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Does Effective Depression Treatment Alone Reduce Secondary HIV Transmission Risk? Equivocal Findings from a Randomized Controlled Trial

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Abstract

Depressed mood has been associated with HIV transmission risk behavior. To determine whether effective depression treatment could reduce the frequency of sexual risk behavior, we analyzed secondary outcome data from a 36-week, two-arm, parallel-design, randomized controlled trial, in which homeless and marginally housed, HIV-infected persons with comorbid depressive disorders were randomized to receive either: (a) directly observed treatment with the antidepressant medication fluoxetine, or (b) referral to a local public mental health clinic. Self-reported sexual risk outcomes, which were measured at 3, 6, and 9 months, included: total number of sexual partners, unprotected sexual intercourse, unprotected sexual intercourse with an HIV-uninfected partner or a partner of unknown serostatus, and transactional sex. Estimates from generalized estimating equations regression models did not suggest consistent reductions in sexual risk behaviors resulting from treatment. Mental health interventions may need to combine depression treatment with specific skills training in order to achieve durable impacts on HIV prevention outcomes.

Keywords

HIV; Depression; Antidepressive agents; Sexual behavior; Protected sex; Homeless persons

Introduction

Although the majority of HIV-infected persons eliminate or reduce HIV transmission risk behaviors upon learning about their diagnosis, some continue to engage in unprotected sexual intercourse [1, 2], thus placing their sexual partners at risk for HIV acquisition. Depression and other psychiatric morbidity, common among HIV-infected persons [3, 4], is one modifiable factor that is thought to have a major impact on continued engagement in HIV transmission risk behaviors. Theoretical work has linked risky sexual behavior to depression within both psychodynamic [5] and cognitive-behavioral frameworks [6], as depressed mood may be associated with cognitive distortions, maladaptive coping, and/or loss of risk aversion. Depressed mood has also occupied a central role in several related conceptual models of sexual behavior and HIV prevention [7-10] and has been linked in empirical studies to HIV transmission risk behaviors [11-15].

Despite the importance of depression to understanding HIV risk, few randomized controlled studies have attempted to determine the extent to which effective depression treatment can reduce the frequency of HIV transmission risk behaviors. Sikkema et al. [16] proposed a conceptual model of secondary HIV prevention in which depression treatment leads to two parallel pathways for reducing secondary HIV transmission risk: reduced sexual risk behavior and improved adherence to HIV treatment. Mixed evidence has been found for the adherence pathway [17-20]. With regard to the sexual risk behavior pathway, a recently published meta-analysis by Lennon et al. [21] showed that, among women-focused HIV prevention studies in which data on depression symptom severity were also collected, a greater reduction in sexual risk behavior was observed among studies that demonstrated greater reductions in depression symptom severity.

At a recent meeting on the intersection of HIV and mental health sponsored by the U.S. National Institute of Mental Health, the role of mental health treatment in improving HIV-

related outcomes was highlighted as a priority research area [22]. To date, however, there have been no randomized controlled trials of psychopharmacological depression treatment interventions aimed at reducing HIV transmission risk behaviors. To address this gap in the literature, we analyzed secondary outcome data from a recently published randomized controlled trial to determine the extent to which effective antidepressant medication treatment alone can reduce sexual risk behaviors among homeless and marginally housed, HIV-infected men and women.

Methods

Participants

This study was a two-arm, parallel-design, randomized controlled trial. English-speaking, HIV-infected adults with comorbid depressive disorders were recruited from 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. A subset of participants was recruited from the Research in Access to Care for the Homeless (REACH) cohort, an observational study of homeless and marginally housed HIV-infected adults who were themselves recruited from the same sampling frame [23, 24]. The primary inclusion criteria were: (a) diagnosis of major depressive disorder, minor depressive disorder, or dysthymia consistent with the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), as determined through structured diagnostic assessment [25]; and (b) confirmation of HIV seropositivity (Quest Diagnostics, Inc., Valencia, Calif.). Participants were randomly assigned to one of two treatment arms: (a) fluoxetine, directly observed for 24 weeks and introduced in two phases of gradually increasing independence, followed by 12 weeks of self-administration; or (b) referral to a public mental health clinic that specializes in the care of HIV-infected persons, located 0.5 miles away from the study site along a major public transportation corridor.

