with the HIV-1 Amplicor Monitor version 1.5 ultrasensitive assay (Roche Molecular Systems, Alameda, CA), with a lower detection limit of 20 copies per milliliter. We assessed all outcomes monthly.

### Statistical Analysis

We used the *t* test for continuous variables and the  $\chi^2$  test for categorical variables to compare the 2 study arms on baseline sociodemographic and clinical characteristics. To estimate the average effect of treatment on outcomes over the entire study, we fit generalized linear mixed models to the data with the SAS procedure GLIMMIX (SAS Institute Inc, Cary, NC). For all analyses, we used an unstructured working covariance matrix. For the continuous dependent variables (Ham-D, BDI-II, ART adherence), we assumed a model relating treatment and time effects linearly to the dependent variable, whereas for the binary dependent variables (response, remission, ART uptake, viral suppression), we assumed a model



Note. ART = antiretroviral therapy; BDI-II = Beck Depression Inventory-II; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; REACH = Research in Access to Care for the Homeless; SCID = Structured Clinical Interview for DSM-IV. Prescreening with self-report of depression; administration of 21-item BDI-II; structured clinical assessment of candidates with a BDI-II score > 13 to confirm diagnosis of major depressive disorder, minor depressive disorder, or dysthymia; and interview with study psychiatrist to confirm interest and psychiatric diagnosis, assess appropriateness of antidepressant medication treatment, and review coordination of care with potential participant's primary care provider.

**FIGURE 1—Stages of screening process for homeless and marginally housed participants with HIV and depression for controlled trial of directly observed fluoxetine treatment.**

**TABLE 1—Baseline Characteristics of Homeless and Marginally Housed Participants with HIV and Depression in Controlled Trial of Directly Observed Fluoxetine Treatment**

Characteristic	Weekly Fluoxetine Arm (n = 64), Mean ±SD or No. (%)	Community Referral Arm (n = 71) Mean ±SD or No. (%)	Test Statistic, <sup>a</sup>	P
Recruited from REACH	10 (15.2)	8 (11.3)	0.45	.615
Age, y	44.2 ±9.09	42.8 ±8.44	-0.94	.348
Female	6 (9.1)	8 (11.3)	0.18	.781
White	32 (48.5)	36 (50.7)	0.07	.795
Ever homeless	45 (72.6)	45 (64.3)	1.04	.307
Illegal drug use <sup>b</sup>				
Ever	52 (82.5)	60 (85.7)	0.25	.642
Past 30 d	10 (16.1)	13 (18.6)	0.14	.82
Crack cocaine use				
Ever	42 (66.7)	46 (65.7)	0.01	.908
Past 30 d	11 (18.0)	9 (12.9)	0.68	.47
Heroin use				
Ever	23 (36.5)	17 (24.3)	2.36	.125
Past 30 d	2 (3.3)	3 (4.3)	0.09	> .999
Methamphetamine use				
Ever	44 (69.8)	48 (68.6)	0.03	.874
Past 30 d	8 (12.9)	11 (15.7)	0.21	.805
Alcohol use: past 30 d	29 (46.0)	34 (48.6)	0.09	.77
DSM-IV diagnosis				
Major depression	50 (75.8)	51 (71.8)		
Minor depression	5 (7.6)	7 (9.9)	0.33	.849
Dysthymia	11 (16.7)	13 (18.3)		
CD4 <sup>+</sup> T-lymphocyte count, cells/mL	388.8 ±269.86	408.9 ±266.73	0.44	.663
CD4 <sup>+</sup> count nadir < 350 cells/mL	34 (51.5)	36 (50.7)	0.01	.924
Receiving antiretroviral therapy	21 (61.8)	25 (69.4)	0.07	> .999

Note. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; REACH = Research in Access to Care for the Homeless.

<sup>a</sup>For continuous variables, comparisons used *t* tests; for categorical variables,  $\chi^2$  tests.

<sup>b</sup>Crack cocaine, heroin, or methamphetamine use.

relating treatment and time effects linearly to the logit of the probabilities. We used the RANDOM statement and specified that the linear predictor contained an intercept term that randomly varied at the level of the participant effect. We modeled the effect of time as a series of dummy variables for each month, with the baseline month as the reference category. We also explored adding treatment-by-time interactions to the models for primary outcomes (but did not do so for secondary outcomes, because of the smaller sample size and lack of sufficient degrees of freedom).

