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Addressing Syndemics and Self-care in Individuals with Uncontrolled HIV: An Open Trial of a Transdiagnostic Treatment

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Abstract

Interventions addressing syndemics and ART adherence are needed for individuals with uncontrolled HIV and psychosocial problems. Twenty-seven participants with detectable HIV plasma viral load (PVL) or recent STI participated in an open trial of transdiagnostic adherence counseling and cognitive behavioral therapy. Outcomes were collected at baseline, 4-, and 8-months. Log PVL improved from baseline to 4-month ($\gamma = -1.13$, 95% CI $-1.72, -0.55$, $p < 0.001$) and 8-month ($\gamma = -0.93$, 95% CI $-1.57, -0.30$, $p = 0.006$), with more participants suppressed at 4- ($\chi^2(1) = 9.09$, $p = 0.001$) and 8-month ($\chi^2(1) = 5.14$, $p = 0.016$). Self-reported adherence improved across major assessments ($\gamma = 0.87$, 95% CI $0.28, 1.46$, $p = .005$); Wisepill adherence did not. Negative affect declined during treatment ($\gamma = -0.28$, 95% CI $-0.40, -0.16$, $p < 0.001$), with improvement at 4- ($\gamma = -4.34$, 95% CI $-6.99, -1.69$, $p = 0.002$) but not 8-month. Positive affect trended positively during treatment and from baseline to 4-month, with significant 8-month improvement ($\gamma = 3.84$, 95% CI $0.33, 7.44$, $p = 0.04$). Depressive symptoms did not change. In a complicated sample of participants selected for uncontrolled HIV, the intervention yielded improved PVL and self-reported adherence. Efforts to end HIV should improve upon strategies such as these, addressing syndemics.

Keywords

Syndemics; HIV; Adherence; Cognitive behavioral therapy; Antiretroviral therapy

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Introduction

Antiretroviral therapy (ART) for HIV has become increasingly potent over time, allowing for many individuals who are in HIV care to attain viral suppression and live extended lives with HIV under control [1]. However, some individuals with HIV are not reaching these outcomes. While the United Nations has interim goals toward HIV eradication that includes 90% of individuals with HIV to be diagnosed, 90% on ART, and 90% virally suppressed by 2020 (90-90-90) [2], at the end of 2015, the CDC estimated national averages of only 86% diagnosed, 63% receiving care, 49% retained in care, and 51% virally suppressed [3]. The U.S. has also set goals for ending the HIV epidemic by 2030, but has identified geographic hot-spots where the epidemic requires improved responses [4]. Miami, one such hot-spot, is the city with the highest incidence and prevalence of HIV in the U.S [5]. and is therefore not yet on track with these goals. As of 2017, in Miami-Dade County 86% of people with HIV were diagnosed, 64% were retained in care, and 58% were virally suppressed [6]. Additionally, the populations of individuals most affected by HIV in Miami are racial and ethnic minorities, with the Black community representing 40% of cases and the Hispanic/Latinx community representing 47% [5].

Psychosocial syndemics, such as depression, anxiety, trauma, and substance use, refer to co-occurring mental health and substance use concerns that synergistically interact to interfere with all components of the HIV treatment cascade, including engagement in treatment, ART adherence, and viral suppression [7–11]. Achieving viral suppression requires adequate adherence to ART medications [12]. Problems such as depression [13, 14], substance use [15], and other mental health concerns such as post-traumatic stress [16] are known correlates of poor adherence. Furthermore, by definition, many psychosocial problems are associated with each other and additional structural syndemics. Both cross-sectional [7] and longitudinal [8, 17–19] data show that syndemics have additive deleterious effects on adherence and viral suppression. These problems are also associated with behavior that could lead to new HIV transmissions for people with HIV [20, 21]. Accordingly, individuals experiencing psychosocial problems may be unlikely to reach 90-90-90 goals, and are likely to be in the remaining 10-10-10, thus requiring additional intervention to eventually achieve the goal of ending the HIV epidemic.

Few behavioral interventions for adherence and viral suppression address psychosocial syndemic conditions. Parsons et al. [22] demonstrated that a cognitive-behavioral intervention focused on alcohol reduction and adherence could improve adherence and viral load/CD4 outcomes, though effects waned in the follow-up. Safren et al. conducted a series of studies testing cognitive behavioral therapy for adherence and depression (CBT-AD), a treatment for depression that integrates adherence counseling following the Life-Steps approach [23, 24]. An initial randomized trial, with a cross-over design, of this intervention with individuals with HIV and comorbid depression showed significant improvements in depression and adherence for the CBT-AD condition compared to enhanced treatment as usual, and improvements in viral load over time [25], though the cross-over design precluded a comparison of viral load with the control group. A more recent three-arm randomized trial with depressed participants with HIV found that CBT-AD led to improvements in depression and adherence that exceeded enhanced treatment as usual [26],

but did not find viral load differences with the vast majority of participants being virally suppressed at baseline, as this was not an exclusion criterion. CBT-AD also improved psychological outcomes and adherence for people with HIV who inject drugs [27] in a two-arm trial. Although viral load did not significantly improve in the treatment condition compared to control, there was a difference in CD4 cell count. A preliminary randomized controlled trial testing culturally adapted CBT-AD showed improvements in depressive symptoms and adherence, with mixed results for biological markers (improvement for CD4 count in the treatment condition but not control, whereas there were reductions in viral load for both conditions) with Latinx individuals on the U.S.-Mexico border [28]. Additionally, a pilot study of a culturally adapted version of CBT-AD delivered by nurses to people with HIV in South Africa showed improvements in depression symptoms and adherence remained stable through 3-month follow up [29]. Another randomized trial tested CBT for body image and self-care (CBT-BISC) for sexual minority men with HIV, finding that the intervention was associated with significant improvements in body image disturbance, depressive symptoms, and adherence [30]. In all of these trials, over 50% of participants had other DSM-IV-TR diagnoses in addition to depression, demonstrating the need for an approach that addresses additional mental health problems to potentially maximize its impact on overall well-being and HIV-related health outcomes, including adherence, viral load, and CD4 count. Additionally, these studies did not select individuals with unsuppressed virus, and generally did not show consistent differential effects on HIV outcomes.