The University of California, San Francisco Committee on Human Research approved all study procedures. Study participants provided informed consent separately for the screening procedures and for the subsequent randomized controlled trial. Potential participants identified with a Beck Depression Inventory-II score exceeding 13 who declined to participate were not enrolled and were offered referral to an outside agency for further evaluation. Data for participants in both the treatment and referral arms were collected at the research study site by clinical raters who were blinded to treatment assignment.

Outcome data were obtained through study visits at 3, 6, and 9 months. More detailed aspects of the design, methods, and primary results have been described in detail [20]. In brief, the study provided convincing evidence for the efficacy of this antidepressant medication treatment strategy in reducing depression symptom severity, as measured by the 17-item Hamilton Rating Scale for Depression (Ham-D) [26], and increasing the probability of response and remission. The observed benefit was strong in statistical significance, large in magnitude, and sustained throughout the 9-month follow-up period. Participants were observed (during the directly observed treatment phase) taking more than 90 % of scheduled observed doses of the study medication and, during the self-administered treatment phase, self-reported taking more than 99 % of scheduled self-administered doses. Only three participants in each arm were lost to follow-up. No statistically significant differences in HIV-related outcomes were observed, including uptake of HIV antiretroviral therapy, adherence to HIV antiretroviral therapy, or HIV-1 RNA viral load suppression.

Statistical Analysis

For this secondary analysis, we analyzed the effects of antidepressant medication treatment on sexual risk behaviors. The outcomes of interest, obtained by structured interview every 3 months, included (a) total number of sexual partners in the prior 90 days; (b) any unprotected sexual intercourse in the prior 90 days; (c) unprotected sexual intercourse with an HIV-uninfected partner or a partner of unknown serostatus, in the prior 90 days; and (d) any transactional sexual intercourse in the prior 90 days. The study was not powered to detect differences in these secondary outcomes.

Due to the repeated measures nature of the data, we used the method of generalized estimating equations to characterize the marginal expectation of sexual risk behaviors as a function of treatment assignment and the baseline value of the dependent variable. The latter was included as a covariate given the notable differences (and, for the outcome of any unprotected intercourse, a statistically significant difference) in baseline rates as described below. A Poisson distribution with log link and independent working correlation was assumed. The exponentiated regression coefficient estimates provide a relative risk ratio interpretation for the regression models with binary dependent variables (unprotected sexual intercourse, transactional sexual intercourse) [27, 28] and an incidence rate ratio interpretation for the regression model with a count dependent variable (number of partners). We assumed missingness completely at random.

We also explored adjusting for time on treatment using a series of dummy variables for each 3-month period (with the baseline month as the reference category), but across all regression models, Wald-type Chi-squared tests suggested that the time dummy variables were jointly not statistically significant. To investigate potential effect modifiers, we fit four regression models for each outcome with interaction terms by sex, sexual orientation, depression diagnosis, and baseline depression symptom severity. We selected these four variables as potential effect modifiers based on previously published studies showing that the efficacy of antide-pressant medication treatment on depression symptom severity may vary by sex [29, 30] or baseline severity of illness [31-33]. While there are no reasons to expect differential efficacy of antidepressant medication treatment by sexual orientation, its effectiveness may vary by sexual orientation when delivered in real-world settings [34]. Furthermore, prior work has documented greater rates of mental health problems among sexual minorities related to stigma-based differentials in status and power [35, 36]. All analyses were conducted using the Stata software package (version 12.0, StataCorp L.P., College Station, Tex.).

Results

One hundred and thirty-seven participants were randomly assigned to the treatment arm (N = 66) or to the referral arm (N = 71). Baseline summary statistics are provided in Table 1. No statistically significant differences were observed in the baseline comparisons of socio-demographic or clinical variables. The median Ham-D score at baseline was 17 (interquartile range, 15–20), suggesting a moderate level of depression symptom severity. In the 90 days prior to baseline, 83 (61 %) participants reported having had no sexual partners, 35 (26 %) reported having one sexual partner, and 19 (14 %) reported having two or more sexual partners; 27 (20 %) participants reported having had any unprotected sexual intercourse; ten (7 %) participants reported having had unprotected sexual intercourse with an HIV-uninfected partner or a partner of unknown serostatus; and four participants (3 %) reported having had transactional sexual intercourse.

