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Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD) in HIV-infected Injection Drug Users: A Randomized Controlled Trial

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Abstract

Objective—Depression and substance use, the most common comorbidities with HIV, are both associated with poor treatment adherence. Injection drug users comprise a substantial portion of individuals with HIV in the U.S. and globally. The present study tested cognitive-behavioral therapy for adherence and depression (CBT-AD) in patients with HIV and depression in active substance abuse treatment for injection drug use.

Method—This is a two-arm, randomized controlled trial (N = 89) comparing CBT-AD to enhanced treatment as usual (ETAU). Analyses were conducted for two time-frames: 1) baseline to post-treatment 2) post-treatment to follow-up at 3- and 6-months after intervention discontinuation.

Results—At post-treatment, the CBT-AD condition showed significantly greater improvement than ETAU in MEMS (electronic pill cap) based adherence (γ_{slope} = 0.8873, t (86) = 2.38, p = .02; $d_{GMA\text{-}raw}$ = .64), and depression, assessed by blinded assessor [Mongomery-Asberg Depression Rating Scale (F(1,79) = 6.52, p<.01); d = .55)] and clinical global impression [(F(1,79) = 14.77, p<.001; d = .85)]. After treatment discontinuation, depression gains were maintained, though adherence gains were not. Viral load did not differ across condition, however, the CBT-AD condition had significant improvements in CD4 cell counts over time compared to ETAU (γ_{slope}= 2.09, t (76) = 2.20, p = .03; $d_{GMA\text{-}raw}$ = .60).

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Conclusions—In patients managing multiple challenges including HIV, depression, substance dependence, and adherence, CBT-AD is a useful way to integrate treatment of depression with an adherence intervention. Continued adherence counseling is likely needed, however, to maintain or augment adherence gains in this population.

Keywords

HIV; AIDS; Antiretroviral therapy; ART; depression; randomized controlled trial; adherence; substance abuse

INTRODUCTION

HIV continues to be a major public health concern in the United States, with no decline in rates of new infections, and prevalence growing steadily (Centers for Disease Control and Prevention, 2008). The two most prevalent and interfering psychosocial comorbidities of HIV infection are clinical depression and substance use (Berger-Greenstein et al., 2007; Bing et al., 2001; Ruiz Perez et al., 2005). In a nationally representative probability sample of 2,864 adults who participated in the HIV Care Services and Utilization Study, 12-month prevalence rates for major depression, substance use without dependence (excluding marijuana use), and substance dependence were estimated as 36%, 25%, and 12.5%, respectively (Bing et al., 2001). Clinical depression and problematic substance use not only can cause significant distress and functional impairment, but also can interfere with HIV treatment and care; both conditions have consistently been associated with poor antiretroviral therapy (ART) adherence (Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; DiMatteo, Lepper, & Croghan, 2000; Lucas, Cheever, Chaisson, & Moore, 2001; Lucas, Gebo, Chaisson, & Moore, 2002; Paterson et al., 2000; Safren et al., 2001). A recent meta-analysis of 99 independent samples revealed a significant relationship between depression and adherence to HIV medications (Gonzalez, Batchelder, Psaros, & Safren, 2011).

Individuals with injection drug use (IDU) histories continue to compose a large proportion of individuals living with HIV in the U.S. (Centers for Disease Control and Prevention, 2010). The most recent estimates available from 37 states with confidential name-based HIV-infection reporting suggest that approximately 12% of men and 15% of women living with HIV in 2008 acquired HIV through IDU (Centers for Disease Control and Prevention, 2010). However, these estimates only account for HIV-infection directly attributable to IDU, and thus do not reflect the secondary impact of transmission through sexual contact with a partner who acquired HIV through IDU.

In addition to the importance of adherence for self-care and optimization of the benefits of ART, adherence may be important in the transmissibility of HIV. HIV transmission is highly dependent on the amount of HIV viral load present in any given individual's blood and genital secretions (Hull & Montaner, 2011). HIV viral load can be reduced to an undetectable level through successful antiretroviral therapy, which seems to significantly reduce transmission risk between HIV-serodiscordant partners (Attia, Egger, Muller, Zwahlen, & Low, 2009). Accordingly, increased adherence to ART among opioid-dependent individuals living with HIV may also provide a secondary public health benefit of contributing to HIV prevention efforts (Hull & Montaner, 2011); and being part of new emerging "test, treat, and retain" strategies.

Injection drug users living with HIV face multiple changes to successful HIV treatment, including a poorer virological response to ART compared to other HIV-infected populations, poor adherence to ART, and increased rates of attrition during interventions (Keiser et al., 2011; Weber et al., 2009). Research suggests that HIV-infected individuals

currently receiving treatment for IDU or opioid dependence continue to struggle with adherence to ART (Weber et al., 2009). Avants, Margolin, Warburton, Hawkins, and Shi (2001), for example found that more than a third of HIV-positive patients receiving methadone maintenance treatment reported less than 80% adherence to their HIV medication regimens, a rate that potentially increases the risk of developing a drug-resistant strain of the virus. Even when ART doses were directly administered and supervised in a methadone clinic-based program, continued substance use was associated with an increased risk of nonadherence and intervention dropout (Lucas et al., 2007).

HIV-positive individuals are also at an increased risk for major depression, with prevalence rates suggesting that twice as many HIV-positive individuals suffer from depression than demographically matched HIV-negative individuals (Ciesla & Roberts, 2001). Among a sample of triply diagnosed patients with HIV, substance abuse, and psychiatric illness, Berger-Greenstein and colleagues (2007) reported that over 70% of participants met criteria for major depression; self-reported depressive symptoms were also significantly related to worse HIV medication adherence and lower CD4 cell count. A prospective observational study by Riera and colleagues (2002) reported that among 202 HIV-positive patients, depression and methadone maintenance treatment were independent predictors of poor adherence to antiretroviral medications. During an evaluation of depressive symptoms and symptomatic response among HIV-infected injection drug users who were enrolled in a randomized controlled trial of directly observed ART, improvements in depression over six months was associated with increases in CD4 cell count and adherence, while worsening in depression was associated with active drug use and increases in plasma viral RNA levels (Attia et al., 2009; Hull & Montaner, 2011; Springer, Chen, & Altice, 2009).