The current study was designed to address several gaps in the literature. First, given the prominence of multiple, co-occurring psychosocial syndemics among people with HIV and unsuppressed viral load, this study employed a transdiagnostic treatment approach, rather than focusing only on one syndemic health concern that may interfere with HIV-related health outcomes. To increase the ability to disseminate evidence-based approaches, and to better equip clinicians to work with individuals with multiple or overlapping problems, transdiagnostic treatments involve using cognitive and behavioral skills to overcome distressing problems that exist across multiple domains of impairment [31]. Second, to tailor efforts to individuals most in need of intervention and at greatest risk for HIV transmission, this study only included people with either uncontrolled virus or a recent sexually transmitted infection (STI). Third, to address the complex nature of addressing syndemics in the context of HIV care in a low-resource U.S. setting, this study conducted an open-pilot trial integrating the treatment of the most frequent psychosocial syndemics with increasing self-care behaviors for individuals with HIV.

Methods

Trial Design

As a Stage 1 treatment development study [32], this was a single-arm, non-randomized open trial. All study procedures were approved by the University of Miami Institutional Review Board.

Participants

Participants were 27 individuals with HIV, with participant flow depicted in Fig. 1. We targeted this sample size as it was a Stage 1 treatment development study. Recruitment began February 23, 2016, and participants were enrolled between March 21, 2016 and September 18, 2018. The trial ended based on reaching enrollment targets to be able to conduct the planned analyses. Participants were eligible if they were between the ages of 18–65 years old, diagnosed with HIV, and had uncontrolled virus (plasma viral load [PVL] reached detectable limits; after our first participant, we imposed a < 200 exclusion criteria) or an STI within the past 3 months. There was initially also the requirement for the participant to have been sexually active in the past 3 months but this criterion was removed prior to enrolling the twelfth participant. Participants were excluded and referred to other services if they were unable or unwilling to provide informed consent, had active untreated or unstable major mental illness (e.g., untreated psychosis or mania) that would interfere with study participation, would be at risk for harm to themselves or others as a result of study participation, were currently receiving CBT for a psychiatric disorder, or received a course of CBT in the past year. Participant demographics are reported in Table 1.

Participants were recruited from local HIV clinics in South Florida. Study staff also recruited participants at a local public HIV clinic in the waiting room. The clinic from which participants were actively recruited is designed to serve all residents of Miami-Dade County, regardless of ability to pay, thus providing services to a largely underserved population. Additionally, flyers were posted at local clinics allowing participants to self-refer. Clinic providers also referred participants for study enrollment if they had a recent STI or uncontrolled viral load. Study staff conducted a brief phone screen to determine initial eligibility for a baseline appointment to determine full study eligibility. Those eligible then were invited to complete the intervention.

Study procedures were carried out in a clinical research building adjacent to the local hospital where active recruitment was conducted. The clinical research building is centrally located, within walking distance to public transportation and with an attached parking garage to enhance participation. Participation was incentivized, such that participants received \$50 for each major assessment that they completed (baseline, 4-month, and 8-month follow up). The majority of weekly visits were incentivized at \$25 per visit. As this was a developmental feasibility open trial, we began the study with a \$15 weekly visit incentive, however, this was changed to \$25 after the ninth participant began treatment.

Intervention

Development of the Intervention—The intervention was designed to address the most frequent and impactful syndemic conditions for individuals with HIV and uncontrolled viral load. To maximize the acceptability, feasibility, and potential opportunity for dissemination of the intervention, we developed the intervention iteratively using participant feedback from a prior trial of CBT for adherence and depression [33], feedback from a Community Advisory Board, and secondary quantitative analyses from prior trials of CBT for adherence and depression in HIV [34, 35]. The intervention modules were then refined with ongoing feedback and clinical experience with participants.

We took a transdiagnostic modular approach, such that the intervention modules (see Table 1) were designed to be relevant to the variety of psychosocial syndemic problems that are common and impairing among people with HIV and uncontrolled virus (see Table 3 for a summary of syndemic problems experienced by the present group of participants). All modules generally integrated CBT with motivational interviewing [36]. In contrast to many manualized interventions, this treatment was designed to be flexible and usable with a complex, underserved population. As such, participants received tailored treatment, such that therapists could select from these modules based on their relevance to a participant's particular syndemic problems. Participants were provided up to 14 total sessions, depending on need (accordingly the number of sessions was flexible), each session being approximately one-hour long and delivered individually. Interventionists were trained to take a collaborative, motivational interviewing approach to their delivery of CBT, with the goal of fostering engagement and motivation to benefit from the CBT-oriented skills.

Because this population was underserved and, as shown in the participant demographics, had received low levels of formal education, we made a concerted effort to adapt the intervention to be relevant to individuals with lower literacy levels. As described elsewhere, treatment modules were reviewed and modified to be at a 4th–6th grade reading level, and were generally administered with worksheets completed interactively in the session with participants [37]. Additionally, visual tools were used to explain concepts such as adherence, viral load, viral suppression, and resistance. Therapist supervision also involved discussing language choices and strategies for explaining abstract concepts in concrete and understandable ways. Therapists were also mindful of the pacing of the intervention delivery, sometimes spreading out one treatment module across several sessions to ensure participants were able to understand and utilize the skill from the module before proceeding to a new module. Similarly, the approach to traditional “homework” in cognitive-behavioral therapy required adaptation because literacy levels were variable and anecdotally, participants reported numerous interpersonal, home, and community-based stressors, therefore home practice was often a thinking or behavioral activity versus traditional written home practice in CBT. Interventionists reviewed participants' home practice at the following session.

