The effect of antidepressant treatment on HIV and depression outcomes: the SLAM DUNC randomized trial

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Background: Depression is a major barrier to HIV treatment outcomes.

Objective: To test whether antidepressant management decision support integrated into HIV care improves antiretroviral adherence and depression morbidity.

Design: Pseudo-cluster randomized trial.

Setting: Four US infectious diseases clinics.

Participants: HIV-infected adults with major depressive disorder.

Intervention: Measurement-based care (MBC) – depression care managers used systematic metrics to give HIV primary-care clinicians standardized antidepressant treatment recommendations.

Measurements: Primary – antiretroviral medication adherence (monthly unannounced telephone-based pill counts for 12 months). Primary time-point – 6 months. Secondary – depressive severity, depression remission, depression-free days, measured quarterly for 12 months.

Results: From 2010 to 2013, 149 participants were randomized to intervention and 155 to usual care. Participants were mostly men, Black, non-Hispanic, unemployed, and virally suppressed with high baseline self-reported antiretroviral adherence and depressive severity. Over follow-up, no differences between arms in antiretroviral adherence or other HIV outcomes were apparent. At 6 months, depressive severity was lower among intervention participants than usual care [mean difference −3.7, 95% confidence interval (CI) −5.6, −1.7], probability of depression remission was higher [risk difference 13%, 95% CI 1%, 25%),and suicidal ideation was lower (risk difference −18%, 95% CI −30%, −6%). By 12 months, the arms had comparable mental health outcomes. Intervention arm participants experienced an average of 29 (95% CI: 1–57) more depression-free days over 12 months.

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Conclusion: In the largest trial of its kind among HIV-infected adults, MBC did not improve HIV outcomes, possibly because of high baseline adherence, but achieved clinically significant depression improvements and increased depression-free days. MBC may be an effective, resource-efficient approach to reducing depression morbidity among HIV patients.

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Introduction

Depression is a major barrier to HIV care. Depressive disorders affect an estimated 20–30% of people living with HIV [1–3] and are strongly associated with reduced antiretroviral medication adherence, virologic failure, and higher mortality rates [4–12].

Depressive disorders are cyclical, with approximately half of the depressive episodes resolving within 12 months without treatment [13]. However, evidence-based treatments such as antidepressants and psychotherapy are critical in speeding the time to recovery and reducing depression morbidity [14]. Although such treatments have demonstrated efficacy for HIV-infected patients [15,16], this population still faces a large mental health treatment gap. Estimates suggest that among HIV-infected patients with depression, only one in five are receiving depression treatment and even fewer are receiving effective (rather than sub-therapeutic) treatment [17–19]. Evidence is needed on the impact of pragmatic, efficient, evidence-based mental health service delivery strategies integrated within HIV primary care.

Despite the associations of depression with adverse HIV outcomes, the impact of effective depression treatment on these outcomes is unclear. Several observational studies as well as trials of counseling interventions have reported a positive association between receipt of depression treatment and antiretroviral adherence [20–23], while two recent randomized trials of medication-based depression treatment found no effect on antiretroviral adherence or other HIV outcomes [24,25]. We report the results of a randomized trial to test the effect of measurement-based care (MBC) – a decision support model for antidepressant management integrated into HIV care, on HIV and mental health outcomes among HIV-infected adults with depression.

Methods

Study design and objective

The Strategies to Link Antidepressant and Antiretroviral Management at Duke University, University of Alabama at Birmingham, Northern Outreach Clinic (Henderson, North Carolina), and University of North Carolina (SLAM DUNC) Study was a single-blind randomized controlled trial (RCT) with the objective of testing whether evidence-based decision support for antidepressant management, integrated into HIV care, would improve antiretroviral adherence and clinical outcomes (ClinicalTrials.gov NCT01372605) [26]. English-speaking adults aged 18–65 years, receiving HIV care, were eligible if they were taking or about to start antiretroviral drugs, scored at least 10 on the Patient Health Questionnaire-9 (PHQ-9) depression screening instrument [27,28], and had a major depressive disorder diagnosis confirmed using the Mini International Neuropsychiatric Interview (MINI) [29]. Patients were excluded who met MINI criteria for bipolar or psychotic disorder history, had failed at least two antidepressant trials of at least 6 weeks at a moderate/high dose during the current depressive episode, were mentally incompetent, or required immediate psychiatric hospitalization. Patients already taking antidepressants were eligible if they met other criteria, since, despite being on treatment, they were currently depressed and therefore could plausibly benefit from the active regimen adjustments conferred by the intervention.