There were notable baseline differences in the sexual risk outcomes (Table 2). At baseline, participants randomized to the referral arm had a sexual risk behavior profile that was riskier

than participants randomized to the treatment arm, and the difference in the baseline rates of unprotected intercourse was statistically significant ($\chi^2 = 4.5$; $P = 0.04$). Over time, the number of sexual partners declined in both arms. The number of participants engaging in any unprotected intercourse actually increased slightly in the treatment arm but decreased in the referral arm.

In our generalized estimating equations analyses, anti-depressant medication depression treatment did not have a statistically significant effect on any of the four sexual risk outcome variables. The incidence rate and relative risk ratios ranged from 0.62 to 0.82 (Table 3). No trends by time on treatment were observed. For each outcome, we explored four potential effect modifiers, fitting a total of 16 regression models. We observed statistically significant effects of antidepressant medication depression treatment in two subgroup analyses: (1) reducing any unprotected sexual intercourse among women (relative risk ratio, 0.15; 95 % confidence interval CI 0.05–0.51; *P* value for interaction term = 0.002), and (2) reducing the number of partners among persons with a greater baseline symptom severity (incidence rate ratio, 0.36; 95 % CI 0.16–0.83; *P* value for interaction term = 0.06). Otherwise, antide-pressant medication depression treatment did not have a statistically significant impact on other measures of HIV transmission risk for the other subgroups.

Discussion

In this secondary analysis of data from a randomized controlled trial, we found that effective antidepressant medication treatment did not reduce sexual risk behaviors among homeless and marginally housed, HIV-infected men and women with comorbid depressive disorders. We also did not estimate statistically significant effects of treatment among four different subgroups. Taken together, these findings do not provide consistent, strong evidence in support of a conceptual model of depression treatment as a sole intervention to prevent secondary HIV transmission [16]. However, there are four competing explanations for our findings: (a) the association between depression and sexual risk behavior observed in prior studies is not causal; (b) the association observed in prior studies is causal, but our randomized trial was unable to detect the specific conditions under which effective antidepressant medication treatment could result in reduced sexual risk behaviors; (c) the association observed in prior studies is causal, but our randomized trial lacked statistical power to demonstrate that effective antidepressant medication treatment would result in reduced sexual risk behaviors; and (d) effective antidepressant medication treatment alone cannot reduce sexual risk behaviors. Adjudicating between these four hypotheses has important conceptual and programmatic implications for treating depression to advance HIV prevention, so we discuss each in turn below.

Our findings are consistent with previously published reviews showing the absence of an association between depression and sexual risk behaviors [37, 38]. Prior studies describing this association have been based solely on observational data, so our estimates (which are substantially less likely to be contaminated by unobserved confounding) may suggest that depression does not have a causal influence on sexual risk behavior. The effect of antidepressant medication treatment on the primary outcome of depression symptom severity was statistically significant, large in magnitude, and sustained throughout the 9-month follow-up period [20]. Therefore, failure to reduce depression symptom severity cannot explain the lack of statistically significant changes in sexual risk behaviors obtained in our study.

A second potential explanation for our findings is related to one of the currently prevailing theories about depression and HIV risk, which holds that the relationship between depression symptom severity and sexual risk behaviors is non-linear: that is, persons with

severely depressed mood may be less likely to engage in sexual risk behaviors due to the preponderance of debilitating neurovegetative symptoms, while persons with moderately depressed mood may be more likely to engage in such behaviors due to greater activation (and assuming that treatment-associated improvement in neurovegetative symptoms precedes treatment-associated changes in cognitions, coping, or risk aversion) [37, 39]. If this were true, then a depression treatment intervention of moderate efficacy might lead to a reduction in sexual risk behavior among persons with moderate depression at baseline while also leading to a paradoxical increase in sexual risk behavior among persons with severe depression at baseline. In this secondary analysis, we attempted to examine this hypothesis by fitting regression models stratified by baseline depression symptom severity. Consistent with prior work [21], we found that the estimated effects of randomization to antidepressant medication treatment on sexual risk behavior were generally larger in magnitude among persons who were more severely depressed at baseline. The interaction terms, however, were not statistically significant. Nonetheless we recognize that these estimates could be potentially interpreted as evidence that the conceptual model of secondary HIV prevention [16] could have greater explanatory power among persons with greater depression symptom severity at baseline.