All participants began with one session of Life-Steps, an adherence counseling intervention that uses motivational interviewing, problem solving, and cognitive behavioral skills training to improve medication adherence and HIV-related self-care behaviors [38, 39]. Skills included identifying motivations for taking ART and using sticker reminders to facilitate associating medication with personal motivations and remembering to take medication. Participants also reviewed the medical rationale for medication adherence, selected a medication time, set phone or watch reminders, and made a plan for keeping “backup” medication available. Participants were offered a watch with an alarm and a portable pill holder, if they wanted either or both to facilitate their adherence.

During the first session, interventionists also reviewed with participants a letter informing their HIV medical provider that they were participating in the study and documenting any psychiatric conditions that they would have met criteria for based on our initial assessment. Participants' remaining sessions were spent on CBT-based modules, which were

operationalized as worksheets that interventionists delivered flexibly based on participant needs. Participants could work on these worksheets in one session or across multiple sessions, and/or review the materials multiple times throughout treatment, depending on participants' presenting problems. Life-Steps medication adherence skills were intertwined so that both mental health and self-care were addressed every session. Typically, interventionists began by introducing participants to the CBT model and building motivation using a decisional balance exercise and discussing a motivational metaphor. The other modules included: (1) behavioral activation and activity scheduling to increase engagement in enjoyable and mastery activities (including medication adherence), (2) examining and restructuring automatic thoughts to facilitate helpful thinking about stressful situations in general and those that may interfere with HIV self-care, (3) problem solving to improve skills in dealing with individual, interpersonal, and structural problems, (4) relaxation training to manage stressful life circumstances and medication side effects, (5) cognitive and behavioral skills to reduce substance use and/or prevent relapse, (6) cognitive processing and restructuring skills to address trauma, and (7) a final relapse prevention module, in which they reviewed treatment gains and strategies to prevent psychosocial or non-adherence relapse in the future. Additionally, between the 4-month and 8-month follow up assessments, participants were offered on an as-needed basis, up to four booster sessions, delivered once per month or longer intervals to review treatment modules and/or problem solve barriers to adherence or coping (see Consort Diagram). Some of the modules were an adaptation of our approach for treating depression and increasing adherence [24], and others were developed from a prior motivational interviewing and CBT intervention for medication adherence among hazardous drinkers [22] and a behavioral activation trial for stimulant use and sexual risk reduction among MSM [40]. The approach to trauma used cognitive processing therapy as a point of departure to develop relevant worksheets involving writing and working on an impact statement and addressing cognitive distortions related to the trauma [41].

Although the intervention was initially conceptualized as addressing psychosocial syndemics that interfere with overall well-being and HIV-related self-care, we learned through the implementation of the intervention that structural syndemic problems also needed to be addressed, as they had a major impact on participants' lives. For example, the problem-solving module was often used to help participants work through transportation problems, trying to find solutions to food insecurity problems via linkage to services, and insurance barriers to healthcare. While therapists were not case managers, they facilitated linkage with case management and other resources that may be needed to address these structural syndemics. Additional detail regarding how structural syndemics were addressed are described elsewhere [37].

Training and Supervision of Interventionists—Interventionists were primarily graduate students with masters level training, as well as a masters level and post-doctoral level therapist. Initial training included approximately eight hours of didactic instruction with the PI and review of intervention materials, mainly addressing the CBT components of the intervention, as well as a 1-day training in motivational interviewing by a study consultant. Interventionists met for weekly group supervision with a licensed clinical psychologist (first author), with additional supervision regarding trauma cases (last author).

Supervision sessions involved review of each participant in treatment, including case conceptualization, treatment plan, implementation of the clinical protocol, and clinical challenges. The first author was also available for additional as-needed consultation throughout the study.

Outcomes

Timing and Structure of Assessments

Participants completed three major assessments of the study outcomes. Each visit included a clinician-administered assessment, a set of self-report measures (completed electronically or on paper), and a biological assessment of plasma viral load and CD4 cell count (blood draw or chart review). The first major assessment was at the baseline where participants were fully screened by a study interventionist and determined whether they were eligible for continuing into the study's treatment phase. They completed the MINI-7 to assess for DSM-5 psychiatric disorders [42]. Medication adherence was assessed throughout the time of participation, and positive and negative affect were assessed at the major study assessments (baseline, 4-month, and 8-month), as well as at each weekly intervention session (up to 14 sessions plus up to monthly as needed booster sessions during follow up) to monitor change during active treatment.

Primary Outcome

HIV Plasma Viral load—The primary outcome was the number of participants who attained a suppressed (< 200) viral load at the 4-month and 8-month assessments. This was assessed by either chart review (past month before visit), or, if not available, by blood draw at the study visit. We also computed a continuous variable, log viral load, to evaluate viral load change across the three assessment visits.

Secondary Outcome

Electronically Monitored Medication Adherence—The secondary outcome was adherence to ART via real-time monitoring [43]. For this, we utilized Wisepill, which registers the date and time the device is opened (reflecting when participants remove their pills) and has been used as an objective indicator of ART adherence. For the study outcome, we calculated a weekly Wisepill adherence score (0–100% adherence). Participants were considered non-adherent on days on which they did not take their ART medication. Participants were given the Wisepill device at their baseline visit and instructed how to use it. Participants were asked to continue using their Wisepill device throughout their participation in the study and follow up assessments.