Maintaining excellent adherence can be a difficult and challenging process for a sizeable proportion of individuals living with HIV. Poor adherence decreases the benefits of ART, as well as chances of prolonged survival (e.g., Garcia de Olalla et al., 2002; Thompson et al., 2010). To address these barriers, there is an emerging evidence base for the efficacy of interventions for ART adherence (Amico, Harman, & Johnson, 2006; Simoni, Amico, Pearson, & Malow, 2008; Simoni, Frick, Pantalone, & Turner, 2003; Simoni, Pearson, Pantalone, Marks, & Crepaz, 2006). However, to date, most interventions have produced only modest effects, have focused directly on adherence, and have not addressed psychosocial comorbidities which may moderate the degree to which the interventions would be successful. When one considers the symptoms of a depressive episode (e.g., persistent sad mood, loss of interest, concentration problems, low energy, feelings of excessive worthlessness/guilt), it is not difficult to see how these symptoms could interfere with the acquisition or use of skills necessary to improve adherence and could potentially minimize the efficacy of adherence training interventions that do not directly treat depression.

Our prior work involved developing (Safren et al., 2004) and initially testing (Safren et al., 2009) cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV. We showed in a cross-over design that integrating adherence counseling using our Life-Steps protocol (Safren et al., 2001) with CBT for depression was successful at both increasing adherence and reducing depression in individuals with HIV and depression (Safren et al., 2009). Although individuals with active substance use were excluded from this initial study, HIV infection due to IDU accounts for 18.5% of cases of HIV among adults in the US (Centers for Disease Control and Prevention, 2008, 2010). As articulated above, these individuals may be particularly at risk for depression due to the multiple stressors involved with managing comorbid HIV-infection and opioid dependence. Triply diagnosed individuals- those with HIV, clinical depression, and substance use (e.g., opioid abuse/ dependence)- represent a population uniquely at risk for nonadherence. Accordingly, in

designing this trial, a-priori, we sought to examine the degree to which intervening on depression would assist the ability to benefit from evidenced-based adherence counseling.

The primary objective of the current study was to test, in a randomized controlled trial, CBT-AD in patients with HIV, depression, and opioid dependence who were undergoing treatment for their substance use disorder. We hypothesized that those who were assigned to the CBT-AD condition would have better adherence (primary outcome), decreased depression, and improved biological outcomes (e.g., decreased viral load and increased CD4+ lymphocyte counts) than the comparison group (ETAU; enhanced treatment as usual), and that these gains would be maintained over the 9 month follow-up period.

METHODS

Study Subjects and Setting

Enrollment occurred between July of 2005 and October of 2008, and included (89 randomized) individuals between the ages of 18 and 65 who were HIV-seropositive, prescribed antiretroviral therapy for HIV, endorsed a history of injection drug use, were currently enrolled in opioid treatment for at least one month, and met criteria for a diagnosis of current or subsyndromal depressive mood disorder (72 major depressive disorder; 1 dysthymia; 16 bipolar disorder, most recent episode depressed). Subsyndromal depression (n = 10) was defined as a past history of major depression, with a current level of residual symptoms (Clinical Global Impression [CGI – see measures section] of at least 2) that did not meet diagnostic threshold (i.e., due to antidepressant therapy).

Treatment for opioid dependence varied, with the majority of participants having received methadone (70%; n = 63), and the remainder receiving suboxone therapy (5.6%, n = 5), group (4.5%, n = 4) or individual substance abuse counseling (7.9%, n = 7), active participation in Narcotics Anonymous (4.5%, n = 4), or other active substance abuse treatment (6.7%, n = 6). There were no significant differences in type of substance abuse treatment between the experimental and control conditions.

Excluded individuals were those with any active untreated or unstable major mental illness that would interfere with study participation (e.g., active mania or psychosis), inability or unwillingness to provide informed consent, or current participation in cognitive behavioral therapy (CBT) for depression.

Participant demographics are depicted in Table 1, and raw study-related outcomes, including baseline, in Table 2 [note, analyses and graphs used general linear modeling (GLM) and hierarchical linear modeling (HLM) adjusted scores]. The study sample was of a predominately lower socioeconomic status, with only 4% working or being in school full-time and 67% on disability. There were no differences on baseline demographic variables across conditions. There was a baseline difference for CD4 count, with the CBT-AD group having a higher CD4 count than the comparison condition ($t(87) = 2.76$), $p < .01$ – see Table 2). Hence, baseline levels were covaried in longitudinal analyses of this variable[2].

The sample had substantial psychosocial comorbidity, with 62% having at least one additional DSM-IV diagnosis besides depression and substance abuse disorder (see Table 2). Sixty five percent of the randomized sample had recent illicit substance use as assessed by a combination of toxicology screening and self-report at baseline. During the clinician-administered assessments administered at baseline, participants were asked to report any substance use over the past 30 days. Approximately one third (30.3%) of randomized participants reported polysubstance use during the past 30 days, 23.6% reported alcohol use, 5.6% reported alcohol use to intoxication, 25.8% reported heroin use, 75.3% reported

methadone use, 23.6% reported either opiate or analgesic use, 37.5% reported either sedative, hypnotic, or tranquilizer use, 25.8% reported cocaine use, 16% reported cannabis use, and 1.1% reported hallucinogen and inhalant use over the past 30 days; there was no reported amphetamine or barbiturate use. In addition to the clinician-administered assessment of substance use over the past 30 days, participants also provided a saliva sample for a toxicology screen. Of the 89 participants randomized, 77.2% tested positive for methadone use, 22.5% for cocaine use, 12.7% for opiate use, 8.8% for benzodiazepine use, 5% for cannabis use, and 1.3% for amphetamine and barbiturate use. There were no significant differences in reported substance use or toxicology results based on randomization condition.

For the first participants (n = 40), all study visits took place at one of four methadone clinics in the greater Boston area. Recruitment was later expanded for two major reasons: 1) we discovered that some potential participants were not comfortable referring themselves or being seen for the study at the methadone clinics despite measures to protect confidentiality about being in an HIV study, and 2) during the time of the study, more options became available for treatment of opioid dependence, such as suboxone. Seventy percent were on methadone at baseline, 6% suboxone, 7% NA/AA only, and 18% counseling (individual or group); 56% were on an antidepressant medication at study entry Hence, participants were then recruited through community outreach and HIV clinics at Massachusetts General Hospital (MGH) (n = 8) and Rhode Island Hospital (n = 9). The remaining participants (n = 32) were referred by other study participants or through community outreach and recruitment flyers posted in other HIV care or substance abuse (including additional methadone clinic) settings, but were seen at an MGH-based research clinic. This adaptive trial design allowed us to keep up with the ever-changing epidemic as the trial was in process.

After a complete description of the study was provided to the participants, study clinicians obtained written informed consent. All study procedures were approved by the Institutional Review Boards at Massachusetts General Hospital (MGH) in Boston, MA and at Rhode Island Hospital in Providence, RI.

