Forty-Eight Week Outcomes of a Site-Randomized Trial of Combined Cognitive Behavioral Therapy and Medication Management Algorithm for Treatment of Depression Among Youth With HIV in the United States

Larry K. Brown, MD,a,b Kristin Baltrusaitis, PhD,c Betsy D. Kennard, PsyD,d Graham J. Emslie, MD,d Miriam Chernoff, PhD,c Sarah Buisson, MSW, MPH,e Kathryn Lypen, MPH,f Laura B. Whiteley, MD,b Shirley Traite, MSW,g Chelsea Krotje, MPH,f Kevin Knowles, PhD,f Ellen Townley, MSN, FNP,f Jaime Deville, MD,h Megan Wilkins, PhD,i Dan Reirden, MD,j Mary Paul, MD,k Christy Beneri, DO,l and David E. Shapiro, PhD,c for the IMPAACT 2002 Team

Background: Studies suggest that manualized, measurement-guided, depression treatment is more efficacious than usual care but impact can wane. Our study among youth with HIV (YWH), aged 12–24 years at US clinical research sites in the International Maternal Pediatric Adolescent AIDS Clinical Trials Network, found a significant reduction in depressive symptoms among YWH who received a manualized, measurement-guided treatment. This paper reports outcomes up to 24 weeks after the intervention.

Methods: Eligibility included diagnosis of ongoing nonpsychotic depression. Using restricted randomization, sites were assigned to either combination cognitive behavioral therapy and medication management algorithm tailored for YWH or to enhanced standard of care, which provided psychotherapy and medication management. Site-level mean Quick Inventory for Depression Symptomatology Self-Report (QIDS-SR) scores and proportion of youth with treatment response (>50% decrease from baseline) and remission (QIDS-SR ≤ 5) were compared across arms using t tests.

Results: Thirteen sites enrolled 156 YWH, with baseline demographic factors, depression severity, and HIV disease status comparable across arms. At week 36, the site-level mean proportions of youth with a treatment response and remission were greater at combination cognitive behavioral therapy and medication management algorithm sites (52.0% vs. 18.8%, P = 0.02; 37.9% vs. 19.4%, P = 0.05) than at usual care sites (58.7% vs. 33.4%, P = 0.047). At week 48, the site-level mean proportion with a treatment response remained significantly greater (58.7% vs. 33.4%, P = 0.047).

Conclusions: The impact of manualized, measurement-guided cognitive behavioral therapy and medication management algorithm tailored for YWH that was efficacious at week 24 continued to be evident at weeks 36 and 48.

Key Words: major depressive disorder, cognitive behavioral therapy, antidepressants, adolescents, human immunodeficiency virus

(J Acquir Immune Defic Syndr 2022;91:296–304)
as 25% in the United States (US).1–5 Depression reduces adherence to antiretroviral treatment (ART), increases risk of disease progression, increases caregiver burden, increases health care costs, and decreases quality of life.5–8 Thus, treatment of depressive disorders is essential for improving both psychiatric and medical outcomes for YWH, especially given that ART adherence dramatically increases life expectancy.3,5

Prior studies indicate that selective serotonin reuptake inhibitors (SSRIs) are generally safe and effective in the treatment of depression in adults with HIV.9,10 and that these treatments not only improve depression outcomes, but also lead to greater ART adherence and increased CD4 T-cell counts.5 Several psychotherapies, including cognitive behavioral therapy (CBT), are effective in treating depression, but therapy needs to be tailored to the unique concerns of YWH such as chronic illness management, transition to adult care, inter-related psychosocial factors, cultural and sexual diversity, and internalized and enacted stigma.11–18 Practice guidelines, including for those with HIV, suggest that a combination of medication management and an evidence-based psychotherapy, such as CBT, show a greater reduction in depressive symptoms than a single treatment modality (ie, either psychotropic medication or CBT).19–22 CBT may be particularly helpful at improving treatment adherence.15,23 Other studies show that measured care treatment (care decisions guided by measures of symptomatology) is more effective than care not guided by measured assessments.24–26

The long-term outcomes of adolescents and adults treated for depression have varied across studies. The STAR*D trial for depressed adult outpatients reported a 67% cumulative remission rate at the 12-month naturalistic follow-up.24 In another adult study of depressed inpatients, 55% were in remission at 48 weeks.27 In the Treatment of Adolescents with Depression Study, the response and remission rates at 48 weeks were 74% and 64%, respectively.28 However, nearly a third of Treatment of Adolescents with Depression Study participants had lost remission status in the next 9 months.28 A lack of response to treatment in adolescents has been associated with greater baseline depression severity, substance abuse, and psychosocial dysfunction, as well as residual symptoms after acute treatment.25,29,30

We previously reported the results through week 24 of our site-randomized trial of a 24-week, combination CBT and medication management algorithm (MMA) (COMB-R) tailored for YWH compared with enhanced standard of care (ESC), which provided the clinic’s routine psychotherapy and medication management.31 At week 24, youth at COMB-R sites, compared with ESC sites, reported significantly fewer depressive symptoms on the Quick Inventory for Depression Symptomatology Self-Report (site-level mean QIDS-SR score 6.7 vs. 10.6, P = 0.01), a greater mean proportion had a treatment response (62.3% vs. 17.9%, P < 0.001), and a greater mean proportion were in remission (47.9% vs. 17.0%, P = 0.01). The site-level mean HIV viral load (VL) and CD4 T-cell level were not significantly different between arms at week 24. The objective of this paper is to assess whether differences in treatment outcome measures are maintained at 12 and 24 weeks after the study’s treatment ended (ie, week 36 and week 48 from study entry).