Many participants reported difficulty and/or inconsistent use of the Wisepill device, regardless of whether they were adherent to ART or not. We took several steps to attempt to account for this. First, interventionists reviewed participants' Wisepill adherence at each intervention visit, noting missing data (i.e., days on which participants reported not using the Wisepill device). For participants who informed their interventionist that they took their medication but did not use their Wisepill box as directed, their Wisepill data was considered missing during that period of time. Some participants who had a suppressed viral load ($<$

200), indicating that they had high ART adherence, yet they had fewer than two Wisepill openings (indicating two or less ART doses) per week. In these cases, we also considered their Wisepill data missing, because it would be typically impossible to have such low adherence while also having suppressed viral load when previously not suppressed at baseline.

Additional Outcomes

Medication Adherence

Self-Reported Medication Adherence: At each of the major study assessments, participants self-reported the percentage of time (0–100%) that they took their HIV medications as prescribed by their doctor, in the past week, past 2 weeks, and past month. They also self-reported their medication adherence using the same scale over the past week at their weekly sessions. Similar self-report percentage scales for adherence are validated and comparable to unannounced pill counts [44].

Mood and Affect

Positive and Negative Affect Schedule (PANAS): We administered the PANAS [45] at the three major assessments and the weekly visits to measure positive and negative affect in the prior week. The PANAS is a widely used, validated measure. Positive affect scores can range from 10 (least positive affect) to 50 (most positive affect) whereas negative affect scores can range from 10 (least negative affect) to 50 (most negative affect). With this sample, the positive affect subscale was highly internally consistent ($\alpha = 0.87 - 0.91$ across the three major assessments). The negative affect subscale varied in its internal consistency across the different assessment points, with it being less internally consistent at baseline ($\alpha = 0.49$) compared to the 4-month ($\alpha = 0.83$) and 8-month ($\alpha = 0.94$) follow-up.

Patient Health Questionnaire (PHQ-9): For mood, we used the PHQ-9 depression self-report measure [46] which can be used as a diagnostic measure and a measure of symptom severity. PHQ-9 scores can range from 0 (least depressed) to 27 (most depressed). For the purpose of this study, we scored symptom severity and utilized this as an additional outcome. The PHQ-9 is a widely used, validated measure. This scale had high internal consistency in the current sample ($\alpha = 0.83-0.91$ across the three major assessments).

Sample Size

We recruited and screened 38 participants in person, and of these 27 screened in and started the intervention. See Fig. 1 for participant flow. Of those who started, 88% ($N = 24$) were retained at the 4-month follow-up and 85% ($N = 23$) at the 8-month follow up. Although this study was not powered for viral load outcomes, we piloted all study procedures that would be used in a future efficacy trial. Thus, we used this sample size to, after completion, develop more fully the intervention and determine how to address the complicated problem of syndemics in the context of adherence and viral suppression.

Statistical Methods

For our dichotomous outcome (suppressed viral load), we used McNemar's test to determine if the percentage of participants with suppressed virus was significantly different from baseline at 4-month and at 8-month.

For our continuous outcomes (log viral load, Wisepill adherence, self-reported adherence, positive and negative affect, and depressive symptoms) we visually inspected plots of the mean scores over time and plots of individual trajectories to determine whether a linear trend was appropriate for each outcome. There appeared to be a linear effect of time for Wisepill adherence (during the active treatment and follow up periods there were two separate linear trends), self-reported adherence, and positive and negative affect (weekly during active treatment but not across the three major assessments). Across the three major assessments, there did not appear to be a linear effect of time for log viral load, positive and negative affect, or depression severity. We used hierarchical linear modeling (HLM) to assess change over time for each outcome. For outcomes that appeared to follow a linear trend, time was included as a continuous predictor, whereas if the effect appeared nonlinear, time was included as a dummy-coded categorical predictor with baseline as the reference.

Some of the outcomes were measured on a weekly basis instead of only at the major assessments, and all of these appeared to follow a linear trend. Specifically, Wisepill adherence was computed as a weekly adherence rating throughout the treatment phase and through all of the follow ups. Self-report adherence as well as positive and negative affect were also measured at each weekly visit. Therefore, we were able to conduct additional HLM models to examine weekly changes in these outcomes during active treatment (time coded continuously from 0 to 15) and, in a separate model, throughout the follow up period for the Wisepill (time coded continuously from 16 to 31).

For all the HLM models that included a linear effect of time, we used a likelihood ratio test (LRT) to compare a model with a fixed effect of time to a model including both fixed and random effects of time. If the LRT was not significant, we retained the fixed effects only model, whereas if it was, we retained the random effect. We report in Table 6 the result of the LRT for each linear test.

All HLM analyses described below were conducted using R, version 3.3.2 (R Development Core Team [47]). The following packages were used in analyses: lmerTest [48], ggplot2 [49], sjPlot [50], and sjmisc [51].

All analyses were completed following an "intention-to-treat" (ITT) approach, which is a frequently used analytic approach for clinical trials [52, 53]. ITT analysis means that all participants who were assigned to the intervention are included in the outcome analyses. ITT approaches are more conservative than completer-only analyses, accounting for variability among participants in completion of the treatment protocol and reducing the possibility of bias toward those participants who benefitted from the treatment [52, 53]. Because a number of participants in this trial did not complete the treatment, ITT is a more appropriate analytic approach that more accurately assesses the total proportion of individuals who benefitted from the intervention and would be likely to benefit from such an intervention in real-world

clinical practice. HLM allows for missing data at any particular assessment point without having to drop participants with incomplete data [54]; therefore, we were able to include all participants in the (ITT) analyses, regardless of how many major assessments they completed.

Results

Participant Descriptive Information

Participants' baseline characteristics are reported in Table 2. The majority of participants identified as non-Hispanic Black (88.9%), with a mean age of approximately 46 years old, and with the majority (63.0%) being cisgender males. The majority of participants identified as heterosexual (70.4%). Table 3 shows the psychiatric, interpersonal, and structural conditions (syndemic indicators) that participants were experiencing at baseline. Table 4 shows the number of sessions participants attended.