Study Design and Procedures

Study visits—After an initial evaluation to determine study eligibility and a two-week period where participants started using the electronic pill caps, there were four major study assessment visits: T1 was the baseline assessment, T2 was the post-treatment outcome which happened at end of intervention for those in the experimental arm (approximately 3-months after baseline for participants in both arms), T3 was a 3-month follow-up (occurring 6 months from baseline), and T4 was a 9-month follow-up (occurring 12 months from baseline). These assessment points were chosen so that we could have four major outcome assessments over the course of one year of study involvement; allowing for longitudinal analyses for the follow-up assessments. The post-treatment assessment was at approximately 3 months, and that was selected in order to allow participants in the CBT-AD condition enough time to come to 9 treatment sessions, accounting for issues such as snow and life-events that might not allow for coming consistently every week. The 3-month (post-treatment) assessment was to examine acute outcomes during the treatment, right after it was discontinued. The T3 and T4 outcomes were to examine short-term and long-term maintenance of gains, as well as have time to see adherence or depression-based changes in any biological outcomes.

These assessments included electronic pill cap evaluations (MEMS; Medication Event Monitoring System; AARDEX) for adherence, assessment of depression by self-report and an independent assessor blinded to study condition, as well as HIV plasma RNA and CD4+

lymphocyte counts either drawn for the study or abstracted from participants' medical records if collected in the month prior to the assessment. Samples acquired during the baseline assessment with a viral load of over 1,000 copies per milliliter were tested for genotypic resistance. Participants received $50.00 for the major assessments (e.g., baseline and three follow-up visits) and $25.00 for the weekly visits during the acute study period.

Randomization—Study coordinators randomly assigned participants at their first visit after the baseline in blocks of two, stratified by biological sex, depression severity (current major depression or residual symptoms only), and adherence (baseline MEMS-based adherence above or below 80%). Assignment to study condition (CBT-AD or ETAU) was concealed from both study therapists and participants until the conclusion of the first counseling visit (see below).

Assessment Measures

Primary Outcome - Adherence—MEMS caps recorded each instance of bottle opening, monitoring the antiretroviral medication that the participants considered the most difficult to remember or the dose taken most frequently. To account for doses that participants may have taken without opening the pill cap (e.g., took out afternoon doses when they opened the pill bottle in the morning), we counted a dose as taken if participants could recall specific instances when they took their medications but did not use the cap (Liu et al., 2001; Liu et al., 2006; Llabre et al., 2006). A dose was considered missed if it was not taken within a 2-hour window of the designated time. If participants were using a pill-box prior to entering the study, we encouraged them to monitor a pill that is taken concurrently with another, with one going in the pill box and the other going in the bottle, so that the function of the pill-box (i.e., knowing if a pill has been taken/organization) could be maintained. In both conditions, if there were discrepancies between self-report and MEMs data, research assistants (RAs) or therapists would interview participants further to determine whether their cap should be replaced and/or try to figure out what may have caused this discrepancy.

For the acute outcome (baseline to post-treatment), adherence was operationalized as the percentage of MEMS-based adherence since the last visit; visits were scheduled weekly or, at most, every two weeks. For the follow-up longitudinal analyses, we used adherence in the past two weeks. This is consistent with our prior studies that used MEMs, and balances having an adequate sampling of time with not overlapping too much with the time that the participants were still potentially improving from the intervention (Safren, Hendriksen, DeSousa, Boswell, & Mayer, 2003; Safren et al., 2004; Safren et al., 2009).

Clinician-administered Assessments

Enrollment Visit: The initial evaluation to establish study eligibility included a diagnostic evaluation of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnoses using the Mini International Neuropsychiatric Interview (MINI), one of the most widely used diagnostic assessments (Sheehan et al., 1998). This evaluation was completed by one of the study therapists, and was presented for review and diagnostic consensus by the study team.

Independent Assessments: An independent assessor (IA), who remained blind to study condition, conducted the clinician-administered outcome assessments. The IA visits included administration of: 1) the Montgomery-Asberg Depression Rating Scale (MADRS), and 2) a rating of global distress and impairment for depression and substance abuse using the Clinical Global Impression (CGI) for severity (e.g., 1 = not ill to 7 = extremely ill) (Montgomery & Asberg, 1979; National Institute of Mental Health, 1985). The MADRS and CGI scores were regularly reviewed through audiotape supervision with another blinded

assessor. Matching the number of study visits between the two conditions helped preserve the blinding (e.g., if the IA saw the participant in the waiting room frequently, the participant could be in either condition). Additionally, participants were reminded before and during the IA visits not tell the assessor which study condition they were in.

Participant Measure of Depression—Participants completed the self-reported Beck Depression Inventory-Short Form (BDI-SF) during each visit (Beck & Beck, 1972). This measure was designed for use with medical populations, removing many of the somatic symptoms of depression that might be confounded with medication side-effects or physical functioning.

Biological Outcome Measures—At the major study assessment visits, participants who did not have an HIV plasma RNA or CD4+ lymphocyte test in the prior month accessible through clinic chart review provided blood for testing.

Intervention Conditions

Participants in both the treatment (CBT-AD) and comparison (ETAU) conditions received a single-session intervention on HIV medication adherence (Life-Steps), which involved 11 informational, problem-solving, and cognitive behavioral steps (Safren, Otto, & Worth, 1999). In each step, participants and the clinician define the problem, generate alternative solutions, make decisions about the solutions, and develop a plan for implementing them. Participants also received adherence tools such as assistance with a schedule and a cue-dosing watch that could sound two alarms per day. To enhance treatment as usual, they also had a letter mailed to their medical providers documenting the participant's depression or other psychiatric disorders, and suggesting that these conditions should continue to be assessed or treated.

In addition to this, those assigned to the experimental condition also received 8 sessions of CBT-AD (Safren, Gonzalez, & Soroudi, 2007a, 2007b). Accordingly, this was 9 sessions total, with Life-Steps being session 1, followed by 8 CBT-AD sessions. This approach integrated continued adherence counseling with traditional CBT techniques for the treatment of depression. Module 1 (≈1 session; average in this study = 1.0 session) provided psychoeducation about HIV and depression, and a motivational interviewing (MI) exercise designed to set the stage for behavioral change. The MI exercise involved examining the pros and cons of changing and not changing self-care behaviors, as well as a discussion of a metaphor about treatment. Module 2 (≈1 session; average in this study = 1.2 sessions across participants) focused on behavioral activation and activity scheduling, which was designed to increase regularly occurring activities that involve pleasure and mastery. Module 3 (≈3 sessions; average in this study = 2.4 sessions across participants), cognitive restructuring, involved training in adaptive thinking, such as identifying and restructuring negative automatic thoughts. Module 4 (≈2 sessions; average in this study = 1.0 sessions across participants), problem-solving, involved training in selecting an action plan for problems, and breaking this plan into manageable steps (Nezu, Nezu, Felgoise, McClure, & Houts, 2003). Module 5 (≈1 session; average in this study = 1.0 session across participants), relaxation, involved training in progressive muscle relaxation and diaphragmatic breathing. Some participants had a review session as needed (average = 0.4 sessions across participants). Sessions were approximately 50 minutes long and occurred weekly, with the goal of completion in approximately three months. A more detailed description of the intervention can be found in our published manuals (Safren et al., 2007a, 2007b). Flexibility in the number of sessions devoted to any module was permitted in order to address the complexity and variability of issues facing participants with HIV, depression, and intravenous drug use histories.