### METHODS (PREVIOUSLY REPORTED AND SUMMARIZED BRIEFLY BELOW)

#### Participants

YWH were eligible if they were aged 12–24 years, engaged in care at a participating International Maternal Pediatric Adolescent AIDS Clinical Trials Network site, had documented HIV-1 confirmed by medical records, had a diagnosis of nonpsychotic depression (either major depressive disorder, depression not otherwise specified, or dysthymia/persistent depressive disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition), had significant symptomatology at entry (as defined by a Quick Inventory of Depressive Symptomatology—Clinician score ≥ 11), were aware of their HIV status as determined by site staff, were English-speaking, and were able and willing to provide written informed assent/consent and written parental or guardian permission (if required by state law and/or institutional review board). YWH were excluded if they had a history of any psychotic disorders or bipolar I or II disorder, had a diagnosis of substance dependence according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition or had moderate symptoms and were experiencing withdrawal or dependence symptoms within the month before enrollment, had symptoms requiring more intensive treatment than the study provided or at immediate risk of being a danger to themselves or others, intended to relocate from the study site within the next 12 months, or were in treatment with a nonstudy clinician (unless willing to switch to a study-trained clinician).

#### Sites and Randomization

Sites in the US were eligible if they had a medication prescriber, a therapist, and the ability to recruit at least 8 English-speaking participants. Participating sites were randomly assigned to either COMB-R or ESC using a restricted randomization procedure to minimize imbalance in participant characteristics between treatment arms. Randomization at the site level was chosen to avoid loss of fidelity or cross-talk that could occur if therapists and medication prescribers at the same site were delivering both ESC and COMB-R. Details of the randomization and enrollment process have been previously described.31 The study protocol was approved by the Institutional Review Boards at all sites.

#### The Combined Treatment (MMA and CBT) Intervention (COMB-R)

The MMA, developed for the previous study and its pilot intervention (details in references 31, 32), was based on previously used algorithms.24–26 The MMA specified the order, length of time, and doses of antidepressant medications at each stage, taking into consideration psychotropic medication history and measurement of current symptoms. It included considerations such as drug–drug interactions and side effects. If measured symptoms indicated only partial or no improvement, doses may have been increased, other medicines added, or treatment could progress to the next
stage. The first 2 stages of the MMA were an SSRI antidepressant, and the third stage was a non-SSRI antidepressant. Staging and augmentation strategies were based on data from randomized trials and expert consensus.24–26

Because CBT decreases negative mood and unhealthy cognitions, while enhancing strengths, positive experiences, and healthy cognitions,33 CBT was adapted for YWH to address factors such as physical symptoms related to diagnosis/treatment, transition from pediatric to adult care, poverty, stigma, and alienation from families. It was informed by motivational interviewing to engage participants.12,16–18,34 The development and feasibility of the manual for YWH was described previously.12,16–18,34 CBT comprised 3 stages of treatment: (1) psychoeducation and motivation for treatment—addresses the psychosocial stresses of HIV infection and treatment of current depressive symptoms; (2) reducing depressive symptoms—teaches core skills of mood monitoring, behavioral activation, reducing negative thinking, and problem solving; (3) achieving and maintaining wellness—identifies strengths and techniques to continue wellness.

All participating sites had a therapist and medication prescriber who participated in training before study initiation. COMB-R therapists received a 4-hour group videoconference training which included review of the CBT manual and skills training. Videotaped illustrative sessions were viewed and discussed, as were clinical vignettes. Medication prescribers received a 2-hour group video training that included instructions, review of the MMA, and discussion of strategies for integration of depression symptom assessments into medication management decisions. To reduce implementation burden, COMB-R therapists and medication prescribers had access to, but were not required to attend, monthly group supervision calls to discuss cases with members of the core protocol team. The initial online trainings were recorded, and materials and videos were preserved to train new staff. COMB-R therapists and medication prescribers were able to access the materials for refresher training, as needed.

**ESC Intervention**

The ESC arm was “enhanced” as ESC site clinicians received a 2-hour training developed by investigators on current principles for the use of medication and on psychotherapy for depression. The webinar-based training, available as a refresher, did not provide details on the MMA or the CBT used in COMB-R treatment.