At baseline the majority of participants (81.5%) met criteria for at least one current psychiatric diagnosis: depression (48.1%), substance use disorder (37.0%), and antisocial personality disorder (25.9%) were most prevalent. Forty-eight percent of the sample met criteria for two or more psychiatric diagnoses, and 22% for three or more. Despite a small subset of participants meeting full criteria for PTSD, past and ongoing trauma was pervasive among participants: 25.9% reported a history of childhood sexual abuse, 22.2% reported experiencing rape as an adult, and 70.4% reported a PTSD qualifying event on the MINI. Although a subset met criteria for current substance or alcohol use disorder, the majority (63.0%) reported a history of problematic substance use. This emerged as an issue relevant to treatment (e.g. how to tailor activity scheduling in the context of substance use triggers in their neighborhood and/or other places they might engage in enjoyable activities).

In addition to these psychiatric diagnoses, participants faced substantial interpersonal and structural syndemics which were also addressed in and/or affected treatment. Participants had low educational attainment and limited employment: nearly half of participants did not complete high school and only one participant was employed full-time, with the majority either on disability or otherwise not working or in school (see Table 2). Participants were also assessed for various problems related to health literacy, social support, and structural barriers to health at baseline. Nearly half reported financial problems related to meeting basic needs (48.1%), with issues including financial problems limiting access to food and hygiene products, being unable to pay utilities (e.g., electricity, phone), or having to negotiate with utility companies to not lose service. Almost half (40.7%) reported needing assistance with food, with problems such as food stamps not covering the cost of food, being unable to buy healthy food, being unable to buy food to offset medication side effects, and not having food to eat with their medication despite being on a medication that has improved tolerance or effectiveness when taken with food. A third of the sample reported transportation difficulties (33.3%), which made it difficult for some to attend healthcare and HIV-related appointments. Although fewer reported insurance or healthcare benefits problems (14.8%), those who did had problems that were substantially interfering, including their insurance being canceled and consequently being unable to attend appointments because of cost prohibitive copays, which in turn prevented those participants from getting

their ART medication. When all of these psychosocial and structural barriers that we systematically assessed were accounted for, all participants met criteria for at least one syndemic problem (see Table 3).

In addition to these syndemic problems, we also learned about additional problems, including additional psychosocial syndemics as well as structural syndemics, which participants faced during treatment delivery. For example, through our clinical work, 40.7% reported histories of incarceration. Another problem participants faced was family rejection based on HIV status, an issue that often emerged in treatment, and affected at least 33.3% of the participants. Altogether, this population was extremely impacted by not only psychosocial syndemics, but also long-standing and interfering interpersonal and structural syndemics. Another challenge faced was participants losing contact with study staff and not returning for visits, sometimes due to relapse of substance use or other life stressors, which led to treatment being a lower priority. Although some participants ultimately resumed sessions at a later date, others did not return after their first visit (see Table 4 and Fig. 1).

HIV RNA Viral Load

McNemar's test showed that at both the 4-month ($\chi^2(1) = 9.09, p = 0.001$) and 8-month ($\chi^2(1) = 5.14, p = 0.016$) follow-up assessments, a significantly greater proportion of participants had PVL < 200 compared to baseline. See Table 5 and Fig. 2 for the distribution of viral load at each major time point. Log PVL scores were significantly lower at 4-month ($\gamma = -1.13, 95\% \text{ CI } -1.72, -0.55, SE = 0.30, p < 0.001$) and 8-month follow up ($\gamma = -0.93, 95\% \text{ CI } -1.57, -0.30, SE = 0.32, p = 0.006$), as compared to the baseline (Table 6).

Adherence

Wisepill Adherence—Based on visual inspection of the data, we separately modeled linear trends of Wisepill adherence during active treatment (baseline to 4-month) and follow up (4-month to 8-month). Wisepill adherence did not change significantly during the active treatment phase ($\gamma = 0.14, 95\% \text{ CI } -0.76, 1.02, SE = 0.44, p = 0.75$). However, Wisepill adherence had a trend to worsen during the follow up phase ($\gamma = -1.33, 95\% \text{ CI } -2.71, 0.06, SE = 0.69, p = 0.07$).

Self-report Adherence—In contrast to Wisepill adherence, self-reported weekly adherence improved during the active treatment phase ($\gamma = 0.06, 95\% \text{ CI } 0.02, 0.11, SE = 0.02, p = 0.003$) by an average of 0.6 percentage points per week. Self-reported adherence (past 2 weeks) across the three major assessment visits also increased ($\gamma = 0.87, 95\% \text{ CI } 0.28, 1.46, SE = 0.30, p = 0.005$) by an average of 8.7%.

Affect and Mood

Positive Affect—Positive affect, assessed on a weekly basis during active treatment, did not significantly change ($\gamma = 0.16, 95\% \text{ CI } -0.69, 0.38, SE = 0.11, p = 0.177$). However, we found that positive affect trended toward significant improvement at 4-month follow up ($\gamma = 3.43, 95\% \text{ CI } -0.02, 6.99, SE = 1.77, p = 0.06$) and was significantly improved at 8-month follow up ($\gamma = 3.84, 95\% \text{ CI } 0.33, 7.44, SE = 1.80, p = 0.04$) compared to baseline.

Negative Affect—Negative affect scores significantly decreased ($\gamma = -0.28$, 95% CI $-0.40, -0.16$, $SE = 0.06$, $p < 0.001$) by an average of 0.28 points per week during treatment. Similarly, we found that negative affect was significantly improved at 4-month follow up ($\gamma = -4.34$, 95% CI $-6.99, -1.69$, $SE = 1.35$, $p = 0.002$) compared to baseline. However, negative affect at 8-month follow up ($\gamma = -0.77$, 95% CI $-3.46, 1.91$, $SE = 1.37$, $p = 0.58$) did not significantly differ from baseline scores.