Conditions

Participants were randomized to MBC ('intervention') or enhanced treatment as usual ('usual care'). In MBC, depression care managers (DCMs) collaborate with medical providers to optimize antidepressant treatment following an evidence-based algorithm [30,31]. MBC emphasizes vigorous antidepressant dosing combined with careful monitoring of depressive symptoms and medication tolerability using standardized measures. Assessments occur at standardized time-points to ensure timely assessment of treatment response and subsequent treatment adjustment if indicated.

Depression care managers in this study were six licensed clinical social workers, one clinical psychologist, and one PhD public health researcher. In prior work, the DCM role had been filled effectively by medical assistants and generalist nurses. DCMs completed a 2-day initial training focused on diagnosis of depression and excluding

diagnoses, response to suicidality, antidepressant dosing and side effects, use of standardized MBC tools to assess treatment response and tolerability, and use of the MBC algorithm to generate treatment recommendations for HIV providers. Ongoing training, quality assurance, and continuous quality improvement occurred through weekly group supervision with psychiatric supervisors. Supervisors reviewed all DCM patient contacts using a web-based participant registry, focusing on review of safety (suicidality) assessments, congruence of treatment recommendations with the algorithm and reasons for divergence, pros and cons of specific antidepressants in specific situations, and troubleshooting issues such as provider ambivalence about treatment adjustments.

In the intervention arm, DCMs met with participants to measure depressive severity (PHQ-9 [27]) and side-effect burden (Frequency, Intensity, and Burden of Side Effects Rating Scale [32]) at weeks 4, 8, and 12, and, guided by the MBC algorithm, provided treatment recommendations to the HIV medical provider (e.g. maintain dose; increase dose; change antidepressant) [30]. Typically, if depression remission had not been achieved and the medication was being tolerated, a dose increase was recommended. If side effects were bothersome, possible strategies included dose timing adjustment, dose decrease, or medication switch. Side effects were also assessed at interim 2, 6, and 10-week contacts. Participants who entered the study already on an antidepressant (but still meeting the eligibility criterion of current major depressive disorder) were handled similarly, with an initial recommendation to either increase dose or switch medication based on duration, dose, and tolerability of current medication. At 12 weeks, participants who had achieved remission entered a maintenance phase (3-monthly assessments to confirm continued response; if a relapse occurred, a new acute phase cycle was initiated). For nonremitting participants, recommendations were made for antidepressant switch/augmentation or an optional 4-week extension of the current regimen. All final treatment decisions were the purview of the treating HIV provider. Intervention participants also received three motivational interviewing sessions focused on barriers to antiretroviral adherence at 7, 8, and 10 months, adapted from the PACT intervention [33]. While completion of the PHQ-9 and discussion of depressive symptoms and side effects during the DCM assessment sometimes led to a broader discussion of the participants' wellbeing, DCMs did not provide any structured cognitive–behavioral or other psychotherapeutic depression treatment during study contacts.

Usual care was enhanced with initial training of all HIV providers in MBC principles, provision of diagnosis information at enrollment, and availability of the MBC algorithm for providers to consult on their own. HIV medical providers could prescribe antidepressants or refer to mental health services, but received no DCM decision support.

Randomization

Pseudo-cluster randomization [34,35] was employed to balance competing concerns of contamination and referral bias [36]. Providers were randomly assigned at baseline to an imbalanced case mix of either 80% intervention/20% usual care, or 20% intervention/80% usual care patients. Using a random number generator, providers were randomized 1 : 1 in blocks of 4 stratified by site and depression treatment experience level. Depression treatment experience was assessed at baseline via a semi-structured interview asking about providers' approaches to antidepressant prescription, monitoring of response, and treatment adjustment [37]. Responses were compared to evidence-based guidelines and scored in standardized fashion. For randomization, depression treatment experience was classified as high, medium, or low based on tertiles of the resulting total scores.

Each provider was then assigned patient slots in blocks of 10 (8 intervention/2 usual care or 2 intervention/8 usual care, randomly ordered). Provider allocation and patient slot order were masked to everyone except the study statistician (B.W.P.). The statistician maintained a document showing each provider's next three open slots, with access granted to five coordinating center staff with no involvement in enrollment. For each new participant, enrollment staff called the coordinating center, identified the participant's provider, and were given the arm assignment for that provider's next slot. Regular checks ensured that arm assignments were given in the correct order.

Blinding

Blinded research assessors collected all research outcomes. Participants, DCMs, medical providers, and investigators were unblinded.