**Trial Procedures**

Throughout the study follow-up, participants at both COMB-R and ESC sites completed assessments through an audio computer-assisted self-interview or on paper at the required baseline and weeks 1, 6, 12, 24, 36, and 48 study visits. The baseline assessment included demographic information. Clinical and virologic data, such as quantitative VL, medication usage, and clinic visits, were abstracted from medical records.

**Outcome Measures**

**Depressive Symptoms**

Participants completed the QIDS-SR, a 17-item scale assessing 9 depressive symptoms in the past 7 days. QIDS-SR is a reliable and valid measure of depression in adults and adolescents.35,36 Total scores range from 0 to 27. Scores of 6–10 reflect mild symptoms, 11–15 moderate symptoms, and ≥16 severe symptoms. Using the QIDS-SR score, response to treatment (defined as >50% decrease in the QIDS-SR score from baseline) and remission from depression (defined as the QIDS-SR score ≤5) were calculated.

**HIV-Related Laboratory Measures**

Quantitative VL (copies/mL) and CD4 T-cell count (cells/μL) were abstracted from the medical records at baseline and weeks 24 and 48, if obtained within the visit window (±14 days); otherwise blood was obtained. Viral suppression was defined as VL < 40 copies/mL, generally the lower level of detection at participating laboratories. Stage 3 HIV infection was defined as CD4 T-cell count <200 cells/μL.

**Medication Use, Visit Attendance, and Safety Events**

Current prescription of any antidepressant medication (and the specific medication) and attendance at weeks 36 and 48 were abstracted from medical or study records. Safety outcome measures included new (postentry) grade 3 or higher signs and symptoms, grade 3 diagnoses, suicide attempts, and psychiatric hospitalizations.37

**Data Analysis**

Because sites were randomized instead of participants, site-level analyses were conducted by calculating summary measures for each site [the mean for continuous outcome measures (eg, QIDS-SR) and the percentage for dichotomous outcomes (eg, remission and viral suppression)] and differences between arms were assessed using t tests at weeks 36 and 48.38 Site-level analyses were also used to compare baseline characteristics across arms. To facilitate these analyses, several baseline characteristics (eg, depression, biological outcomes, and safety outcomes) were dichotomized. For nadir CD4 T-cell count, we applied the Centers for Disease Control and Prevention–specified age-based criteria for the HIV infection table.39 Safety data assessed the occurrence of new grade 3 or higher signs and symptoms, diagnoses, and the occurrence of psychiatric hospitalization or suicide attempt before week 36 and before week 48. Data were included if collected within 30 days before or after the projected study week. In general, statistical tests were 2-sided with a P value <0.05 considered to be statistically significant, and there were no adjustments for multiple testing. SAS software v9.4 (SAS Institute, Cary, NC) was used for analysis.

Given the small numbers of sites per arm, the Wilcoxon rank-sum test, a nonparametric test that does not rely on a normality assumption, was performed as a sensitivity analysis.38 Additional sensitivity analyses were performed after
excluding 2 sites in the ESC arm with low accrual (2 and 5 participants). To assess the potential impact of missing data on conclusions, QIDS-SR outcome measures were reanalyzed after singly imputing missing data using 2 methods: (1) imputing missing values with a series of site-level percentiles according to the intervention arm, assigning the “better” percentiles to the ESC arm and the “worse” percentiles to the COMB-R arm (“percentile imputation”) and (2) using patterns of data at prior study visits to randomly select the imputed values (“past pattern imputation”).

RESULTS
Seventeen of 21 International Maternal Pediatric Adolescent AIDS Clinical Trials Network-funded US sites were applied for participation. Of these, 14 sites were chosen (Fig. 1). Six COMB-R and 7 ESC sites enrolled 156 YWH between March 2017 and March 2019, with a median (range) of 13 per site (2–16). One COMB-R site, concerned about recruiting sufficient participants, withdrew after randomization but before enrollment. The final assessment was completed on January 21, 2020, and data for these analyses were retrieved on December 7, 2020.

At baseline, site-level analysis showed no significant differences between arms on demographic factors, severity of depression, or HIV disease status (Table 1). The average of the mean participant age of all sites was 21.4 years (21.8% ≥18 years); 44.7% were male, 60.7% were Black, 52.9% had acquired HIV through perinatal transmission, 47.7% had severe depressive symptoms (Quick Inventory of Depressive Symptomatology-Clinician ≥16), 24.5% were prescribed psychiatric medication, nearly all were prescribed ART (92.5%), and 57.5% were virally suppressed.

At week 48, most participants were retained on study [136 (87.2%) participants]. The QIDS-SR score was available for 127 (81.4%) participants, and CD4 count and VL were available for 129 (82.7%) participants.