Study interventionists included clinical psychologists, psychology pre- and post-doctoral fellows in clinical psychology, and one master's level psychologist. Training involved didactic learning from the modules and supervision using audio-recordings of sessions. To maximize therapist adherence to the intervention, all sessions were audio-recorded for monitoring and supervision. Interventionists met with a clinical supervisor on a weekly basis for clinical supervision where cases and interventions were discussed. For new interventionists, all sessions were listened to by the clinical supervisor, for at least the clinician's first participant, for feedback purposes. On an ongoing basis, one therapist per week was assigned an audiotape (of a different therapist's session) to review and complete a checklist for interventionist adherence, including whether the specific components of the modules of treatment were, in fact, delivered. Traditional monitoring of treatment fidelity, as typically done in randomized controlled trials of psychological treatments with circumscribed samples (usually individuals meeting criteria for one psychological disorder, and receiving treatment for that disorder), was not possible for this study population of triply-diagnosed individuals because urgent life events often occurred and were addressed in treatment. Hence, the supervision sessions and fidelity ratings were used to develop a process for future research. This balanced the need for therapists to adhere to the general principals of CBT and intervening with respect to self-care behaviors, while being flexible regarding the order of the manualized modules, fitting the manualized modules to the clients' needs, and providing CBT strategies to assist with depression and self-care regardless of what particular chapter would have been next in the treatment protocol. Accordingly, by the end of this process, approximately 5% of sessions were rated using the system that was developed during the study. A future manuscript will more fully detail these data, and a current trial that seeks to examine active components of treatment (e.g., that compares this intervention to a credible, time-matched, active control treatment with both fidelity and contamination ratings) is currently underway.

After the Life-Steps adherence counseling session, participants in the ETAU condition also had 8 study visits before the post-treatment assessment (to make the 9 sessions total). During these visits, participants had their MEMS cap downloaded, completed the BDI-SF, and received the same number and timing of visits as those in the CBT-AD condition.

Statistical Analyses

Our prior study had an effect size of 1.0 for the primary MEMS-based adherence intent to treat outcome (Safren et al., 2009). That study, however, did not include those with comorbid substance dependence and hence we powered the study for an effect size of d = .8, which yielded a goal of approximately 100 participants using ANOVA analysis for MEMS-based adherence. Longitudinal modeling, however, as described next, allows for greater power using all available data. The actual sample size included 89 randomized participants.

Hierarchical Linear Models (HLM) with HLM 6.06 software were used to evaluate acute study outcomes when there were at least three data points (Raudenbush, Bryk, Cheong, & Congdon, 2004): this included MEMS-based adherence during the pre-post treatment phase which was collected at each study visit, self-reported depression during the pre-post treatment phase which was also collected at each study visit, and follow-up analyses for all study outcomes.

Repeated measures (general linear models - GLM) were used for pre-post assessments of depression by independent assessors (e.g., MADRS and CGI) and pre-post biological markers of HIV disease (e.g., plasma RNA viral copies and CD4 cell count), as there were only two assessment time points, and HLM or other mixed effects modeling could not be used. In these analyses, study condition assignment was the between-subjects factor. This

was part of the apriori analysis plan; to first examine pre-post outcomes, and secondly examine maintenance of any gains and biological endpoints over the longitudinal follow-up.

For pre-post HLM analyses where we had repeated measures (MEMs-based adherence and BDI), the Level 1 HLM model included the Time variable (weeks since baseline), which provided the structure of the model for the outcome variable of interest. The Level 2 model tested the significance of the treatment effect, and is estimated from the significance of the slope (gamma coefficient) associated with the random assignment variable (CBT-AD or ETAU). As there were significant differences between the randomly assigned conditions on CD4 cell number at study entry baseline, CD4 cell number was controlled in each of the main outcomes analyses[2].

For maintenance of treatment effects HLM analyses, to model the slope in study outcomes across the follow-up assessments using baseline values, the Level 1 model included time, and the Level 2 model tested study condition, controlling for pre-randomization levels. Treatment effects on log viral load and CD4 cell count change across the follow-up time period were estimated by controlling for resistance to at least one antiretroviral medication in the Level 2 model.

For the HLM models, all continuous measures in the Level 2 model were centered about their group means, and all dichotomous variables were coded 1/0. Model parameters were estimated using full maximum likelihood estimation with robust standard errors. In all analyses that used HLM, unconstrained models were run to confirm significant individual variation about the slope and intercept before accounting for random assignment. For all analyses, the Type 1 error rate adopted was a p of .05. Effect sizes for HLM growth estimates were calculated for statistically significant outcomes using the formula $d_{\text{GMA-raw}} = \gamma_{11}(\text{time})/SD_{raw}$ in line with current recommendations for communicating effect magnitude (Feingold, 2009; Raudenbush & Liu, 2001).

For all analyses involving comparing the two study arms, analyses presented controlled for baseline CD4 cell count differences between groups (there were no other baseline differences between the two study conditions). When the same analyses were conducted not controlling for baseline CD4 cell count differences between groups, the pattern of results were the same. [2]

RESULTS

Participant Characteristics

Participant flow throughout the duration of the study is depicted in Figure 1. Ninety-one percent of those randomized were retained for the acute outcome assessment (n = 86), and 84% (n = 79) returned to at least one post-treatment follow-up and hence could be used for follow-up analyses. Although there was a raw number greater loss to attrition at the final assessment point in the ETAU condition (8 out of 44 participants) compared to the CBT-AD condition (15 out of 45 participants), this difference was not statistically significant. Raw scores for study outcomes are presented in Table 2 by study condition (note that HLM and GLM analyses use adjusted scores). At baseline, 11.2% of the sample collapsed across condition had genotypic resistance. There were no study-related adverse events that occurred during the study.