Data collection

The primary outcome was antiretroviral adherence, measured monthly for 12 months by unannounced telephone-based pill count. Unannounced telephone-based pill counts have been shown to provide valid, accurate measures of adherence [38] and are more sensitive than self-report to changes over time [39]. Adherence was calculated as (observed pills taken/expected pills taken). 'Observed pills taken' was defined as the pills at the previous count minus the pills at the current count, corrected for pills gained (e.g. new bottles) or lost (e.g. given away) in the interim. 'Expected pills taken' was defined as the prescribed number of daily pills times the number of days between counts. Extensive probes about pills gained or lost were used to maximize accuracy.

Secondary outcomes included depressive severity [Hamilton Rating Scale for Depression (HRSD)] [40–42],

depression remission (HRSD <8), self-reported antiretroviral adherence (30-day visual analog scale) [43], and HIV-related symptoms (recent headaches, fever, pain in gums, white patches in mouth, rashes, nausea, trouble with eyes, sinus pain, numbness in hands or feet, cough, diarrhea, or weight loss) [1], measured at 3, 6, 9, and 12 months; virologic suppression (viral load <50 copies/ml) and physical and mental health-related quality of life (SF-12) [44,45], measured at 6 and 12 months; and depression-free days [46,47] and HIV medical appointment adherence (proportion of kept visits), measured cumulatively over the 12-month follow-up period. An annualized measure of depression-free days (DFDs) was calculated by first assigning a value of 1 (depression-free) to HRSD values less than 8, and a value of 0 (severely depressed) to HRSD values greater than 21 at each of the 0, 3, 6, 9, and 12-month assessments [46,47]. HRSD scores 8–21 were assigned a proportionately weighted value. To annualize DFDs, for each 3-month interval, the DFD values on each side were averaged and multiplied by the interval duration, and then the values for all intervals were summed.

Data quality assurance

Each pill count was reviewed by the original and a second data collector. Pill counts were ruled invalid if insufficient information was available to link to the previous count (e.g. >1 month had elapsed and the number of bottles dispensed was unknown) or if the data collector noted substantially conflicting or suspicious information (e.g. hostile behavior; open bottles that were not newly dispensed, but had not been presented in previous counts). If the two reviewers disagreed on validity, all data collectors and the PI jointly reviewed the pill count (blinded to arm) and came to consensus.

Sample size

The target sample of 390 (195/arm) was calculated to have 80% power to detect a 10 percentage point improvement in antiretroviral adherence at 6 months. Power calculations assumed pooled SD equal to 25–29% [22], two-tailed α equal to 0.05, design effect equal to 1.04, 5–10% contamination, and 6-month retention of 80%. The design effect assumed a mean of nine patients per provider, intraclass correlation coefficient ρ equal to 0.02 [48–51], and an 80%/20% within-provider intervention allocation ratio in the pseudo-cluster design [35].

Statistical analysis

The primary time-point was defined as 6 months; data collection continued through 12 months to assess longer-term outcomes. The primary intention-to-treat analysis addressed the pseudo-cluster randomization design with clustering by provider and fixed effects for site and provider depression treatment experience level. To address missing data, the Statistical Analysis Plan, approved by the Data Safety and Monitoring Board, adopted a direct modeling approach [52]. Correlates of missingness and earlier (months 1–5) pill count measures were modeled as additional outcome variables along with the primary outcome using a multivariate normal distribution. If the included correlates of missingness capture the important differences between those with and without outcome data, this approach yields an effect estimate corrected for selection bias from the missing data. This approach was implemented using linear mixed models with PROC MIXED (SAS 9.3, Cary, North Carolina, USA), specifying random intercepts for providers and for patients within providers. For secondary binary outcomes, risk differences were estimated using generalized linear models (identity link, binomial error distribution). Since the linear mixed-model approach was inappropriate for binary outcomes, correction for missing data was implemented using inverse probability of observation weighting, with correlates of missingness serving as explanatory variables in the weight estimation model (see e-Appendix, http://links.lww.com/QAD/A744).

Ethical review

Each site's Institutional Review Board approved all study activities. Equipoise was reasonably present with respect to the study's primary endpoint, and providers were free to prescribe antidepressants to usual care participants or refer them to other mental health services.

Results

Enrollment occurred from April 2010 to October 2013, and follow-up continued through April 2014. As recruitment was slower than expected, the trial ended due to funding constraints before achieving full enrollment. A total of 304 participants were randomized to intervention ($n=149$) or usual care ($n=155$) (Fig. 1). Seventy-seven percentage of participants had at least one valid antiretroviral adherence measure (78% intervention/76% usual care); 60% had a valid primary (6-month) outcome measure (58% intervention/61% usual care).

Participants

The majority of participants were aged 30–55 years, men, black non-Hispanic, and unemployed (Table 1). Participants had high depressive severity and prevalence of psychiatric comorbidities. Participants had strong HIV clinical indicators and high self-reported antiretroviral adherence. There were small differences between arms in certain demographic characteristics, but the arms were well balanced on baseline physical and mental health measures.