Depressive Symptom Outcome Measures
Week 36
The site-level mean proportion of youth with a treatment response was significantly greater in the COMB-R arm compared with the ESC arm (52.0% vs. 18.8%, \( P = 0.015 \)), and a greater site-level mean proportion of youth had remission of symptoms in COMB-R (37.9% vs. 19.4%,
**TABLE 1. Site-Level Baseline Characteristics by the Treatment Arm**

| Characteristic                        | COMB-R (N = 6) | ESC (N = 7) | *P*† |
|---------------------------------------|---------------|-------------|------|
| % Male                                | 44.9 (24.4)   | 44.6 (24.5) | 0.98 |
| Mean age (yrs) at entry               | 21.5 (0.6)    | 21.3 (1.8)  | 0.74 |
| % Younger (12–18 yrs)                 | 17.1 (11.0)   | 25.8 (28.3) | 0.50 |
| % Black                               | 65.1 (40.0)   | 57.0 (32.6) | 0.69 |
| % With perinatal transmission        | 49.1 (26.3)   | 56.2 (21.1) | 0.61 |
| Mean QIDS-C‡‡                         | 16.6 (1.4)    | 15.1 (2.0)  | 0.15 |
| Mean ordinal QIDS-C§                  | 3.7 (0.4)     | 3.5 (0.3)   | 0.25 |
| % With severe QIDS-C‡‡                | 53.8 (21.9)   | 42.6 (32.3) | 0.49 |
| Mean QIDS-SR†§                        | 16.2 (1.3)    | 14.5 (3.2)  | 0.26 |
| Mean ordinal QIDS-SR§                 | 3.6 (0.3)     | 3.3 (0.8)   | 0.35 |
| % With severe QIDS-SR§                | 55.2 (16.5)   | 39.3 (32.0) | 0.30 |
| Mean log10 RNA/mL                    | 2.2 (0.7)     | 2.1 (0.3)   | 0.82 |
| % With viral suppression (<40 copies/mL) | 59.1 (27.3) | 56.2 (10.0) | 0.81 |
| Mean CD4 count/µL                    | 679.2 (150.7) | 704.7 (203.8)| 0.81 |
| % With stage 3 CD4 count (<200 cells/µL) | 9.8 (11.4)  | 7.9 (9.9)   | 0.76 |
| % With stage 3 nadir CD4 count| 28.3 (23.1)   | 25.7 (21.1) | 0.83 |
| % With stage 3 CDC class              | 20.3 (29.1)   | 22.0 (21.5) | 0.91 |
| % On ARVs                             | 93.2 (6.7)    | 92.0 (18.7) | 0.88 |
| % On integrase inhibitors‡            | 73.8 (15.7)   | 66.6 (32.1) | 0.63 |
| % On psychiatric medications#        | 28.0 (13.2)   | 21.4 (19.0) | 0.49 |
| % On 2 or more psychiatric medications#| 30.0 (20.0)  | 44.8 (42.2) | 0.45 |
| % On antidepressant medications       | 25.2 (9.8)    | 21.4 (19.0) | 0.67 |
| % On SSRI antidepressant medications  | 20.3 (10.5)   | 15.8 (16.8) | 0.58 |

*For dichotomous variables, summaries are mean (SD) of site-specific percentages.
†P value based on t test with equal or unequal variances, as appropriate based on F tests.
‡QIDS-C and QIDS-SR are scored from 0 to 27 with a higher score indicating greater symptom severity: 0–5 not depressed, 6–10 mild, 11–15 moderate, 16–20 severe, and 21+ very severe.
§Mean ordinal QIDS-C and QIDS-SR measures are ranked from 1 to 5 (none to 5 not depressed, 6–10 mild, 11–15 moderate, 16–20 severe, and 21+ very severe).
¶Denominator for the percent of participants on integrase inhibitors is the number on any ARV.
#Denominator for the percent of participants on 2 or more psychiatric medications is the number on any psychiatric medication.
ARV, antiretroviral; CDC, Centers for Disease Control and Prevention; QIDS-C, Quick Inventory of Depressive Symptomatology-Clinician.

P = 0.05). The site-level mean QIDS-SR was lower at COMB-R sites compared with ESC sites (mean score 7.45 vs. 9.75, P = 0.05, Table 2; Figs. 2 and 3).

**Week 48**

The site-level mean proportion of youth with a treatment response was greater in the COMB-R arm compared with the ESC arm (58.7% vs. 33.4%, P = 0.047). While COMB-R arm improvements in remission and reduction in depressive symptoms were generally maintained, ESC arm outcomes continued to improve, with differences no longer statistically significant (remission: 43.7% vs. 27.5%, P = 0.24; mean QIDS-SR score: 7.09 vs. 9.08, P = 0.14, Table 2; Figs. 2 and 3; Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/B939). Results were similar in nonparametric analyses, and similar trends were observed in the sensitivity analyses that excluded low enrolling sites (data not shown).

For missing data sensitivity analyses, the percentile imputation analyses that use median imputation and the imputation using prior patterns of data show similar results (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B939, which shows the results of the singly imputed percentile analysis of QIDS-SR measures at week 48; Table S2, Supplemental Digital Content, http://links.lww.com/QAI/B939, which shows the results of imputing missing week 48 values based on prior patterns of observed data).