Baseline to Post-Treatment Outcomes

Adherence (MEMS)—There was a significant upward slope in MEMS-based adherence ($\gamma_{\text{slope}} = 0.47$, t (88) = 2.16, p = .033) during the treatment period, indicating improved adherence for the study participants as a whole. In addition, there was significant individual

variation about the slope (ρ_{slope} = 2.35 df(87), χ^2 = 203.01, p < .001) providing the justification for conducting the analysis by randomized group (Level 2 analysis). When adding treatment condition, and, as a covariate, baseline CD4, to the model, the increase in adherence was significantly greater over time in the CBT-AD condition (11.8 percentage points) than in the comparison condition (0.5 percentage points) (γ_{slope} = 0.887, t (86) = 2.38, p = .02; $d_{GMA\text{-}raw}$ = .64, see Figure 2).

Depression Rated by Independent Assessor—There were significantly greater reductions in depression for the CBT-AD condition relative to the comparison condition for both the MADRS (F (1, 78) = 9.72, p =.<..01; d = .55) and CGI (F (1, 78) = 17.14, p <.001; d = .85. see Table 2). These analyses used baseline CD4 as a covariate.

Self-reported Depression (BDI-SF)—There was a significant decreasing slope (γ_{slope} = −0.23, t (88) = −3.52, p < .01) for self-reported depression over time. When accounting for treatment condition, and controlling for baseline CD4 as a covariate, those in the CBT-AD condition experienced a significant estimated reduction in depression symptoms (5.1 points on the BDI-SF) compared to a non-significant change in the control condition (< 1 point on the BDI-SF) (γ_{slope} = −0.320, t (86) = −2.39, p =.02; $d_{GMA\text{-}raw}$ = .63).

Biological Outcomes—Although treatment effects on HIV viral load and CD4 count were more likely to emerge only at follow-up, acute effects (e.g., baseline to post-treatment) were examined and are presented in Table 2 for consistency. Controlling for medication resistance, randomized effects were not significant for either CD4 cells (F (1, 74) = 1.92, p = .32, d = .10) or for log viral load (F (1, 71) = 1.08, p = .30, d = .20) with the additional control for baseline CD4.

Post-Intervention Follow-Up Assessments at 3 and 9-Months

Adherence (MEMS)—MEMS-based adherence gains acquired across CBT-AD treatment were not maintained during follow-up as evidenced by the significant downward slope for MEMS-based adherence (γ_{slope}= −0.294, t (79) = −3.24, p < .01) that did not differ by study condition (γ_{slope}= 0.20, t (76) = 1.23, p = .22; $d_{GMA\text{-}raw}$ = 0.21). Baseline CD4 differences were controlled for as a covariate in these analyses.

Clinician-assessed Depression (MADRS and CGI)—Depression gains as assessed by blinded clinicians were maintained, which was demonstrated on the CGI by a trend for continued improvement during the follow-up time period (γ_{slope} = −0.008 t (80) = −1.93, p = .06) with no differential improvement by condition over follow-up after acute treatment ended (γ_{slope} = 0.011, t (78) = 1.59, p = .12; $d_{GMA\text{-}raw}$ = 0.51). Similarly, the MADRS also demonstrated a trend for a continued improvement for the group as a whole (γ_{slope} = −0.052, t (80) = −1.69, p = .09), with no differential improvement by condition (γ_{slope} = 0.078, t (78) = 1.47, p = .14; $d_{GMA\text{-}raw}$ = 0.61). These analyses had baseline depression scores and baseline CD4 as covariates.

Self-reported Depression (BDI-SF)—Improvements in depression acquired during the CBT-AD intervention and assessed via self-report were maintained during follow-up as evidenced by no significant change in self-reported depressive symptoms for the whole sample (γ_{slope} = 0.03, t (73) = −1.27, p = .21) or by group assignment when controlling for baseline BDI and CD4 differences (γ_{slope} = −0.01, t (72) = −0.30, p = .76; $d_{GMA\text{-}raw}$ = 0.13).

Biological Outcomes (HIV viral load, CD4 cell count)—There was no significant change in log viral load over the follow-up time period for the group as a whole (γ_{slope} = −0.0015, t (75) = −0.40, p = .69), or based on group assignment (γ_{slope} = 7.28 × 10^{-x4}, t

(74) = −0.165, p = .87; $d_{GMA\text{-}raw}$ = 0.02), controlling for baseline log viral load, CD4 cell number, and resistance. There were also no differences across the two conditions in the percent of participants who attained a suppressed viral load ($\gamma_{slope} = 5.0 \times 10^{-\times 5}$, t (74) = −0.002, p = .98; $d_{GMA\text{-}raw} < 0.01$).

Over the follow-up period, the slope of CD4 cell number was non-significant for the entire sample (γ_{slope} = 0.590, t (79) = 1.08, p = .29). When condition was added to the model, there was a significant increase in CD4 cells in the CBT-AD condition compared to the control condition, controlling for baseline CD4 and medication resistance (61.2 CD4 cell increase vs 22.4 CD4 cell decrease; γ_{slope} = 2.09, t (76) = 2.20, p = .03; $d_{GMA\text{-}raw}$ = .60). Note these differences were also significant without controlling for baseline CD4 and medication resistance.

DISCUSSION

The current study examined the use of a time-limited intervention (CBT-AD) addressing both adherence and clinical depression in a sample of triply-diagnosed individuals with HIV. The intervention had acute and significant effects on both adherence and depression during the time in which the intervention was being delivered. MEMS-based adherence in the CBT-AD group improved approximately 11.8% from baseline and 11.3% over the comparison condition during treatment. The magnitude of this effect is potentially clinically significant in that it has been suggested that a 10% change in adherence can result in improved HIV outcomes (Bangsberg, 2006; Liu et al., 2001). However, after the intervention ended, MEMS-based adherence decreased while intervention-related improvements in depression remained relatively stable. By way of contrast, our prior study of CBT-AD with depressed HIV-infected participants who were not also struggling with IDU histories and substance dependence showed sustained effects on both adherence and depression, and improvements in viral load over time (Safren et al., 2009). As such, it appears that our intervention was not resilient to the psychosocial challenges magnified by the context of opioid dependence, HIV, and depression. It is not clear which aspect or aspects of substance dependence (e.g., lapses in substance use, neuropsychological impairment, psychosocial stress, schedule disruptions, altered motivation, altered meaning of pill taking, etc.) may have contributed to this loss of efficacy for the adherence but not depression outcomes, and moderators will be explored in future secondary papers. Our findings indicate that, for triply-diagnosed individuals, continued adherence counseling may be necessary to maintain or potentially augment adherence gains, even when depression symptoms improve.

With respect to the depression findings, the average depression score on the MADRS for those in the CBT-AD conditions at baseline was in the range for ‘moderate’ severity and only ‘mild’ at the 12-month follow-up assessment. This 40% decrease in symptoms at post-treatment, which was maintained at 12-months, represents a clinically meaningful reduction (Muller, Himmerich, Kienzle, & Szegedi, 2003; Robertson, 1983).