Treatment

Intervention participants had a mean of 8.9 DCM contacts (Table 2). At study enrollment, 44% of

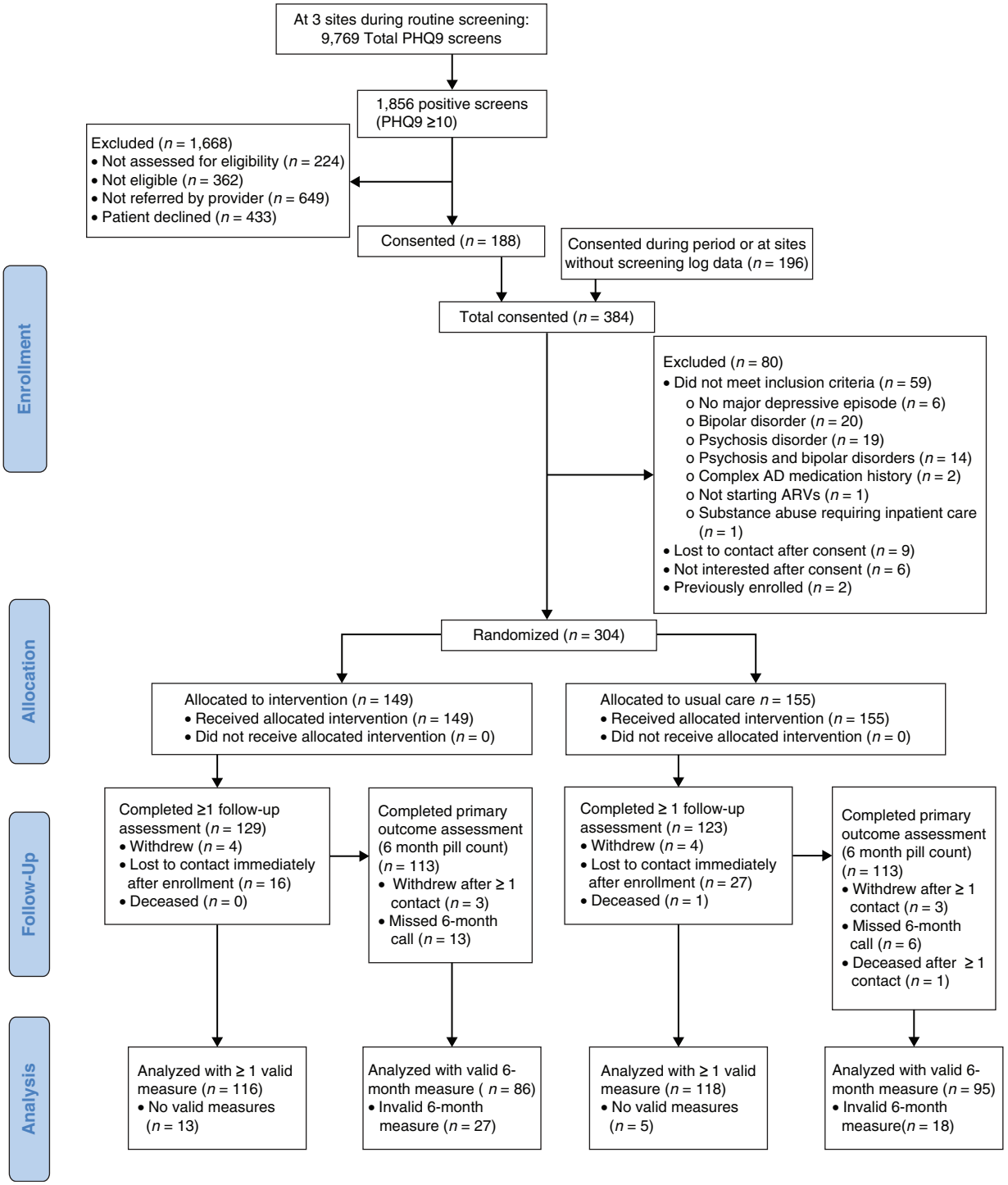

Fig. 1. Trial flowchart. Total PHQ-9 screens and positive screens include multiple screens per patient. Participants were defined as receiving the allocated intervention if their provider received at least one antidepressant treatment recommendation from the depression care manager (intervention arm) or received no antidepressant treatment recommendations from the depression care manager (usual care arm). PHQ-9, Patient Health Questionnaire-9.

intervention and 40% of usual care participants were already on an antidepressant; 17% of intervention and 21% of usual care participants were on a moderate/high antidepressant dose (as defined previously based on standard dosing guidelines; [30,53]). Antidepressant prescription and moderate/high dosing increased in both arms during the study, but more rapidly and substantially in the intervention arm. External mental health referrals and nonstudy treatment sessions were similar between arms.