Depressed Mood—Although depression scores on the PHQ-9¹ trended down at 4-month follow up compared to baseline, this difference was not significant ($\gamma = -1.87$, 95% CI $-3.94, 0.13$, $SE = 1.03$, $p = 0.07$), nor was it significantly different at 8-month follow up compared to baseline ($\gamma = -1.60$, 95% CI $-3.68, 0.44$, $SE = 1.05$, $p = 0.13$).

Discussion

In the present study, we sought to adapt an evidence-based set of cognitive-behavioral therapy techniques, compiled as a transdiagnostic treatment approach that could be flexibly delivered to address syndemic problems and self-care/adherence for individuals with HIV and uncontrolled virus. As evidenced by the profile of mental health and substance use syndemics, as well as many structural syndemics, and by the inclusion criteria of having uncontrolled HIV or a recent STI, despite being in care, this population is at high risk for dropping off the HIV treatment cascade. Although we used a combination of techniques, incentivized participation, provided flexible scheduling, and engaged in extensive retention efforts, the intervention was only moderately successful. In terms of the primary outcome, HIV viral load suppression, although there were statistically significant improvements both in the percentage of individuals with suppressed virus at follow-ups compared to baseline, and in continuous log RNA viral load values, only 50% and 36% achieved suppression at the 4-month and the 8-month visits. Although there was evidence for significant improvements in adherence via self-report, the electronically monitored Wisepill data did not change over time. Therefore, when examining the HIV adherence and viral load outcomes, it appears that this intensive individually-delivered intervention is helpful as a “proof of concept,” and it needs refinement and further testing in a randomized trial to fully evaluate its clinical and public health significance. We did not select on the basis of psychiatric or other syndemic conditions as an inclusion criteria, only on indicators of uncontrolled HIV, yet participants still had a high syndemic burden. Therefore, the intervention may also require even further augmentation to fully address the complex interplay of psychosocial, interpersonal, and structural syndemics that this underserved population was facing. For instance, building in case management and intensive, proactive linkage to wrap around services may help to further address the many structural syndemics participants faced, therefore facilitating change in other areas of participants’ lives. Among this sample, one-third had six or more syndemic conditions, which is a higher syndemic burden even among other samples of people with HIV and co-occurring syndemic problems [i.e., 7, 8]. Thus, the treatment effects

¹During data cleaning, we found that five participants completed some but not all of the PHQ-9 items ($n = 5$), with the maximum number of items missed being two. For these five cases, we imputed the missing values with the mean of the participants’ responses on the other completed items in order to retain their data.

observed should be considered in light of the substantial barriers to health experienced by this group of participants.

The pattern of results showing improvements in viral load and self-reported adherence, but no change in adherence as assessed by Wisepill, in combination with anecdotal participant report about Wisepill non-use, reveal the possibility that consistent Wisepill use as an adherence assessment may be challenging with this population. Despite potential advantages of electronic adherence monitoring, studies have documented some drawbacks, such as discordance between self-report and electronically monitored adherence due to technology difficulties and limited pill storage capacity [55] and possible underestimation of adherence via Wisepill [56]. Although self-report may overestimate adherence, in this sample, it appears that Wisepill may have underestimated adherence. Participants in the study reported a variety of barriers to consistent use of their Wisepill devices, such as losing the device (e.g., due to unstable housing) or not using it (e.g., due to confidentiality fears or concerns about what others might think the device is for), and having inconsistent schedules that limited their access to the device depending on their location. The lack of change in Wisepill adherence data may also be due to its novelty of electronic drug monitoring at the beginning and then a waning over time as seen in other studies [57].

Self-reported mood and affect results were also mixed. Although there was some evidence for improvement during treatment for positive and negative affect as assessed by the PANAS, there was not for depressed mood as assessed by the PHQ-9, and change in negative affect was not sustained at follow up. In the present study, we used the PANAS to assess positive and negative affect because we sought to use a transdiagnostic psychosocial outcome variable. The pattern of results shows either inconsistent improvements (and some areas of non-improvement) or that the approach of having a transdiagnostic distress indicator (PANAS) was difficult for participants with such a broad range of syndemic problems. Another potential challenge of this transdiagnostic indicator of distress was the reading level of the measure; anecdotally, many participants did not initially understand all of the words on the measure, requiring research staff to explain the meaning of the words, suggesting that more concrete wording or a measure with a reading level matched to the education level of the participants may be more appropriate.

When starting this study, we originally sought to develop a unified protocol [58–60] whereby all participants received the same material regardless of which syndemics they were experiencing. In practice, we found this to be impossible, and therefore utilized the approach described above whereby participants and interventionists selected modules based on clinical presentation and utilized relevant worksheets developed for the current study. This module-based design is consistent with an approach used to treat children with negative affect disorders [61] whereby specific modules, following a combined motivational interviewing and CBT-style approach [36], are selected based on need. In the current complex population, presenting problems were so varied that intervention material needed to be selected based on the life circumstances and particular set of mental health and social-structural comorbidities that were occurring.