**HIV-Related Laboratory Outcome Measures**

The site-level mean log10 RNA VL (2.12 copies/mL for COMB-R and 2.09 copies/mL for ESC) and the mean proportion of participants with viral suppression (64.1% for COMB-R and 57.6% for ESC) were not significantly different between intervention arms at week 48 in parametric (Table 2) and nonparametric analyses and sensitivity analyses (data not shown). The same was true for the site-level mean CD4 T-cell counts (698 copies/µL for COMB-R and 660 copies/µL for ESC) and the mean proportion with CD4 T-cell counts less than 200 (8.0% for COMB-R and 10.5% for ESC) at week 48.

**Medication Use and Visit Attendance**

At week 48, a site-level mean proportion of 39.0% of youth at COMB-R sites were prescribed an antidepressant medication vs. 32.9% at ESC sites (P = 0.58). The use of an SSRI was not significantly greater at COMB-R sites than at ESC sites (34.1% vs. 20.8%, P = 0.20). There was no significant difference in site-level means in attendance at the required study visits and any interim visits (eg, counseling sessions) over the 48 weeks (14.5 visits for COMB-R and 11.9 visits for ESC, P = 0.30). Attendance at interim visits after week 24 was not recorded.

**Safety Events**

On average by site, between 13% and 20% of participants experienced a grade 3 or higher sign, symptom, or diagnosis after baseline. Five participants in COMB-R and 4 participants in ESC experienced a psychiatric hospitalization or suicide attempt over the 48 weeks, which was not significantly different between arms (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/B939, results of the safety analysis).

**DISCUSSION**

This rigorously designed study with high retention demonstrates that manualized CBT and medication algorithms guided by symptom measurement for depression in YWH continues to have an impact after the intervention...
The intervention’s impact was stable: COMB-R sites’ average proportion with a treatment response at weeks 24 and 48 was 62% and 59%, respectively; the average proportion in remission was 48% and 44%. The proportion in remission during the follow-up period is comparable with those observed in other studies of outpatient treatment for youth and adults.24,27,28,30 A continued remission from or response to treatment of depression is important because it is associated with better psychosocial functioning, better physical health, and fewer behavioral problems, such as substance misuse.30,40 This combined CBT and MMA intervention delivered in HIV medical care clinics delivered by existing staff demonstrates continuing impact. These results suggest feasibility in clinic settings because existing staff can deliver these interventions successfully after a short videoconference training and with availability of monthly telephone supervision. Of note, the intervention impact was achieved without increasing the burden on patients by additional clinic visits.

There was also evidence of continued improvement of depression in the ESC sites, compared with stability of COMB-R outcomes. For example, mean depression remission proportions at ESC increased from 17% at week 24 to 28% at week 48, whereas COMB-R remained at 44%. There are several possible reasons for the continued improvement in ESC. Patients in ESC received care at centers with special expertise in HIV and access to ongoing mental health treatment. In addition, the study included quarterly self-report assessments of their depressive symptoms, which may have influenced participant’s awareness of their symptoms and functioning. In addition, factors outside of treatment may

### TABLE 2. Between Arm Differences in Site-Level Depressive Symptom and HIV-Related Laboratory Outcome Measures

| Week | Outcome Measure | COMB-R (N = 6) | ESC (N = 7) | Mean Difference (95% CI)* | P† |
|------|-----------------|---------------|------------|---------------------------|----|
| 36   | Mean QIDS-SR‡   | 7.45 (5.33 to 9.57) | 9.75 (8.10 to 11.39) | -2.30 (-4.62 to 0.02) | 0.052 |
|      | % With QIDS-SR response§ | 52.0 (23.8 to 80.2) | 18.8 (6.2 to 31.5) | 33.1 (7.8 to 58.5) | 0.015 |
|      | % With QIDS-SR remission¶ | 37.9 (17.4 to 58.4) | 19.4 (10.0 to 28.8) | 18.4 (-0.1 to 37.0) | 0.051 |
| 48   | Mean QIDS-SR‡   | 7.09 (5.05 to 9.13) | 9.08 (6.79 to 11.36) | -1.99 (-4.74 to 0.76) | 0.14 |
|      | % With QIDS-SR response§ | 58.7 (38.7 to 78.7) | 33.4 (13.8 to 53.0) | 25.3 (0.5 to 50.0) | 0.047 |
|      | % With QIDS-SR remission¶ | 43.7 (20.3 to 67.1) | 27.5 (5.2 to 49.8) | 16.3 (-12.3 to 44.8) | 0.24 |
|      | Mean log10 RNA VL (copies/mL) | 2.12 (1.44 to 2.80) | 2.09 (1.45 to 2.73) | 0.03 (-0.80 to 0.85) | 0.95 |
|      | % With viral suppression (<40 copies/mL) | 64.1 (40.8 to 87.5) | 57.6 (32.0 to 83.2) | 6.5 (-24.5 to 37.5) | 0.65 |
|      | Mean CD4 count (copies/µL) | 698 (494 to 902) | 660 (502 to 819) | 37 (-186 to 261) | 0.72 |
|      | % With CD4 ≥ 200 copies/µL | 92.0 (78.3 to 100.0) | 89.5 (78.8 to 100.0) | 2.4 (-12.5 to 17.4) | 0.73 |
|      | % With CD4 < 200 copies/µL | 8.0 (0.0 to 21.7) | 10.5 (0.0 to 21.2) | -2.4 (-17.4 to 12.5) | 0.73 |