Table 1. Comparison of baseline participant characteristics by study arm assignment.

	Intervention ($n = 149$)		Usual care ($n = 155$)	
	% (n)	Mean (SD)	% (n)	Mean (SD)
Sociodemographics				
Age (years)		42.8 (10.3)		44.9 (9.9)
Present sex				
Male	75% (112)		64% (100)	
Female	24% (35)		34% (52)	
Transgender and other	1% (2)		2% (3)	
Sexual orientation				
Heterosexual	40% (58)		53% (81)	
Gay/Lesbian	46% (67)		34% (51)	
Bisexual	11% (17)		10% (16)	
Other	3% (4)		3% (4)	
Race/ethnicity				
White non-Hispanic	36% (54)		25% (39)	
Black non-Hispanic	56% (83)		68% (105)	
Hispanic	6% (9)		3% (4)	
Other	2% (3)		4% (7)	
Employment status				
Employed full time	15% (22)		14% (22)	
Employed part time	12% (17)		13% (20)	
Unemployed	73% (108)		73% (111)	
Mental health indicators				
Depressive severity (HAM-D)		20.3 (6.9)		19.9 (6.9)
Suicidality	23% (32)		20% (26)	
Comorbid anxiety disorder	59% (88)		64% (99)	
Comorbid substance use disorder	32% (47)		25% (38)	
SF-12 mental functioning score		30.5 (9.4)		30.3 (10.4)
HIV-related indicators				
$CD4^+$ cell count (cells/μl)		607 (371)		569 (354)
HIV-RNA viral load <50 copies/ml	69% (91)		68% (98)	
Self-reported antiretroviral adherence (%)		85.8 (23.3)		87.2 (22.2)
Number of HIV symptoms		5.2 (2.9)		5.1 (3.1)
SF-12 physical functioning score		44.1 (11.8)		43.8 (12.1)

Table 2. Indicators of mental health treatment by study arm assignment.

	Intervention ($n = 149$)		Usual care ($n = 155$)	
	Range	Mean (SD) or % (n)	Range	Mean (SD) or % (n)
DCM contacts, 12 months	1–21	8.9 (4.4)	n/a	n/a
Duration, weeks 4, 8, 12 (min)	5–165	36 (20)	n/a	n/a
Duration, weeks 2, 6, 10 (min)	3–90	23 (17)	n/a	n/a
On antidepressant				
Baseline		44% (66)		39% (60)
6 months		79% (112)		53% (78)
12 months		79% (98)		53% (71)
On moderate to high[a] antidepressant dose				
Baseline		17% (25)		20% (31)
6 months		39% (55)		28% (42)
12 months		37% (46)		33% (44)
Nonstudy mental health counseling sessions, 12 months[b]	0–294	6.9 (29.8)	0–66	4.6 (11.1)
Referred for mental health treatment[c]		20% (30)		18% (28)
Baseline antidepressant				
Citalopram		12% (18)		12% (19)
Sertraline		5% (7)		4% (6)
Mirtazapine		5% (7)		3% (5)
Bupropion		5% (7)		3% (4)
Fluoxetine		3% (4)		3% (4)
Venlafaxine		3% (4)		2% (3)
Other[d]		11% (16)		4% (6)
Multiple		2% (3)		9% (14)

[a]As defined previously, on the basis of standard dosing guidelines [30,53]; for example, at least 40 mg citalopram or at least 100 mg sertraline daily.
[b]One intervention arm participant started daily outpatient mental health and substance use treatment after study enrollment. Excluding this outlying participant, mean (SD) number of mental health counseling sessions in the intervention arm was 4.5 (13.9).
[c]Any referral for nonstudy-related mental health treatment within or outside the ID clinic.
[d]In both arms combined, sic or fewer participants taking amitriptyline, duloxetine, escitalopram, or paroxetine.