Differences in viral load did not emerge across the two conditions over time, however, there were differential improvements in CD4 in those who received CBT-AD versus those who received ETAU when statistically controlling for baseline group differences. Although preliminary, this finding is consistent with the results of other HIV-related psychosocial interventions demonstrating that psychosocial interventions can directly improve biological indicators of HIV pathogenesis including CD4 cells counts (Petrie, 2004) and HIV viral load (Antoni et al., 2006). This finding, that there were differences in depression and CD4, but not long-term differences in adherence or viral load, is noteworthy but certainly requires replication. Despite the absence of viral load change, it is possible that our participants still reaped some psychoneuroimmunological benefit due to sustained reductions in depression

as evidenced by an increase in CD4 lymphocyte count over time, which occurred after covarying out baseline differences. The reduction of the immunosuppressive effects of depression-related dysregulation of the catecholaminergic (norepinephrine) or HPA (cortisol) axis may support sustained increases in CD4 cell counts (Leserman, 2003). In fact, Antoni and colleagues (2006) reported that treatment-related decreases in HIV viral load were mediated by reductions in depressed mood. The preliminary finding that treating depression is associated with improved immunity is also consistent with non-interventional studies showing a relationship between depressive symptoms and change in CD4 cells over time (Ickovics et al., 2001; Ironson et al., 2005; Leserman, 2008). Future secondary analyses will examine mediational or other potential pathways with these data. This immunological finding requires replication, as it is possible that there are other explanations for these results, such as regression to the mean after different values at baseline. Additional randomized controlled trials (RCTs) of interventions that improve depression on immunologic outcomes are required to examine this further. With respect to the absence of viral load findings, it is possible that the ability to detect viral load differences was limited due to the relatively low average viral load levels at baseline.

It is noteworthy that prior studies have found short-term ART adherence gains simply as a result of using a MEMS cap for monitoring without additional intervention, gains sometimes lasting up to 40 days (Deschamps, Van Wijngaerden, Denhaerynck, De Geest, & Vandamme, 2006; Wagner & Ghosh-Dastidar, 2002); though our post-treatment outcome assessment target time window was 90 days. Accordingly, it is possible that the first set of MEMS-based adherence assessments (at baseline – first two weeks) represent an improvement over what their true baseline adherence would have been. Hence, decreases in MEMS-based adherence over time to the final follow-up may be due to the waning effects of adherence monitoring with MEMS on adherence over time. The randomized design with the post-treatment outcome being approximately 3 months after randomization (i.e., more than 40 days), showed differences between the intervention and comparison conditions at post-treatment, indicating that it is unlikely that there would be a difference in a sensitization effect to MEMS-based adherence across the two study conditions.

There were 8 out of 44 individuals lost to follow-up in the CBT-AD condition and 15 out of 45 from the ETAU condition. Although this was not statistically significant, it raises an issue that may be common to adherence interventions. More specifically, if depression is associated with adherence, and those who are adherent to study participation are more likely to also be adherent to HIV medications, it is possible that attrition is associated with poorer adherence and more severe depression. In this scenario, the actual treatment effect would be greater than what was observed because the control participants who dropped out would be those with worse depression and adherence. Conversely, it is also possible that control participants who dropped out did so because they did not perceive benefit from participation in the study. Our clinical experience meeting with these participants, however, suggests that that the latter was not the case.

There are several additional limitations to the present study that should be noted. First, although MEMS are an objective indicator of adherence, it is possible that adherence was underestimated if the MEMS cap was not used. Accordingly, we asked participants at each assessment whether they recalled taking pills without using the cap and used a corrected adherence score (Liu et al., 2001; Liu et al., 2006; Llabre et al., 2006). Second, as part of a program of research to test a treatment, and to examine whether treating depression is necessary to benefit from an adherence intervention before trying to dismantle the “active ingredients,” the comparison group was not attention-matched. Although CBT-AD and ETAU participants came for the same number of visits and had the same incentive payments, we do not know if the positive acute adherence outcomes are related to specific

elements of CBT-AD beyond the Life-Steps adherence counseling. Third, despite procedures to ensure confidentiality, we discovered that individuals in methadone treatment centers may have been reluctant to refer themselves to the study due to the fear of having their HIV status "outed". Recruitment efforts that were expanded to address this barrier threatened internal validity, but this concern was balanced by achieving greater participant heterogeneity and therefore generalizability. Fourth, the participant incentives may have driven participation, and generalization of findings to opioid-stabilized patients who are less likely to come for such counseling may be limited. Fifth, we had hoped for a sample size of 100, and only 89 could be randomized due to the complexities of recruitment. Finally, given the complexity of the population, monitoring fidelity to the intervention was a work-in-progress throughout the study. Accordingly, by the later half of the study we had developed a fidelity monitoring checklist that allowed for therapist flexibility when emergent life-events would occur, with the ability to change the order of modules and/or utilize the treatment module most relevant to an emergent concern when it would occur. While this can be seen as a threat to internal validity, it conversely increases the external validity of the intervention as this is what clinicians would likely do in real-world clinical practice.

Future research should examine the cost-effectiveness of the intervention as part of a larger effectiveness trial involving substance abuse treatment programs that have high numbers of HIV-infected patients in their practice base. Accordingly, if substance abuse counselors or less trained interventionists could integrate this intervention into their current counseling, there would not be incremental costs, and adherence counseling could be maintained, potentially allowing for sustained benefits.

The findings, however, suggest that CBT-AD is a potentially useful strategy for increasing adherence and decreasing depression in HIV-positive patients with a history of IDU who are in substance abuse treatment. Adherence gains were only present during the time that the treatment was ongoing, suggesting that booster, additional, or continued adherence counseling sessions may be needed to sustain improvements in adherence outcomes in this population of individuals struggling with multiple comorbidities. It appears that this intervention, integrated into substance use counseling in methadone or other drug treatment programs, would be beneficial for individuals with HIV and substance abuse disorders. For depression, this intervention resulted in sustained improvement, and CD4 cell counts increased in the CBT-AD condition compared to the control condition over time. Whereas prior studies have found correlational associations of depression to CD4, this is the first study to suggest a possible effect when depression was successfully treated.

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We thank the anonymous reviewers for suggesting that we control for CD4 in all outcome analyses, as CD4 differed in magnitude between study arms. Analyses were initially conducted without controlling for baseline CD4, and the pattern of results was the same when controlling for and when not controlling for CD4 in these analyses.