We used the *F* test to assess whether the interaction terms were jointly statistically significant. For example, the models with binary

dependent variables were represented mathematically as follows:

$$(1) \text{logit}(\pi_{ij}) = \alpha_i + X_{ij}\beta = \alpha + \varepsilon_{ij} + X_{ij}\beta,$$

where  $\pi_{ij}$  denotes the outcome for participant *i* in month *j*,  $X_{ij}$  denotes the design matrix for the explanatory variables for treatment assignment and time,  $\beta$  denotes the vector of regression coefficients for the explanatory variables, and the random intercepts  $\alpha_i$  are a linear combination of a grand mean ( $\alpha$ ) and a normally distributed deviation ( $\varepsilon_{ij}$ ) from the mean. We conducted all analyses in SAS version 9.2.

To estimate the sample size needed for the study, we assumed equal sample sizes for each

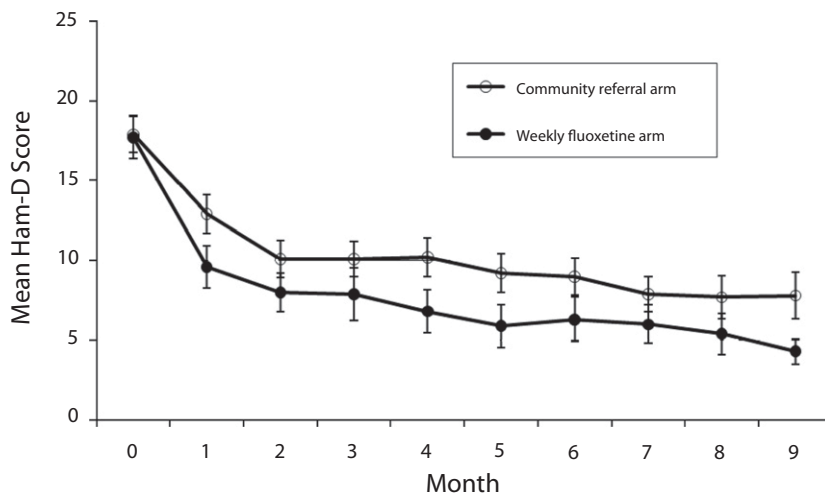
treatment arm, with 10 proposed monthly time points and 1% relative attrition in both treatment arms at each time point after the first. We also assumed that the pairwise correlations of the quarterly repeated measures on the primary outcome would be 0.6. We then sought to obtain a sample size sufficient to have 80% power for a 2-tailed 0.05 hypothesis test of a medium effect size<sup>37</sup> for the primary outcome over the course of treatment. With these assumptions, we used a previously published formula for determining sample size in longitudinal study designs<sup>38</sup> to estimate that we would need to enroll 117.7 participants per treatment arm, rounding upward for a total estimated sample size of 236.

## RESULTS

We screened 1744 potential participants, 1555 from the community and 189 from the Research in Access to Care for the Homeless cohort (Figure 1). Nearly two thirds were found to be ineligible during the prescreening process; the most common reason was self-report of alternative diagnoses such as bipolar disorder (25.3%) and schizophrenia (16.5%). Of the 647 potential participants who underwent screening with the BDI-II, 471 (73%) had a BDI-II score higher than 13. These potential participants were eligible to undergo structured diagnostic assessment, and nearly two thirds did not meet DSM-IV criteria for inclusion. A study psychiatrist reviewed the remaining 190 potential participants: 137 were confirmed to be eligible and appropriate for the study and consented to participate in the randomized trial. Thus, the trial did not meet its enrollment goal.

Sixty-six participants were randomly assigned to the intervention arm and 71 to the referral arm. Participants recruited from the Research in Access to Care for the Homeless cohort differed from those recruited from the community on history of homelessness (94% vs 64%; *P* = .012) and recent alcohol use (22% vs 51%; *P* = .024) but were otherwise comparable. A slightly higher proportion of participants in the intervention arm than in the referral arm reported a history of ever using heroin (36.5% vs 24.3%; *P* = .125), and a slightly smaller proportion were on ART at baseline (61.8% vs 69.4%; *P* = .07), but they





No. of patients

Treatment	64	59	58	58	57	56	55	55	55	55
Control	71	69	68	68	68	68	67	67	65	64

Note. HAM-D = Hamilton Rating Scale for Depression. Error bars indicate 95% confidence intervals.

**FIGURE 2—Mean depression symptom severity by treatment and time among homeless and marginally housed participants with HIV and depression in controlled trial of directly observed fluoxetine treatment.**

were otherwise statistically comparable (Table 1). Mean Ham-D scores at baseline (intervention participants = 17.7; referral participants = 17.9;  $P = .787$ ) indicated moderate levels of depression severity.