*For dichotomous variables, summaries are mean (95% CI) of site-specific percentages. †P value based on t test with equal or unequal variances, as appropriate based on F tests. ‡QIDS-SR is scored from 0 to 27 with a higher score indicating greater symptom severity: 0–5 not depressed, 6–10 mild, 11–15 moderate, 16–20 severe, and 21+ very severe. §A participant had a QIDS-SR response if their score decreased by more than 50% from baseline. ¶Remission was defined as a score ≤5.
have led to the improvement for some at ESC sites. The overall impact of COMB-R remained stable but did not improve over the 24-week post-treatment follow-up period, despite continued care offered at the sites. It is possible that the rates of remission and response observed are the best possible outcomes using tailored CBT and antidepressant medication for patients with the complex challenges of HIV infection, depression, and numerous psychosocial issues. In addition, a study examining relapse prevention of depression in youth found that 96% of those who remitted, did so by week 30, suggesting that continued treatment by the same modality may not bring further improvement. In addition, some aspects of COMB-R believed to be crucial to its impact may have been difficult to maintain. For example, self-report of symptoms with a standard checklist at regular intervals (ie, measured care) guided treatment, but it may not have become integrated into the functioning of the clinic. In addition, the opportunity for monthly supervision of CBT and the MMA had stopped and may have resulted in a loss of fidelity to the tailored manuals. Further studies are needed to examine these issues.

Despite nearly all youth being prescribed ART at baseline, less than two-thirds were virally suppressed. The suppression levels and CD4 T-cell counts did not change significantly over 48 weeks and were unrelated to the treatment condition. The lack of COMB-R’s impact on health indices may reflect the multitude of barriers to ART adherence for YWH, of which, depressive symptoms are just one. Economic hardships, limited employment and occupational opportunities, racial and sexual stigma, and social/family stressors all influence ART adherence. Amelioration of depressive symptoms are unlikely to immediately change these chronic issues, and they were not assessed in this project. Patients may need more time to apply their CBT skills, which have effectively reduced their depressive symptoms, to improve ART adherence and alleviate other stressors. For example, shame about HIV infection and annoyance about taking medications daily could be reduced with cognitive reframing. Furthermore, adherence might have improved had the ART adherence component been delivered throughout treatment, rather than only at the beginning. Structural changes may be needed (eg, improved economics, biomedical agents such as long-acting ART) in conjunction with continued remission from depression, to allow for increased ART adherence.

Despite the strengths of this study, there are a number of limitations. The sample was recruited from HIV clinical care sites, so results may not be generalizable to all YWH. While the rigorous design of the site-randomized trial balanced participant demographic characteristics, other site-specific characteristics of participants and staff may have contributed to the outcomes, such as inherent differences in skill or impact of clinicians. Depression was only assessed with the QIDS, and measures of other relevant constructs, such as hopelessness, may have revealed additional intervention impacts. In addition, the study did not collect data on the exact nature of the psychotherapies used in either arm after 24 weeks, so fidelity to the manuals in COMB-R or changes in strategies in ESC cannot be assessed. Finally, there were no adjustments for multiple testing for these secondary analyses (the week 24 QIDS-SR score analysis was the prespecified primary analysis). Interpretation of results focused on effect sizes and consistency of results across analyses.