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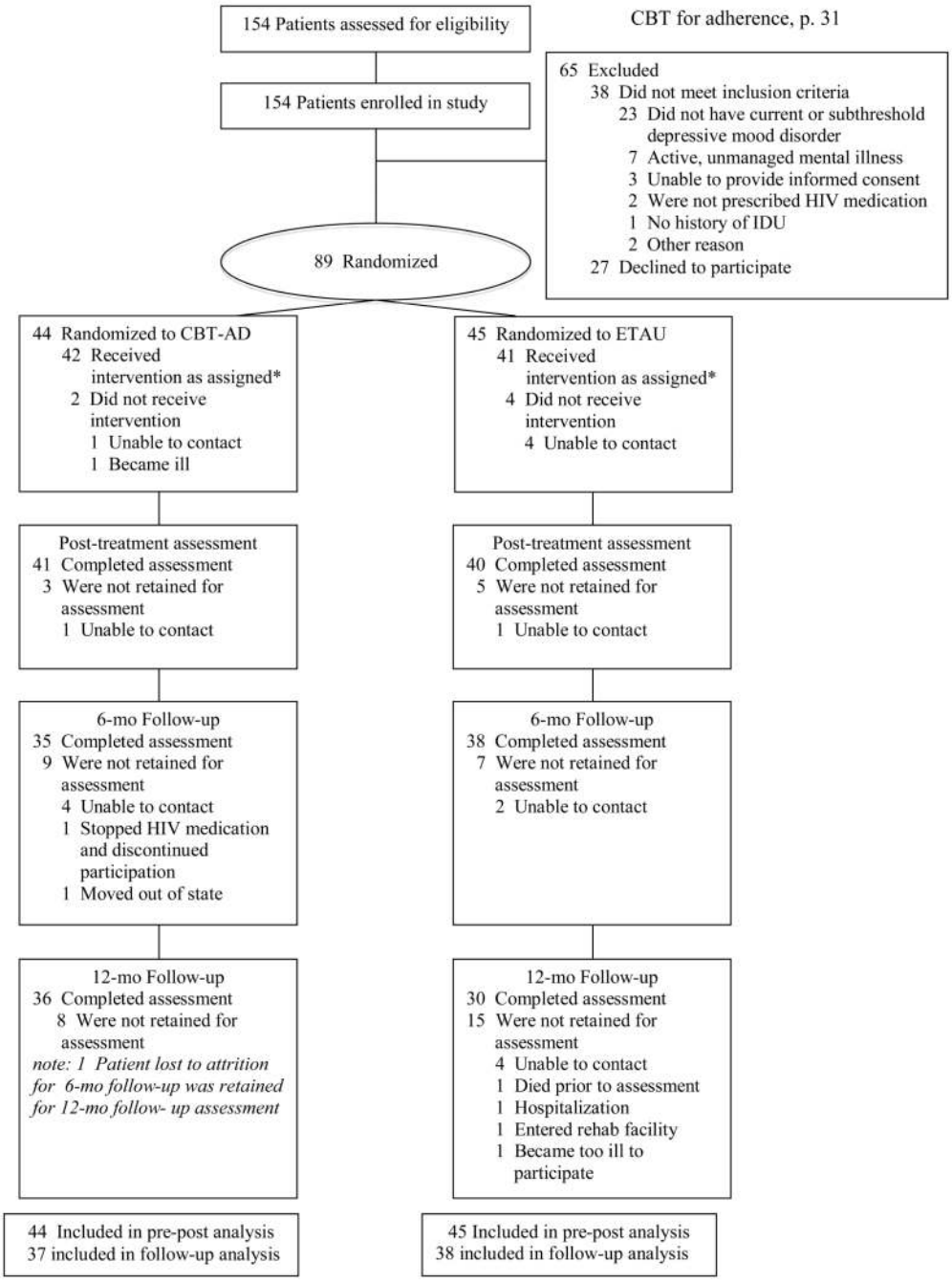