There are limitations to this study as a feasibility non-randomized trial with mixed results. Due to the open, non-randomized design, it is possible that positive findings were a function of secular trends in time, regression to the mean, and/or common factors of psychotherapy (e.g., active listening, warmth, empathy). As mentioned, the interpretability of the negative Wisepill data in the context of improved viral outcomes is unclear. Even with this intensive and flexible intervention with incentives for participation, outcomes were, as depicted, mixed, suggesting the potential need for further modification of the intervention in terms of intensity or focus, including to address the numerous structural syndemics faced by this population. Although we, based on the work leading up to this, found that flexibility of intervention delivery would be necessary for working with this population given the complex interrelated syndemic problems, there was not a single set of modules that each participant received. Hence, this is a limitation to internal validity with the attempt of maximizing external validity in that mental health practitioners vary what interventions they deliver in actual clinical practice based on client need. Accordingly, a conclusion from this study may be that clients may benefit from the integration of adherence counseling into mental health based treatment, regardless of what specific mental health interventions would be employed. Finally, it should be mentioned that approximately 76% of those screened in person started the treatment. This could be due to the intense level of structural barriers to care, which may not have been sufficiently addressed by the financial reimbursements for travel and time.

The breadth and intensity of the many psychosocial, interpersonal, and structural syndemic conditions that participants faced were not fully anticipated. Because of this, we did not assess some of these syndemic problems at baseline (e.g. incarceration history and family HIV stigma). Furthermore, among those factors that we did assess and were pervasive, we learned through delivering the intervention that many of these concerns were likely underreported at baseline. For example, some participants did not meet criteria for depression at baseline, yet it became clear through treatment that they in fact did meet criteria, but potentially only discussed these symptoms once they established rapport with their study therapist. Related, some initially denied difficulties with insurance, food access, or transportation, but during treatment it was clear that these issues were affecting their HIV self-care and mental health. Finally, it is important to note that although 25.9% met criteria on the MINI for Antisocial Personality Disorder, this finding likely reflects behavior related to social/economic disadvantage rather than any innate psychopathology among this population [62, 63]. Prior work has shown substantial overlap between Antisocial Personality Disorder and substance abuse [64, 65]. Diagnostic criteria such as skipping school or running away from home, doing things that are illegal, behaving “irresponsibly” by failing to pay for things, or starting fights or threatening/intimidating others, for example, may be driven by contextual factors, such as violent or unsafe home environments, not having access to needed resources, and needing to protect oneself from real threats. Although the DSM-5 provides guidance to distinguish between illegal behavior that is contextually driven versus inflexible, maladaptive, and persistent behavior, the MINI, used to assess all DSM-5 disorders for this study, does not make this distinction as clear. Thus, although these factors led to meeting criteria to Antisocial Personality Disorder for some participants, clinically, it may be more useful to understand the context of these behaviors and work toward addressing the contextual/structural issues that lead to potentially

problematic behaviors. Related, although CBT skills may not be as tailored to treat Antisocial Personality Disorder, to the extent that this rate of diagnosis reflects sociostructural circumstances leading to behaviors consistent with this diagnosis, CBT treatment may be more relevant. Altogether, these findings highlight that further development of the intervention in the context of these multilevel factors, with a particular focus on addressing structural syndemics in addition to psychosocial syndemics, may be needed to optimize benefits of this intervention.

Despite these limitations, this is the first study to try to address mental health and related syndemics in individuals with HIV and uncontrolled virus, and using a transdiagnostic psychosocial treatment approach integrated with an evidence-based approach to adherence counseling. Looking towards the U.N. 90-90-90 goals [2], and the U.S. goals of ending the HIV epidemic [4], approaches to effectively treat HIV in those with psychosocial and structural problems are needed. This approach can be seen as a first step “proof of concept” towards such a goal, laying the groundwork for trials that address comorbid syndemics in those most at risk to fall off the treatment cascade.

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Fig. 1.
Participant flow

Fig. 2.
Viral load over time

Table 1

Intervention modules and descriptions

Module	Description
Life-Steps	Identify adherence goals, potential barriers, and how to overcome those barriers. Although this is completed in the first 1–2 sessions, it is also integrated across all sessions
Introduction to CBT and motivation	Introduce the idea of how thoughts, feelings, and behaviors are related. Discuss pros and cons of changing current behaviors
Behavioral activation	Identify pleasurable activities and complete an activity log to increase engagement in pleasurable and mastery activities, including adherence to HIV-related self-care behaviors
Cognitive restructuring	Identify common cognitive distortions and practice generating alternative thoughts in relation to psychosocial concerns and HIV-related self-care. Complete a thought record
Problem solving	Identify a current problem (e.g., problems related to HIV self-care or other syndemic problems). Develop a list of possible solutions to the problem and describe the pros and cons of each one. Rank all possible solutions and choose the best one. Make a plan to implement the solution. Differentiate between problem solving and emotion-focused coping
Relaxation	Deep belly breathing and progressive muscle relaxation to facilitate coping with psychosocial difficulties and managing HIV medication side effects
Substance use (if applicable)	Introduce behavior chains, managing thoughts about substance use, and getting through a difficult situation without relapsing. Explain lapse vs. relapse. Discuss relevance of HIV-related self-care to substance use
Trauma coping (if applicable)	Informed by cognitive processing therapy; discuss beliefs related to self and others and challenging these beliefs. Discuss HIV-related self-care behaviors in the context of coping with trauma
Relapse prevention	Review skills learned and plan for the future

The number of sessions per module varied depending on participant’s clinical presentation and needs

Table 2

Participant demographics observed at baseline

Variable	N (%)
Race/ethnicity	
Black non-Hispanic	24 (88.9%)
White Hispanic	1 (3.7%)
Non-Hispanic White	2 (7.4%)
Age M(SD)	46.15 (11.72)
Gender	
Male, cisgender	17 (63.0%)
Female, cisgender	9 (33.3%)
Female, transgender	1 (3.7%)
Sexual orientation	
Straight or heterosexual	19 (70.4%)
Bisexual	3 (11.1%)
Gay or homosexual	5 (18.5%)
Born outside U.S	3 (11.1%)
Education	
Partial high school	13 (48.1%)
High school graduate	8 (29.6%)
Partial college	4 (14.8%)
College graduate	2 (7.4%)
Have children	14 (51.85%)
Employment ^a	
Full-time work	1 (3.7%)
Part-time work	4 (14.8%)
Full or part-time school	1 (3.7%)
Neither work nor school	6 (22.2%)
On disability	14 (51.9%)
Retired	1 (3.7%)
Other/decline to answer	2 (7.4%)