This study examined the longer-term impact of a 24-week combined CBT and stepped-care MMA guided by symptom measures compared with enhanced standard care. The average proportion of youth with a response to treatment of depression remained significantly greater at week 48 in the intervention sites and the average proportion in remission from depression remained stable. The evidence for a continued impact of the intervention suggests its promise, but the lack of continued improvement points to the need to
investigate methods to prevent depression relapse and promote wellness among those not helped initially. Some elements of the intervention (eg, monthly supervision calls and symptom measurement) may need to be continued to prevent relapse or promote a treatment response. Examining the predictors of response and remission (eg, income level), structural moderators of the intervention’s impact (eg, stigma), and the unique contributions of the medication algorithm and the tailored CBT will also be important. Future research will also determine how to extend the skills for reducing depressive symptoms to improving ART adherence and reducing VL.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of the site investigators and staff who conducted the IMPAACT 2002 study across the United States: BronxCare Health System, Bronx, NY: Luz Holguin, LMSW; Marvin Alvarado, MD; Martha Cavollo, CPNP; and Mahboobullah Mirza Baig, MBBS. Jacobi Medical Center, Bronx, NY: Michael G. Rosenberg, MD, PhD; Marlene Burey, NP, and Raphaëlle Auguste, RN, BSN. University of Colorado School of Medicine, Children’s Hospital Colorado, Denver, CO: Daniel Reirden, MD; Kim Pierce, DNP, RN, CPNP; Carrie Chambers, BSN, RN; and Christine Kwon, BS. University of California, San Diego, CA: Sharon Nichols, PhD; Veronica Figueroa, MS; and Megan Loughran, BA. Johns Hopkins University, Baltimore, MD: Mary Anne Knott-Grasso, CRNP; Aleisha Collinson-Streng, RN, BSN; Thuy Anderson, RN, BSN; and Bonnie Addison, BA. David Geffen School of Medicine at the University of California, Los Angeles, CA: Jaime G. Deville, MD; Michele F. Carter, RN; Shelly Jones, LCWS; and Patricia Tan, PhD. Rush University Cook County Hospital, Chicago, IL: Mariam Aziz, MD; Maureen McNichols, RN, MS, CRC; Ischell Ortiz Estes, NP; and Katy Howe, LCWS. Children’s Diagnostic and Treatment Center, Fort. Lauderdale, FL: Lisa-Gaye Robinson, MD, MPH; Patricia A. Garvie, PhD; Kathleen Graham, PharmD; and Hanna Major-Wislon, ARNP. Emory University School of Medicine, Atlanta, GA: Andres Camacho-Gonzalez, MD, MSc; Chanda Graves, PhD; LaTessha Thomas-Seaton, MS, APRN; and Nisha George, MPH. St. Jude Children’s Research Hospital, Memphis, TN: Megan L. Wilkins, PhD; Colin Quillian, MS; and Shelley Ost, MD; Sandra Jones, DNP. Texas Children’s Hospital/Baylor College of Medicine, Houston, TX: Mary Paul, MD; Chion McMillen-Jackson, RN, BSN, CCRP; Kathy Pitts, PhD, APRN, CPNP, MPH; and Terry Raburn, RN. Stony Brook Medicine, Stony Brook, NY: Sharon Nachman, MD; Allison Elsicu, MD; Melissa Shikora, LMSW; and Barsha Chakraborty. Los Angeles County and University of Southern California Medical Center, Keck School of Medicine, Alhambra, CA: Yvonne Morales, L VN; LaShonda Spencer, MD; and Allison Bearden, MD.

REFERENCES

1. Brown L, Whiteley L, Harper G, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry. 2001;58:721–728.

2. Bing EG, Burnam M, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry. 2001;58:721–728.

3. Guahan DM, Hughes MD, Oleske JM, et al. Psychiatric hospitalizations among children and youths with human immunodeficiency virus infection. Pediatrics. 2004;113:e544–e551.

4. Gadow KD, Angelidou K, Chernoff M, et al. Longitudinal study of emerging mental health concerns in youth perinatally infected with HIV and peer comparisons. J Dev Behav Pediatr. 2012;33:456–468.

5. Horberg MA, Silverberg SJ, Hurley LB, et al. Effects of depression and selective serotonin reuptake inhibitor use on adherence to antiretroviral therapy and on clinical outcomes in HIV-infected patients. J Acquir Immune Defic Syndr. 2008;47:384–390.

6. Uthman OA, Magidson JF, Safren SA, et al. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. Curr HIV/AIDS Rep. 2014;11:291–307.

7. Vreeman RC, McCoy BM, Lee S. Mental health challenges among adolescents living with HIV. J Int AIDS Soc. 2017;20(suppl 3):21497.

8. Fields EL, Bogart LM, Thurston IB, et al. Qualitative comparison of barriers to antiretroviral medication adherence among perinatally and behaviourally HIV-infected youth. Qual Health Res. 2017;27:1177–1189.

9. Caballero J, Nahata MC. Use of selective serotonin-reuptake inhibitors in the treatment of depression in adults with HIV. Ann Pharmacother. 2005;39:141–145.

10. Elliott AJ, Russo J, Roy-Byrne PP. The effect of changes in depression on health-related quality of life (HRQoL) in HIV infection. Gen Hosp Psychiatry. 2002:24:43–47.

11. Parsons JT, Golub SA, Rosof E, et al. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. J Acquir Immune Defic Syndr. 2007;46:443–450.

12. Kennard BD, Brown LK, Hawkins L, et al. Development and implementation of health and wellness CBT for individuals with depression and HIV. Cogn Behav Pract. 2014;21:237–246.

13. Sweeney M, Robins M, Ruberu M, et al. African-American and Latino families in TADS: recruitment and treatment considerations. Cogn Behav Pract. 2005;2:221–229.

14. Castr-o-Couch M. Review of cognitive-behavioral therapies with lesbian, gay, and bisexual clients. Arch Sex Behav. 2007;36:626–627.