### Medication Delivery

Participants randomized to the intervention arm were observed receiving 2233 (92.9%) of 2403 scheduled observed doses of daily fluoxetine and 3374 (90.9%) of 3713 scheduled observed doses of weekly fluoxetine, on weekdays. They also reported having taken 1215 (99.5%) of 1221 scheduled self-administered doses of daily fluoxetine on weekends. Among the 55 participants retained at 36 weeks in the intervention arm, 27 (49.1%) reported taking fluoxetine alone, 20 (36.4%) reported taking fluoxetine in combination with another type of psychotropic medication (most commonly mirtazapine [ $n = 9$ ]), and 5 (9.1%) reported not taking any fluoxetine but reported taking other psychotropic medications (most commonly bupropion [ $n = 2$ ]).

The mean dose of fluoxetine achieved was 18 milligrams ( $\pm 4.4$  mg) per day among participants still taking daily fluoxetine by the end of the study and 137 milligrams ( $\pm 73.5$  mg) per week among those taking weekly

fluoxetine. Among the 64 participants retained at 36 weeks in the referral arm, 7 (10.9%) reported taking fluoxetine and 16 (25.0%) reported taking another type of psychotropic medication (most commonly bupropion [ $n = 5$ ]).

### Treatment Efficacy and Continuation

Participants in both study arms experienced improved mood, but mean depression severity was lower in the intervention arm at each assessment (Figure 2). We observed similar trends on the BDI-II and on response and remission (Table 2). The mixed-model analysis confirmed a statistically significant main effect of treatment on the Ham-D ( $b = -1.97$ ; 95% confidence interval [CI] =  $-0.85, -3.08$ ;  $P < .001$ ) and a treatment-by-time interaction ( $F = 6.25$ ;  $P = .014$ ). We obtained similar results when we used the Ham-D to categorize participants as responders (adjusted odds ratio [AOR] = 2.40; 95% CI = 1.86, 3.10;  $P < .001$ ) and remitters (AOR = 2.97; 95% CI = 2.29, 3.87;  $P < .001$ ). In the mixed-model analysis for BDI-II score, we found a statistically significant main effect of treatment ( $b = -4.00$ ; 95% CI =  $-1.65, -6.35$ ;  $P = .001$ ) but not a treatment-by-time interaction ( $F = 1.74$ ;  $P = .19$ ). Use of the BDI-II to categorize participants also

yielded similar results (responders, AOR = 2.01; 95% CI = 1.56, 2.59;  $P < .001$ ; remitters, AOR = 3.11; 95% CI = 2.36, 4.11;  $P < .001$ ).

By the end of the study, similar proportions of ART-eligible participants in each study arm were receiving ART (intervention, 73.1%; referral, 75.0%;  $P > .999$ ). The mixed-model analysis revealed no statistically significant effects of the intervention on ART uptake (AOR = 1.18; 95% CI = 0.83, 1.68;  $P = .34$ ). Participants in the intervention and referral arms had a similar average percentage of ART adherence ( $b = 0.05$ ; 95% CI =  $-0.02, 0.12$ ;  $P = .2$ ). We found no statistically significant difference in viral suppression (AOR = 1.04; 95% CI = 0.97, 1.12;  $P = .23$ ).

Fifty-five (83.3%) of 66 participants assigned to intervention completed the study: 2 died, 6 dropped out (including 2 who dropped out prior to baseline assessment and therefore did not contribute data to Table 1), and 3 were lost to follow-up. Sixty-four (90.1%) of 71 participants assigned to the referral arm completed the study: 1 died, 3 dropped out, and 3 were lost to follow-up. There were no suicides. Eight of 9 dropouts and all deaths occurred in the first 2 months.

### DISCUSSION

We showed that directly observed treatment with fluoxetine improved depression symptom severity but not average ART adherence or probability of viral suppression in a group of homeless and marginally housed persons with comorbid HIV and depression. The observed benefit was substantial: at the 36-week follow-up, the average 3.5-point Ham-D treatment difference was equivalent to a Cohen's  $d$  effect size greater than the mean effect size observed in short-term trials of serotonin-specific reuptake inhibitors ( $d = 0.40$ ).<sup>39</sup> Our estimated effect of fluoxetine treatment also compared favorably to the mean estimated effect observed in other classic long-term trials of serotonin-specific reuptake inhibitors (AOR = 1.66; 95% CI 1.12, 2.48).<sup>40</sup>

Our study added to the literature with 2 notable features. Our intervention specifically targeted homeless and marginally housed HIV-positive persons, a vulnerable population with a tremendous burden of unmet mental health