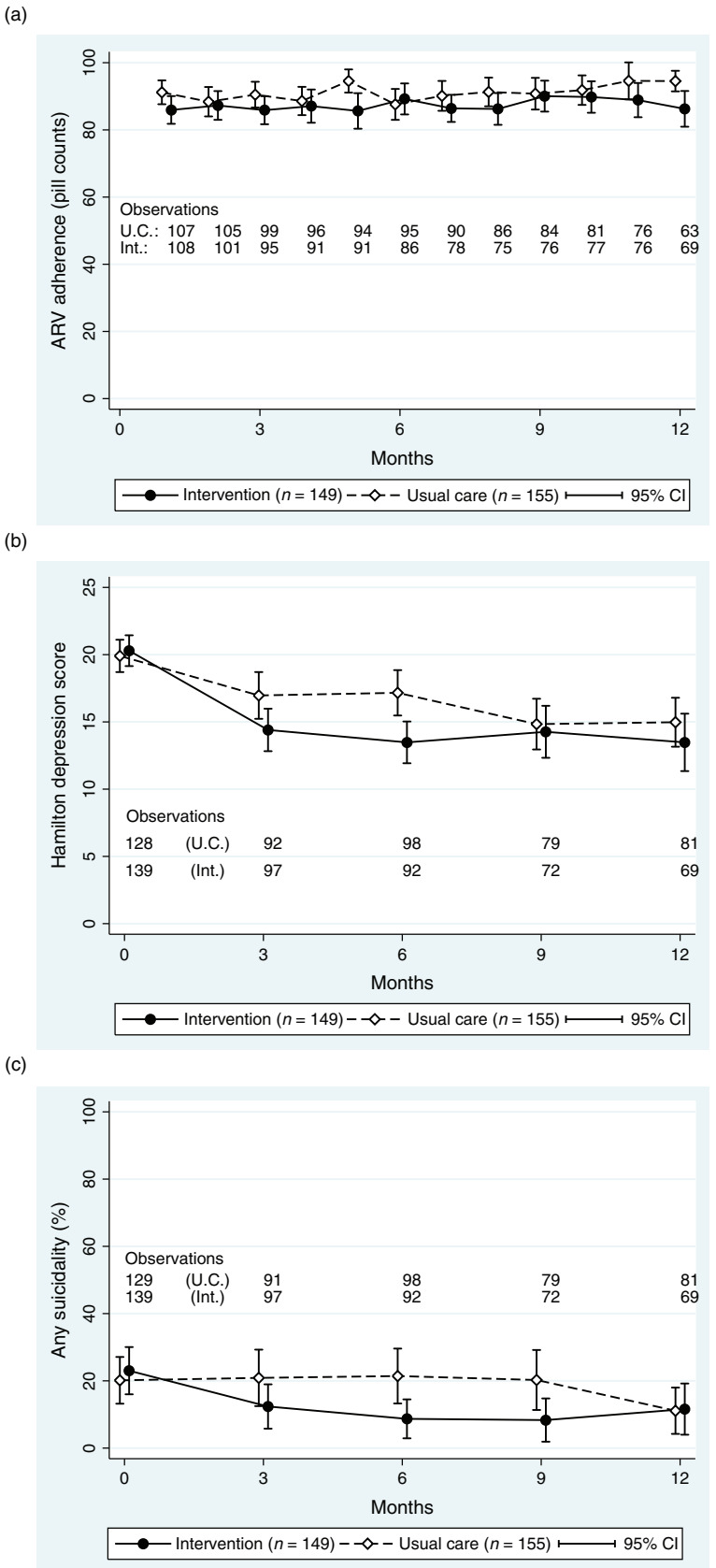

Fig. 2. HIV medication adherence (a), depressive severity (b), and suicidality (c) over time by study arm (uncorrected for design or missing data).

Table 3. Crude and corrected differences in HIV-related and mental health outcomes and healthcare utilization between arms at 6 months (primary time-point).

	Intervention		Usual care		Adjusted for design[a]			Adjusted for design[a] and missing data[b]		
Outcome	*n*	Mean/%	*n*	Mean/%	Difference	95% CI	*P* value	Difference	95% CI	*P* value
HIV-related outcomes										
Percentage adherence, pill count	86	89.2	95	87.6	1.2	(−4.0, 6.5)	0.64	1.4	(−3.9, 6.7)	0.61
Percentage adherence, self-report	92	92.7	98	93.9	−0.8	(−4.6, 3.1)	0.69	−1.3	(−5.8, 3.3)	0.59
Number of HIV symptoms (range 0–12)	92	4.5	98	4.7	−0.3	(−1.0, 0.5)	0.51	−0.2	(−0.9, 0.4)	0.48
Viral load, log-10	79	1.6	98	1.9	−.2	(−0.5, 0.0)	0.06	−0.2	(−0.6, 0.2)	0.28
Viral load <50 copies/ml (%)	79	86.1	98	76.5	9.8	(−0.9, 20.5)	0.07	9.8	(−0.9, 20.5)	0.07
Percentage HIV appointment adherence[c]	146	81.3	151	80.1	0.8	(−4.6, 6.2)	0.77	1.2	(−2.8, 5.3)	0.56
Physical health-related quality of life (range 0–100)	92	42.8	98	43.7	−1.1	(−4.4, 2.3)	0.52	−1.0	(−5.0, 3.0)	0.64
Mental health-related outcomes										
Depressive severity (range 0–50)	92	13.5	98	17.2	−3.6	(−5.9, −1.2)	0.00	−3.7	(−5.6, −1.7)	0.00
Depression remission (%)	92	20.7	98	17.3	0.3	(−12.1, 12.7)	0.97	12.8	(1.2, 24.3)	0.03
Any active suicidality (%)	92	8.7	98	21.4	−12.7	(−23.3, −2.1)	0.02	−18.1	(−29.9, −6.4)	0.00
Mental health-related quality of life (range 0–100)	92	41.6	98	37.6	3.7	(0.3, 7.1)	0.04	3.8	(−0.1, 7.8)	0.06
Depression-free days[c]	143	160	137	136	25	(1, 49)	0.04	29	(1, 57)	0.04
Healthcare utilization										
Any emergency department visit (%)	92	18.5	96	20.8	−5.3	(−25.2, 14.7)	0.60	0.6	(−16.0, 17.3)	0.94
Any hospitalization (%)	92	7.6	96	4.2	3.4	(−2.4, 9.3)	0.25	5.8	(−0.9, 12.4)	0.09