Figure 1.
CONSORT participant flow chart

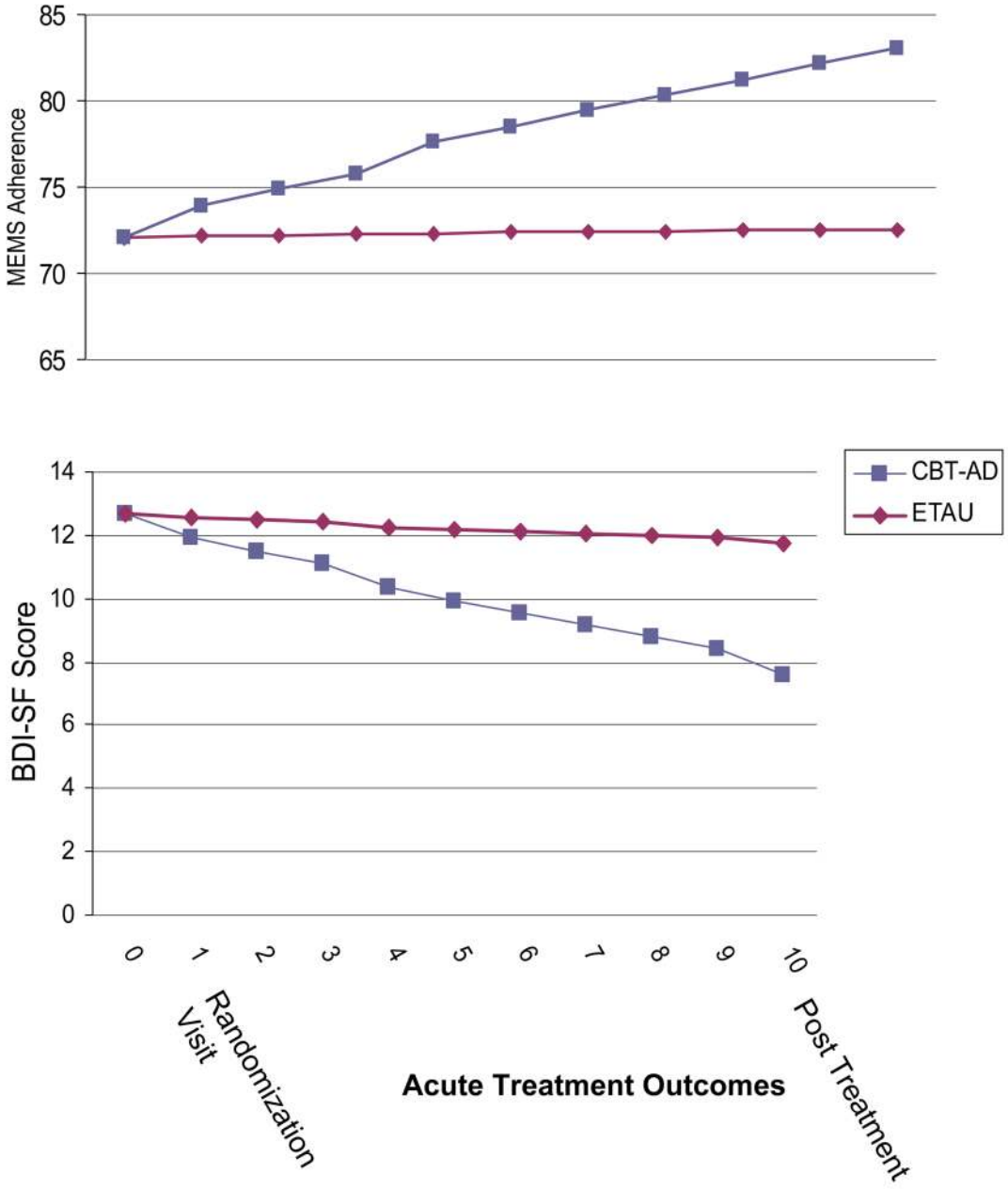

Figure 2.

Pre-Post Outcomes: Longitudinal (HLM) Analysis of MEMS-based adherence and Depression (BDI-SF)

Note. CBT-AD = Cognitive Behavioral Therapy for Adherence and Depression; ETAU = Enhanced Treatment as Usual; MEMS = Medication Event Monitoring System; BDI = Beck Depression Inventory - Short Form. Data points are adjusted scores using MEMs-based adherence and BDI-SF scores for the time since prior visit.

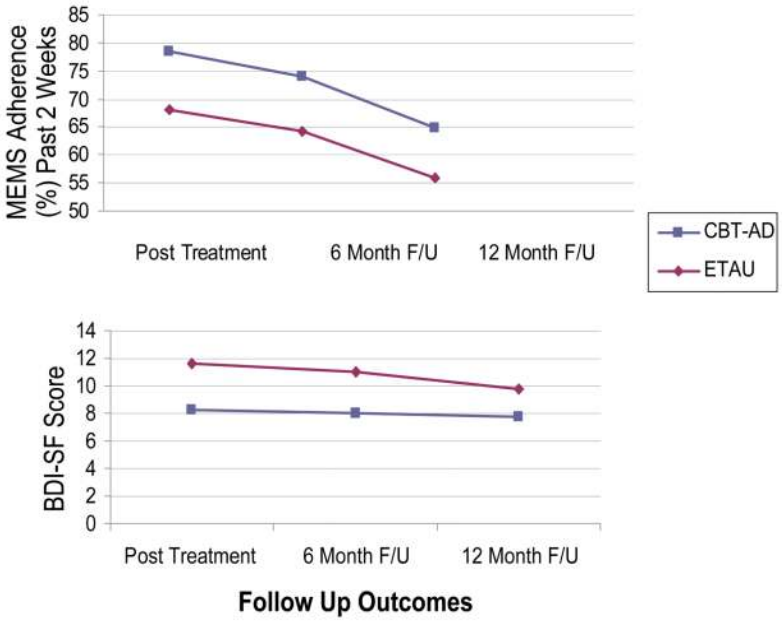

Figure 3.

Follow-up Outcomes: Analysis of MEMS-based Adherence and Depression (BDI-SF)

Note. CBT-AD = Cognitive Behavioral Therapy for Adherence and Depression; ETAU = Enhanced Treatment as Usual; BDI-SF = Beck Depression Inventory - Short Form. Follow-up outcomes used HLM adjusted scores for prior two weeks MEMs-based adherence.

TABLE 1

Sociodemographic Characteristics of Participants

Variable	N	%
Gender		
Male	54	61
Female	35	39
Race		
African American/Black	26	33
White	38	48
Native American	2	3
Ethnicity		
Hispanic or Latino	23	30
Sexual Orientation		
Exclusively heterosexual	60	79
Bisexual	5	7
Exclusively homosexual	2	3
Employment		
Full-time work or school	3	4
Part-time work or school	8	10
Neither work nor school	17	22
On disability	53	67
Education Level		
Eighth grade or lower	12	15
Partial high school	21	26
High school graduate/GED	23	29
College graduate	6	8
Psychiatric Comorbity		
At least one additional DSM-IV diagnosis	55	62
Two or more additional DSM-IV diagnoses	37	42
Additional DSM-IV Diagnoses		
Panic Disorder	17	30
Generalized Anxiety Disorder	10	18
Social Anxiety Disorder	8	14
	M	**SD**
Age	46.85	7.15

Note. Percentages do not always add up to 100 due to overlap or some participants reporting more than one demographic category.

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TABLE 2

Unadjusted Mean Descriptive Scores for Outcomes Across Conditions and Time

	Baseline	3 Month	6 Month	12 Month
Adherence (past 2 weeks)				
CBT-AD	63.73 (27.97)	79.02 (23.23)	65.65 (32.57)	64.49 (31.34)
ETAU	74.18 (25.77)	73.66 (25.15)	63.90 (30.81)	61.11 (34.94)
MADRS				
CBT-AD	25.75 (10.33)	17.02 (10.62)	17.40 (11.10)	15.28 (9.22)
ETAU	25.40 (10.05)	22.70 (10.19)	22.45 (10.03)	20.00 (10.97)
CGI				
CBT-AD	4.39 (1.30)	2.76 (1.53)	3.11 (1.32)	2.58 (1.08)
ETAU	4.33 (1.38)	3.85 (1.25)	3.76 (1.36)	3.37 (1.35)
BDI				
CBT-AD	13.05 (6.54)	8.70 (7.31)	8.24 (5.87)	7.03 (5.68)
ETAU	12.38 (7.41)	11.71 (7.88)	9.94 (7.08)	9.83 (7.29)
Log Viral Load				
CBT-AD	2.387 (0.917)	2.349 (0.928)	3.458 (1.242)	2.203 (0.687)
ETAU	2.229 (0.749)	2.044 (0.509)	2.894 (1.401)	2.177 (0.820)
% (n) with suppressed PVL				
CBT-AD	65.12% (28)	73.68% (28)	67.65% (23)	73.53% (25)
ETAU	77.27% (34)	84.62% (33)	82.35% (28)	74.19% (23)
CD4				
CBT-AD	375.57 (212.40)	380.97 (266.62)	386.61 (235.38)	452.94 (235.00)
ETAU	524.42 (289.65)	539.29 (293.61)	539.50 (293.61)	502.33 (314.19)

Note. CBT-AD = Cognitive Behavioral Therapy for Adherence and Depression; ETAU = Enhanced Treatment as Usual; MADRS = Montgomery-Asberg Depression Rating Scale; BDI = Beck Depression Inventory; CGI = Clinical Global Impression Score.