**TABLE 2—Depression Outcomes at Baseline and Follow-Up Among Homeless and Marginally Housed Participants With HIV and Depression in Controlled Trial of Directly Observed Fluoxetine Treatment**

Measure	Weekly Fluoxetine Arm, Mean $\pm$ SD or No. (%)	Community Referral Arm, Mean $\pm$ SD or No. (%)	Test Statistic <sup>a</sup>	P	Mixed-Effects Estimate, <sup>b</sup> b or AOR (95% CI)
Ham-D					-1.97 (-0.85, -3.08)
Baseline	17.7 $\pm$ 5.38	17.9 $\pm$ 4.95	0.27	.787	
12 wk	7.9 $\pm$ 6.33	10.1 $\pm$ 4.55	2.16	.033	
24 wk	6.3 $\pm$ 5.10	9.0 $\pm$ 4.58	3.00	.003	
36 wk	4.3 $\pm$ 3.86	7.8 $\pm$ 5.68	4.02	< .001	
Response					2.40 (1.86, .310)
Baseline	NA	NA	NA	NA	
12 wk	37 (62.7)	25 (36.8)	8.51	.004	
24 wk	35 (64.8)	30 (44.8)	4.83	.028	
36 wk	46 (82.1)	37 (56.9)	8.88	.003	
Remission (Ham-D $\leq$ 7)					2.97 (2.29, 3.87)
Baseline	0	0	NA	NA	
12 wk	29 (50.9)	21 (30.9)	5.17	.023	
24 wk	34 (65.4)	27 (40.3)	7.37	.007	
36 wk	48 (88.9)	35 (53.9)	17.17	< .001	
BDI-II					-4.00 (-1.65, -6.35)
Baseline	29.2 $\pm$ 8.71	32.4 $\pm$ 9.97	2.12	.035	
12 wk	14.4 $\pm$ 10.78	20.0 $\pm$ 10.66	2.91	.004	
24 wk	11.3 $\pm$ 10.28	17.3 $\pm$ 10.98	2.98	.004	
36 wk	8.2 $\pm$ 8.76	15.0 $\pm$ 9.85	3.94	< .001	
Response					2.01 (1.56, 2.59)
Baseline	30 (52.6)	27 (39.7)	2.09	.148	
12 wk	37 (72.6)	32 (50.0)	6.01	.014	
24 wk	43 (78.2)	33 (51.6)	9.08	.003	
Remission (BDI-II $\leq$ 8)					3.12 (2.36, 4.11)
Baseline	0	0	NA	NA	
12 wk	20 (35.1)	12 (17.7)	4.95	.03	
24 wk	26 (51.0)	18 (28.1)	6.28	.01	
36 wk	40 (72.7)	21 (32.8)	18.86	< .001	

Note. AOR = adjusted odds ratio; BDI-II = Beck Depression Inventory-II; CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; NA = not applicable.

<sup>a</sup>For continuous variables, comparisons used *t* tests; for categorical variables,  $\chi^2$  tests.

<sup>b</sup>Derived from generalized linear mixed models relating treatment and time effects either linearly to the dependent variable (for depression scores) or linearly to the logit of the probabilities (for response and remission).

needs<sup>16–18</sup> and for whom novel evidence to inform practice and policy is urgently needed.<sup>41</sup> Persons with substance use disorders may have difficulty adhering to clinical trial protocols and are frequently excluded from antidepressant medication treatment trials conducted in outpatient settings.<sup>42</sup> Homeless and marginally housed persons have high rates of substance use disorders<sup>3–5</sup> and are therefore de facto excluded. Yet we obtained adherence rates

comparable to those achieved in other studies,<sup>43</sup> and our retention rate (85%) over 9 months compared favorably with those observed in both long-term<sup>40</sup> and short-term<sup>44</sup> studies conducted among outpatients with fewer psychosocial comorbidities. Directly observed ART has been shown to improve ART adherence in marginalized populations with multiple psychosocial adherence barriers.<sup>45</sup> Fluoxetine is uniquely suited for directly

observed treatment and can easily be incorporated into substance use treatment or other structured counseling programs.