CI, confidence interval.
[a]Via ordinary least-squares regression (continuous outcomes) or generalized linear model with identity link and binomial error distribution (binary outcomes), with fixed effects for site and depression treatment experience level and clustered by provider.
[b]Via linear mixed model (continuous outcomes) or generalized linear model with identity link, binomial error distribution, and inverse probability of observation weighting (binary outcomes), with fixed effects for site and depression treatment experience level and clustered by provider.
[c]Over 12 months of study enrollment.

HIV-related outcomes

When comparing crude (not accounting for design effects or missingness) outcome measures by original arm assignment, antiretroviral adherence measured by unannounced telephone-based pill count was high overall and showed little change in either arm over time (Fig. 2a). Self-reported antiretroviral adherence, viral load, appointment attendance, HIV-related symptoms, physical health-related functioning, emergency department use, and hospitalizations were also similar between the arms over time (supplemental figures, http://links.lww.com/QAD/A744).

Mental health outcomes

When comparing crude outcome measures by original arm assignment, the arms had comparable baseline depressive severity (Fig. 2b). Intervention arm scores improved 7 points at 6 and 12 months. Usual care scores improved 3 points at 6 months and 5 points at 12 months. Other mental health indicators also showed early gains in the intervention group, with the usual care group mostly closing the gap by 12 months (Fig. 2c, supplemental figures, http://links.lww.com/QAD/A744). The intervention group experienced an average of 160 DFDs during the 12 months of follow-up compared to 136 days among usual care participants.

Effect estimates

In intent-to-treat analyses adjusted for design elements and corrected for missingness, no effect was evident on antiretroviral adherence (the primary outcome) or other HIV-related outcomes at the primary time-point (6 months) (Table 3). At the primary 6-month time-point, the intervention demonstrated an effect on depressive severity, achievement of depression remission, and suicidality, as well as a trend toward an effect on mental health-related functioning. By 12 months, the usual care group had achieved comparable mental health outcomes to the intervention group on most indicators, but participants in the intervention group maintained their advantage in depression remission [relative advantage of 16.0 (2.6, 29.4) percentage points] (data not shown). Over 12 months, the intervention arm experienced 29 (1, 57) more DFDs. Correction for missing data had little impact on most effect estimates.

Secondary comparisons

In prespecified secondary comparisons, there was no evidence of stronger intervention effectiveness in an 'as-treated' analysis (ignoring arm and comparing those who had vs. had not been on antidepressants for $\geq$90 days) or a 'completers' analysis (ignoring arm and comparing those who did vs. did not complete $\geq$3 treatment adjustment contacts with the DCM) (data not shown). There was

no evidence of stronger intervention effectiveness in prespecified subgroups (those with baseline self-reported adherence <80%, unsuppressed HIV-RNA viral load, PHQ-9 ≥20, or comorbid anxiety/substance use disorders) (data not shown).

Discussion

The present study represents the largest trial to date of a collaborative care antidepressant management intervention integrated into HIV primary care, and the first such trial to our knowledge outside of the Veterans Administration system. The MBC depression management approach was effectively integrated in four HIV clinics, with high uptake of antidepressants and timely dose escalation in the intervention arm. No differences between arms were observed in the primary outcome – antiretroviral adherence – or other HIV outcomes, including HIV symptoms, viral load, or appointment adherence. At 6 months, relative to usual care, the intervention had reduced depressive severity by a clinically meaningful margin, increased depression remission, reduced suicidality, and improved mental health-related functioning. By 12 months, the usual care arm had caught up on most mental health outcome measures. However, by shortening the course of depressive episodes, the intervention conferred nearly an additional month of DFDs over the 12 months of study participation.