Third, lack of statistical power could explain our findings, as the study was neither powered nor designed to detect an effect of antidepressant medication treatment on sexual risk behaviors. The estimated confidence intervals could not exclude potentially sizeable effects. For example, in the analysis of antidepressant medication treatment to reduce unprotected sexual intercourse with an HIV-unin-fected partner or a partner of unknown serostatus, the largest estimated relative risk ratio consistent with the 95 % confidence interval was 0.41. The ongoing Strategies to Link Antidepressant and Antiretroviral Management Study (clinicaltrials.gov identifier #NCT01372605) is also not set up or powered to detect differences in sexual risk behaviors [40], but with its larger target sample size ($N = 390$) it may be able to exclude smaller, but potentially still clinically relevant, treatment effects.

The fourth potential explanation for our findings is that effective antidepressant medication treatment alone may not be sufficient to induce changes in sexual risk behavior. This hypothesis was identified as an important, unresolved issue for the field by Sikkema et al. [16]: “An important conceptual issue is whether mental health interventions must be tailored specifically to HIV-related issues…or whether more standard mental health treatment (e.g., antidepressant medication, interpersonal therapy for depression) can produce transmission risk behavior change” (p.258). The fact that we did not observe statistically significant changes in sexual risk behaviors despite effective antidepressant medication treatment suggests that multi-component interventions that incorporate HIV prevention skills training in addition to effective depression treatment may be needed to produce durable changes in behavior. Similar conclusions have been derived from other studies of depression treatment and its lack of impact on HIV treatment adherence among HIV-infected persons [20] or on glycosylated hemoglobin levels among persons with diabetes [41]. Also consistent with this hypothesis is a cross-sectional structural equation modeling analysis showing that an empirically validated social-cognitive model of sexual risk behavior had substantially reduced explanatory power among study participants with probable depression [10]. Taken together, these findings suggest that, while effective antidepressant medication treatment alone may not reduce sexual risk behaviors, it may enhance the utility of interventions based on models of health behavior aimed at reducing sexual risk.

We believe several limitations, in addition to those described above, are important to keep in mind when interpreting our findings. The primary publication from this randomized controlled trial highlighted two important limitations (lack of a placebo control group and the extensive screening efforts required to achieve the sample size) and two important

strengths (recruitment of a vulnerable population with numerous psychosocial comorbidities and the extended duration of follow-up) [20]. To these we would add two additional limitations: (a) Among homeless and marginally housed HIV-infected adults living in San Francisco, food insecurity [42, 43] and unmet subsistence needs [44, 45] are highly prevalent. Under such highly insecure conditions of daily living, the need to attend to basic subsistence needs may substantially reduce the explanatory power of the conceptual model of secondary HIV prevention elaborated by Sikkema et al. [16]. Potentially consistent with this hypothesis are the low overall rates of sexual risk behavior observed in this study despite the selection of participants with depressive disorders. In previous studies of HIV-infected men and women aware of their seropositivity but unselected for depressive disorders, rates of unprotected intercourse have ranged from 25 to 40 %, while rates of unprotected intercourse with an HIV-uninfected partner or partner of unknown serostatus have ranged from 16 to 28 % [1]. (b) The sexual risk behavior outcomes were entirely based on self-report. Given the experimental design, we do not anticipate any scenarios in which differential reporting could have biased the findings away from the null. However, random measurement error in the dependent variable, such as which could result from random recall errors, in general would be expected to bias estimates towards the null.

In summary, we analyzed secondary outcome data from a randomized controlled trial conducted among homeless and marginally housed, HIV-infected men and women to address a question of substantive research interest: can effective antidepressant medication treatment alone help to prevent the secondary transmission of HIV? Our findings suggest that the answer to this question is “no”, with the important caveat that the trial was not powered to detect an effect on sexual risk behavior outcomes. Future intervention studies may need to combine depression treatment with HIV prevention skills training in order to achieve durable reductions in sexual risk behaviors.