^aIndicates that several items could be endorsed, therefore numbers and percentages do not add up to the total participant amount

Table 3**Syndemics**

Variable	N (%)
Psychiatric diagnoses and psychosocial issues ^a	
Depression	13 (48.1%)
Social anxiety	4 (14.8%)
Bipolar disorder	2 (7.4%)
Panic disorder	3 (11.1%)
Obsessive-compulsive disorder	1 (3.7%)
Post-traumatic stress disorder	5 (18.5%)
PTSD-qualifying event	19 (70.4%)
Binge eating disorder	1 (3.7%)
Antisocial personality disorder	7 (25.9%)
Substance use problems	
Alcohol use disorder	4 (14.8%)
Substance use disorder	10 (37.0%)
History of self-reported problematic substance use	17 (63.0%)
Structural issues ^a	
Financial instability	13 (48.1%)
Transportation instability	9 (33.3%)
Food insecurity	11 (40.7%)
Interpersonal issues ^a	
Childhood sexual abuse	7 (25.9%)
Rape in adulthood	6 (22.2%)
Total syndemics ^b	
0	0 (0%)
1	2 (7.4%)
2	5 (18.5%)
3	5 (18.5%)
4	3 (11.1%)
5	3 (11.1%)
6–9	9 (33.3%)

^aIndicates that several items could be endorsed, therefore numbers and percentages do not add up to the total participant amount

^bTotal syndemics count is a sum score of: depression, social anxiety, bipolar disorder, OCD, binge eating disorder, antisocial personality disorder, trauma (PTSD or PTSD-qualifying event), rape as an adult, childhood sexual abuse, substance use problem (alcohol use disorder, substance use disorder, and/or history of problematic substance use), financial instability, transportation instability, and food insecurity Syndemics displayed in this table were systematically assessed at baseline. See “Results” section for additional syndemics that were not systematically assessed at baseline

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Table 4

Number of sessions participants completed

Number of sessions	N (%)
14	13 (48.1%)
13	2 (7.4%)
12	2 (7.4%)
11	1 (3.7%)
10	2 (7.4%)
9	1 (3.7%)
8	2 (7.4%)
6	1 (3.7%)
5	1 (3.7%)
1	2 (7.4%)

Table 5

Participant outcomes observed longitudinally

Variable	BL (N = 27)	4MFU (N = 24)	8MFU (N = 23)
Viral load			
Log PVL <i>M(SD)</i>	4.06 (1.04)	2.49 (2.14)	2.77 (2.12)
Undetectable (< 200) <i>Frequency (%)</i>	1 (3.7%)	12 (50%)	8 (36.4%)
PVL Not Available <i>Frequency (%)</i>	0 (0%)	0 (0%)	1 (4.5%)
Self-report adherence			
Percent prior 2 weeks <i>M(SD)</i>	68.1 (31.99)	81.7 (28.39)	85.7 (23.71)
Wisepill adherence			
Percent prior week ^a <i>M(SD)</i>	68.75 (33.36)	74.06 (31.15)	47.06 (46.23)
PHQ-9 depression			
<i>M(SD)</i>	6.12 (6.56)	3.68 (4.43)	4.08 (4.54)
PANAS: positive affect			
<i>M(SD)</i>	31.76 (10.71)	35.08 (10.16)	35.86 (10.65)
<i>Missing F(%)</i>	2 (7.4%)	0 (0%)	1 (4.5%)
PANAS: negative affect			
<i>M(SD)</i>	17.74 (7.84)	13.38 (4.02)	16.91 (8.91)
<i>Missing F(%)</i>	4 (14.81%)	0 (0%)	0 (0%)

^a Average percent adherence is presented for the week following the baseline visit, the 16th week (approximation of 4 months from baseline), and the 32nd week (approximation of 8 months from baseline)

Table 6

Parameter estimates for change in outcomes over time

Study outcome ^a	Time period	Tests of linear trends	
		Estimate (SE)	LRT ^d
Wisepill adherence			
Active treatment	Weekly (baseline to 4-month)	0.14 (0.44)	$\chi^2(2) = 22.15^{**}$
Follow up	Weekly (4-month to 8-month)	− 1.33 (0.69)	$\chi^2(2) = 56.42^{**}$
Self-report adherence			
Active treatment	Weekly (treatment phase)	0.06 (0.02) ^{**}	$\chi^2(2) = 1.81$
Full study period	Major assessments only	0.87 (0.30) ^{**}	$\chi^2(2) = 5.18$
Positive affect			
Active treatment	Weekly (treatment phase)	0.16 (0.11)	$\chi^2(2) = 29.24^{**}$
Negative affect			
Active treatment	Weekly (treatment phase)	− 0.28 (0.06) ^{**}	$\chi^2(2) = 1.26$

Study outcome^b Non-linear comparisons

	Baseline vs. 4-month	Baseline vs. 8-month
Log PVL	- 1.13 (0.30) ^{**}	- 0.93 (0.32) ^{**}
Positive affect	3.43 (1.77)	3.84 (1.80) [*]
Negative affect	- 4.34 (1.35) ^{**}	- 0.77 (1.37)
PHQ depression	- 1.87 (1.03)	- 1.60 (1.05)

The HLM parameter estimates are reported, followed by the standard error in parentheses

^aThe results of the LRT determine whether we retained a fixed effects only model or if we retained the random effects as well for the linear test. A significant finding on the LRT means that we included the fixed *and* random effects in the linear test

^bReference = baseline

^{*}Significant at $p < .05$

^{**}Significant at $p < .01$