Similar to this study, two other randomized trials of antidepressant-focused depression treatment strategies reported substantial improvements in mental health measures, but no effect on HIV-related measures. A trial of directly observed weekly fluoxetine compared to referral to standard mental health services among 137 homeless or marginally housed men in San Francisco reported a strong effect of the intervention on depression outcomes, but no statistically significant differences in HIV outcomes [24]. A trial of collaborative care for depression relative to usual care among 249 patients at three Veterans Administration HIV clinics found a mental health benefit of the intervention at 6 months, but usual care participants had caught up by 12 months. The intervention lowered HIV symptoms, but had no effect on antiretroviral adherence or other HIV outcomes [25]. In contrast, three trials of cognitive behavioral therapy for depression with integrated adherence counseling (CBT-AD) have shown improvements in both depression and adherence among 45 adults with HIV and depression [22]; 89 adults with HIV, depression, and injection drug use histories [54]; and 40 Latino adults with HIV and depression [55].

Two differences in the above studies are apparent. First, the three trials that identified an effect of depression treatment on antiretroviral adherence [22,54,55] were conducted among participants with relatively poor adherence or viral suppression at baseline. In contrast, participants in the present study and the two trials that did not identify such effects [24,25] had high baseline levels of adherence and rates of viral suppression, potentially introducing a ceiling effect on HIV outcomes. Second, the trials that found effects on adherence deployed an intervention that explicitly targeted both depression and adherence through counseling and/or reminder components, whereas the present study and the trials that did not find such effects primarily targeted depression through medication management.

In contrast to the mixed trial results, most observational studies have reported a positive association between depression treatment and antiretroviral adherence. A meta-analysis of 29 studies encompassing more than 12 000 individuals estimated that depression treatment improved the odds of satisfactory antiretroviral adherence by 83%, with a stronger association among observational than experimental studies [20]. Estimates from observational studies may be confounded by characteristics that are difficult to measure. For example, among depressed patients, those willing to initiate depression treatment may be more compliant with medical treatment in general. It is also possible that trials tend to enroll generally compliant patients whose adherence has little room to improve, whereas observational studies are able to include patients with a wider distribution of adherence.

Among this study's strengths are its size, multiple sites, duration of follow-up, objective adherence measure, rigorous pseudo-cluster randomization design, and high level of fidelity to protocol achieved through weekly supervision. An additional strength is the broad inclusion criteria. While many depression treatment trials exclude individuals with anxiety or substance use disorders to achieve a 'clean' participant pool, this study did not, since such a set of participants would bear little resemblance to patients with depression in real-world HIV care [56]. Similarly, many adherence trials restrict enrollment to individuals with low adherence or viral failure, but this study did not, since we sought to estimate the impact of a clinic-wide collaborative depression care intervention on HIV outcomes.

A major challenge for this study was missing data. While 77% of participants completed at least one follow-up, 60% had a valid 6-month primary outcome measure. Some of those lost may have discontinued antiretroviral therapy (ART); this is unknown. Importantly, missingness was balanced between arms, and sophisticated missing-data correction methods had little impact on effect estimates. Loss to follow-up could also be related to clinical comorbidities such as immune reconstitution inflammation syndrome (IRIS), although most participants were on stable ART at entry, no instances of IRIS were

documented during follow-up, and correction for baseline clinical status did not substantively change effect estimates. An additional limitation is the possibility that contamination may have diluted the true effect size, even with the pseudo-cluster design. While there were large differences in antidepressant prescription and dose escalation between the arms, these measures did improve somewhat among usual care participants over time, suggesting that some of the mental health gains of the usual care group by 12 months could be explained by contamination. Alternatively, this convergence could simply reflect the episodic nature of depressive disorders, for which treatment shortens the course of illness, but up to 50% of episodes resolve spontaneously within a year [13].

Depression is highly prevalent among people living with HIV [57,58]. Despite the known efficacy of depression treatments in this population [15,16], depression remains widely underdiagnosed and untreated or undertreated in HIV primary care [17,18]. New care models that build on the success of collaborative depression treatment, in general primary care [59], are critically needed to address the large mental health treatment gap among people living with HIV. Models such as MBC efficiently leverage clinic staff time to provide antidepressant prescription decision support to HIV medical providers. This trial demonstrates that such a real-world strategy can significantly shorten the course of depressive illness for HIV patients and reduce overall morbidity from depression.

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Conflicts of interest

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