15. Safren SA, Bedoya CA, O’Clereigh C, et al. Cognitive behavioural therapy for adherence and depression in patients with HIV: a three-arm randomised controlled trial. Lancet HIV 2016;3:e529–e538.

16. Wiener LS, Kohrt B, Battles HB, et al. The HIV experience: youth identified barriers for transitioning from pediatric to adult care. J Pediatr. 2011;159:141–145.

17. Gilliam PP, Ellen JM, Leonard L, et al. Transition of adolescents with HIV to adult care: characteristics and current practices of the adolescent trials network for HIV/AIDS interventions. JANAC 2011;22:283–294.

18. Rysavcage P, Macharia T, Patel D, et al. Linkage to and retention in care among hazardous drinkers: a randomized controlled trial. J Gen Intern Med. 2010;25:627–633.

19. Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management. Pediatrics. 2018;141:e20174081.

20. Richardson L, Ludman E, McCaulley E, et al. Collaborative care for adolescents in primary care. JAMA 2014;312:809–816.

21. American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients With Major Depressive Disorder 3rd ed. Washington DC: American Psychiatric Association Publishing; 2010.

22. American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients With HIV/AIDS. Washington DC: American Psychiatric Association Publishing; 2000.

23. Spoolstra SL, Schueller M, Hilton M, et al. Interventions combining motivational interviewing and cognitive behaviour to promote medication adherence: a literature review. J Clin Nurs. 2015;24:1163–1173.

24. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–1917.

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. www.jaids.com | 303
25. Emslie GJ, Mayes T, Porta G, et al. Treatment of resistant depression in adolescents (TORDIA): week 24 outcomes. Am J Psychiatry 2010;167:782–791.

26. Hughes C, Emslie GJ, Crismon M, et al. Texas children’s medication algorithm project: update for Texas consensus conference panel on medication treatment of childhood major depressive disorder. J Am Acad Child Adolesc Psychiatry 2007;46:667–686.

27. Seemüller F, Obermeier M, Schennach R, et al. Stability of remission rates in a 3-year follow-up of naturalistic treated depressed inpatients. BMC Psychiatry 2016;20:153.

28. March J, Silva S, Curry J, et al. The Treatment for Adolescents with Depression Study (TADS): outcomes over 1 year of naturalistic follow-up. Am J Psychiatry 2009;166:1141–1149.

29. Kennard BD, Silva SG, Tonev S, et al. Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): acute and long-term outcomes. J Am Acad Child Adolesc Psychiatry 2009;48:186–195.

30. Vitiello B, Emslie G, Clarke G, et al. Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. J Clin Psychiatry 2011;72:388–396. Erratum in: J Clin Psychiatry, 2019;80:23.

31. Brown LK, Chernoff M, Kennard BD, et al. Site-randomized controlled trial of a combined cognitive behavioral therapy and a medication management algorithm for treatment of depression among youth living with HIV in the United States. J Acquir Immune Defic Syndr. 2021;88:497–505.

32. Brown LK, Kennard BD, Emslie G, et al. Effective treatment of depressive disorders in medical clinics for adolescents and young adults living with HIV: a controlled trial. J Acquir Immune Defic Syndr. 2016;71:38–46.

33. Kennard BD, Hayley C, Hughes J, et al. CBT Treatment Manual for Adolescent AIDS Trials Network Protocol 080, unpublished, 2010.

34. Naar-King S, Suarez M. Motivational Interviewing With Adolescents and Young Adults New York, NY: Guilford Press; 2011.

35. Bernstein IH, Rush AJ, Trivedi MH, et al. Psychometric properties of the quick inventory of depressive symptomatology in adolescents. Int J Methods Psychiatr Res. 2010;19:185–194.

36. Moore HK, Hughes CW, Mundt JC, et al. A pilot study of an electronic, adolescent version of the quick inventory of depressive symptomatology. J Clin Psychiatry 2007;68:1436–1440.

37. US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases and Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

38. Hayes RJ, Moulton LH. Cluster Randomised Trials. Boca Raton, FL: Chapman and Hall/CRC; 2009.

39. Selik RM, Mokotoff ED, Branson B, et al. Revised surveillance case definition for HIV infection—United States, 2014. MMWR Recomm Rep. 2014;63:1–10.

40. Mojtabai R. Nonremission and time to remission among remitters in major depressive disorder: revisiting STAR*D. Depress Anxiety 2017;34:1123–1133.

41. Emslie GJ, Kennard BD, Mayes TL, et al. Continued effectiveness of relapse prevention cognitive-behavioral therapy following fluoxetine treatment in youth with major depressive disorder. J Am Acad Child Adolesc Psychiatry 2015;54:991–998.

42. Kahana SY, Jenkins RA, Bruce D, et al. Structural determinants of antiretroviral therapy use, HIV care attendance, and viral suppression among adolescents and young adults living with HIV. PLoS One 2016;11:e0151106.