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Table 1

Baseline characteristics of the sample

	N (%) or median (interquartile range)	
	Treatment (*N* = 66)	**Referral (*N* = 71)**
Age (years)	44 (37–53)	42 (37–49)
Women	6 (9 %)	8 (11 %)
Caucasian	32 (48 %)	36 (51 %)
Ever homeless	45 (68 %)	45 (63 %)
DSM-IV diagnosis		
Major depressive disorder	50 (76 %)	51 (72 %)
Minor depressive disorder	5 (8 %)	7 (10 %)
Dysthymia	11 (17 %)	13 (18 %)
Sexual orientation		
Gay/lesbian	37 (56 %)	47 (66 %)
Bisexual	8 (12 %)	5 (7 %)
Straight	18 (27 %)	17 (24 %)
Any illicit drug use, past 90 days	17 (26 %)	21 (30 %)
Any alcohol use, past 90 days	31 (47 %)	38 (54 %)
CD4+ T cell count nadir (cells/mm^3)	330 (182–518)	340 (220–494)
Hamilton Rating Scale for Depression	17 (13–20)	17 (15–21)

Table 2

Changes in sexual risk behaviors over time, by treatment assignment

	Baseline	3 months	6 months	9 months
Number of partners				
Mean (SD)				
Treatment	0.55 (0.14)	0.53 (0.11)	0.64 (0.25)	0.44 (0.12)
Referral	1.32 (0.41)	1.46 (0.44)	1.54 (0.44)	0.80 (0.1)
Median (interquartile range)				
Treatment	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–1)
Referral	0 (0–1)	0.5 (0–1)	0 (0–1)	0 (0–1)
Any unprotected intercourse, *N*(%)				
Treatment	7 (11 %)	10 (15 %)	8 (12 %)	11 (17 %)
Referral	19 (27 %)	18 (25 %)	21 (30 %)	15 (21 %)
Unprotected intercourse with HIV-uninfected partner or partner of unknown serostatus, *N*(%)				
Treatment	3 (5 %)	7 (11 %)	6 (9 %)	5 (8 %)
Referral	7 (10 %)	11 (15 %)	13 (18 %)	8 (11 %)
Any transactional intercourse, *N*(%)				
Treatment	1 (2 %)	2 (3 %)	3 (5 %)	0 (0 %)
Referral	3 (4 %)	3 (4 %)	3 (4 %)	4 (6 %)

Table 3

Effect of antidepressant medication treatment on sexual risk behaviors

	Number of partners	Any unprotected intercourse	Unprotected intercourse with HIV-uninfected partner or partner of unknown serostatus	Any transactional intercourse
	IRR (95 % CI)	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)
Randomized to antidepressant medication treatment arm	0.62 (0.38–1.02)	0.82 (0.75–1.19)	0.72 (0.41–1.28)	0.75 (0.31–1.80)
Stratified by sex				
Men	0.64 (0.38–1.08)	0.94 (0.65–1.37)	0.84 (0.46–1.54)	0.75 (0.30–1.86)
Women	0.26 (0.04–1.69)	**0.15 (0.05–0.51)**	*a*	*a*
z-test for interaction (*P* value)	1.27 (0.21)	3.15 (0.002)		
Stratified by sexual orientation				
Gay, lesbian, or bisexual	0.59 (0.35–1.01)	0.82 (0.55–1.20)	0.64 (0.35–1.16)	1.61 (0.28–0.27)
Straight	0.65 (0.29–1.43)	0.33 (0.03–3.64)	0.48 (0.05–5.02)	0.63 (0.12–3.46)
z-test for interaction (*P* value)	0.88 (0.38)	0.41 (0.68)	1.06 (0.29)	0.89 (0.37)
Stratified by diagnosis				
Major depression	0.58 (0.32–1.04)	0.84 (0.55–1.28)	0.74 (0.36–1.52)	0.62 (0.25–1.57)
Minor depression or dysthymia	0.65 (0.36–1.19)	0.80 (0.40–1.61)	0.65 (0.28–1.50)	1.19 (0.08–18.2)
z-test for interaction (*P* value)	0.34 (0.73)	0.14 (0.89)	0.34 (0.73)	0.72 (0.47)
Stratified by baseline symptom severity				
Ham-D ≥17	**0.36 (0.16–0.83)**	0.61 (0.35–1.07)	0.25 (0.04–1.40)	*a*
Ham-D <17	0.68 (0.41–1.15)	0.86 (0.56–1.32)	0.81 (0.45–1.45)	0.99 (0.41–2.45)
z-test for interaction (*P* value)	1.91 (0.06)	1.38 (0.17)	1.62 (0.11)	

Bold values indicate statistical significance with $P < 0.05$

[a]Could not fit regression model due to small cell sizes