A second notable feature of our study is that it adds to the scant evidence<sup>40</sup> on the long-term ( $\geq 6$  months' duration) treatment of depressed mood. Most of the data supporting this practice come from randomized withdrawal studies, which generalize poorly and can be problematic to interpret.<sup>46</sup> The 2-arm parallel (classic) randomized controlled trial has been described as more closely approximating real-world effectiveness,<sup>46</sup> but few such trials of antidepressant medications exist. One research team screened 2693 abstracts for a meta-analysis on serotonin-specific reuptake inhibitor treatment of major depression but discovered only 6 long-term, 2-arm parallel randomized controlled studies.<sup>40</sup>

We observed no statistically significant improvement in secondary HIV outcomes among participants randomized to the intervention arm. Lack of statistical power likely contributed to our lack of a statistically significant estimated effect, because we were unable to recruit the planned number of participants. However, other studies have also had mixed findings. Similar to our analysis, a study of collaborative care for depression implemented in 3 Veterans Affairs HIV clinics showed improvements in depression and HIV symptom severity but not ART adherence.<sup>23</sup> A marginal structural model analysis demonstrated an effect of depression treatment on virological outcomes,<sup>22</sup> but the authors explicitly noted that the data did not permit them to determine what additional counseling and social support services may have been delivered along with antidepressant medication treatment. An intervention among HIV-positive persons that combined cognitive behavioral therapy and adherence counseling yielded improvements in both depression and ART adherence but not virological outcomes.<sup>21</sup> In other fields of medicine, randomized trials of depression interventions have also failed to improve clinical outcomes such as glycemic control,<sup>47</sup> suggesting that barriers other than depressed mood are interfering with adherence.<sup>48</sup> Taken together, these studies suggest that improving ART adherence may require more than improvements in mood alone and that adherence counseling<sup>49</sup> and mobilizing other forms of social support may be necessary to improve adherence.

## Limitations

Our study lacked a placebo control group. Even though use of placebos is common in psychopharmacological research,<sup>39,50,51</sup> depression is known to adversely affect HIV outcomes and is treatable with medication.<sup>13–15</sup> Therefore, we considered offering a 9-month placebo to be unethical. Intervention arm participants had intensive clinical contact with study staff, which itself may be therapeutic.<sup>52</sup> However, participants in the referral arm also had significant contact with study staff, which would tend to mitigate this effect. Our positive finding on the primary outcome is all the more notable in light of the documented crossover contamination by referral arm participants who obtained mental health treatment outside the study.

The recruitment phase lasted more than 5 years because of the large screening sample needed to identify eligible participants. Although the refusal rate was low (5.6%), the large proportion of potential participants found to be ineligible may have compromised our ability to generalize the findings to all HIV-positive homeless and marginally housed adults with symptoms of depression. We were unable to formally compare the characteristics of potential participants who were screened for eligibility but declined to participate with those of study participants. However, our study sample was broadly similar to those obtained by systematic sampling.<sup>4,16,28,53</sup>

Notably, up to 12% of potential participants with symptoms of depression who underwent structured diagnostic assessment may have instead met diagnostic criteria for bipolar disorder, a proportion similar to the findings of a previous study.<sup>54</sup> Our results highlight the importance of carefully assessing persons presenting with depressive symptoms, so as to avoid exposing patients with unrecognized bipolarity to antidepressant medications that may be ineffective or destabilizing.<sup>55</sup>

## Conclusions

Our randomized controlled trial demonstrated that directly observed treatment with weekly fluoxetine resulted in improved mood among a cohort of homeless and marginally housed persons living with HIV. The statistically and clinically significant effects on mood

that we observed are especially notable because they occurred in a population with ongoing substance abuse problems, homelessness, and other psychosocial comorbidities. Directly observed weekly fluoxetine may be an effective strategy to treat depression and potentially improve HIV treatment outcomes in individuals who might otherwise be considered poor candidates for treatment because of multiple barriers to treatment adherence. ■

## About the Authors

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## Contributors

A. C. Tsai, D. H. Karasic, G. P. Hammer, E. D. Charlebois, A. R. Moss, J. L. Sorensen, J. W. Dilley, and D. R. Bangsberg conceptualized and designed the study. D. R. Bangsberg acquired data and obtained funding. A. C. Tsai, K. Ragland, and D. R. Bangsberg analyzed and interpreted the data. A. C. Tsai and K. Ragland did statistical analysis. D. H. Karasic, G. P. Hammer, E. D. Charlebois, J. L. Sorensen, J. W. Dilley, and D. R. Bangsberg provided administrative support. A. R. Moss provided supervision. A. C. Tsai drafted the article, and all authors critically revised it.

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## Human Participant Protection

The University of California, San Francisco committee on human research approved all study procedures. Study participants provided informed consent separately for screening and the subsequent randomized controlled trial. Potential participants identified with a BDI-II higher than 13 who declined to participate were offered referral to an outside agency for further evaluation.

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