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Feasibility randomized-controlled trial of online acceptance and commitment therapy for painful peripheral neuropathy in people living with HIV: The OPEN study

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Abstract

Background: Neuropathic pain negatively affects quality of life among people living with HIV (PLWH). This study examined the feasibility of conducting a full-scale randomized-controlled trial of online acceptance and commitment therapy ("ACT OPEN") for neuropathic pain in PLWH.

Methods: Using a parallel-groups design, thirty-eight participants were randomized to ACT OPEN or a waitlist control (2:1). Participants completed standard self-report outcome measures at baseline, and two- and five-months post-randomization. Participants were aware of their allocation, but assessment was blinded.

Results: Twenty-five participants were randomized to ACT OPEN and 13 to the control (of 133 referrals). ACT OPEN completion was 69% and two-month trial retention was 82%. Treatment credibility and satisfaction scores for ACT OPEN were comparable to scores reported in previous trials of cognitive-behavioural treatments for pain. Four adverse events were reported during the study, including one serious adverse event; all of these were unrelated to the research procedures. Small to moderate effects and 95% confidence intervals suggest that the true effect may favour ACT OPEN for improvements in pain intensity/interference and depression.

Conclusions: A full-scale RCT of online ACT for pain management in PLWH may be feasible with refinements to trial design to facilitate recruitment.

Significance: Research on pain management in people living with HIV has primarily focused on pharmacological treatments with limited success. This is the first study to show the potential feasibility of a psychological treatment based on acceptance and commitment therapy delivered online and tailored for pain management in people with HIV ("ACT OPEN"). ACT OPEN may be a promising treatment in this population and further evaluation in a full-scale randomized-controlled trial appears warranted.

Trial Registration: The trial was registered (clinicaltrials.gov; NCT03584412).

1 | INTRODUCTION

People living with HIV (PLWH) identify pain as a priority quality of life limiting outcome (Bristowe et al., 2019). Pain is reported by 54–83 percent of PLWH (Parker et al., 2014). Neuropathic pain, related to the effects of the virus, the immune system or older neurotoxic antiretroviral therapy (ART) on the nervous system, is particularly prevalent. Neuropathic pain due to distal symmetrical polyneuropathy affects 22%–44% of PLWH and is strongly associated with reduced quality of life (Ellis et al., 2010; Pillay et al., 2017; Wadley et al., 2011).

Persistent pain in PLWH is associated with depression, post-traumatic stress, substance misuse, sleep disturbance, unemployment, health service use and reduced ART adherence (Scott, Arkuter, et al., 2018). However, research on pain management in PLWH has primarily focused on pharmacological treatments. Systematic reviews of randomized-controlled trials (RCTs) indicate that pharmacological interventions are not effective for neuropathic pain in this population (Finnerup et al., 2015; Phillips et al., 2010). More holistic treatments that consider the psychosocial complexities of pain in PLWH are needed.

Cognitive-behavioural therapy (CBT) improves pain-related disability and distress in chronic pain in general (Williams et al., 2012). Acceptance and commitment therapy (ACT), a form of CBT, focuses on developing psychological flexibility – the ability to experience pain with openness, consciously focus on experiences in the present, and consistently pursue personally meaningful activities (McCracken & Vowles, 2014). RCTs show that ACT for chronic pain may also improve disability and mood (Veehof et al., 2016). The capacities developed in ACT are applicable to a range of health and mental health problems (A-tjak et al., 2015; Hayes et al., 2012). Therefore, ACT may be well-suited to address the multiple symptoms and psychosocial challenges comorbid with pain in PLWH.

There is growing evidence that ACT for pain can be delivered online (Buhrman et al., 2016; Lin et al., 2017; Scott, Chilcot, et al., 2018; Trompetter et al., 2014). Internet-delivered pain management reduces access barriers (Eccleston et al., 2020), is easily standardized, and requires fewer clinician resources than face-to-face delivery. Thus, online ACT represents a potentially scalable treatment for pain in PLWH, although it has not been evaluated in this context.

To date, there are no full-scale RCTs of psychological treatments for PLWH and chronic pain. A 2003 trial investigated CBT versus supportive psychotherapy in 61 PLWH and neuropathic pain; 57% CBT non-completion suggested limited acceptability (Evans et al., 2003). Three more recent pilot RCTs (n = 23–43) in the United States demonstrate better completion within cognitive-behavioural treatments for pain in PLWH (George et al., 2017; Merlin, Westfall, et al., 2018; Uebelacker et al., 2016). Two of these showed preliminary evidence of between-groups improvements in pain interference favouring CBT (Merlin, Westfall, et al., 2018; Uebelacker et al., 2016). However, these studies did not focus on neuropathic pain. Online ACT has not been studied in this population and the feasibility of a larger trial of this treatment is not yet known. The purpose of this study was to examine the feasibility of conducting a full-scale RCT evaluating online ACT for neuropathic pain in PLWH.

2 | METHODS

2.1 | Trial Design and Randomization

This was a parallel-groups feasibility RCT. All participants provided informed consent. Study approvals were obtained by the National Research Ethics Service (18/LO/0559). The study was performed in accordance with the ethical standards in the 1975 Declaration of Helsinki and its later amendments. Block randomization (2 ACT OPEN: 1 waitlist) stratified by recruitment site was conducted independently by the King's College London Clinical Trials Unit to ensure allocation concealment. This ratio was decided

in collaboration with patient partners to facilitate recruitment and retention considering the 5-month wait for control participants to receive ACT OPEN. The wait for speciality pain management services within the National Health Service can be longer than 5 months. However, patient partners – identified through their membership in the UK Community Advisory Board, a widely respected HIV advocacy organization – felt 5 months was too long to wait for any type of pain management treatment. A shorter waiting list control was not chosen as 5 months post-randomization (i.e., 3-months post-treatment) was deemed the minimum needed to investigate possible maintenance of effects. Therefore, the 2:1 ratio was chosen to balance optimization of recruitment and retention while ensuring the ability to collect meaningful follow-up data.

2.2 | Blinding

Given the nature of treatment and control, blinding of therapists and participants was not possible. Follow-up outcome assessment was conducted by two researchers (JB and ED) blinded to allocation. Although participants were asked not to disclose their allocation to the assessors, a small minority did so (13.7% for both follow-ups combined). Standardized questionnaire instructions were used to minimize bias. Given the allocation ratio, it was not possible to blind analyses.

2.3 | Recruitment and Eligibility

Participants were recruited from HIV clinics at Guy's & St Thomas' Hospital, King's College Hospital, and Chelsea & Westminster Hospital NHS Foundation Trusts in London, UK. Clinicians identified potential participants during routine care and advertisements were placed in clinics. Additionally, people with HIV and painful peripheral neuropathy from previous studies by our group ((Scott et al., 2020) and NCT02555930) who consented to be re-contacted were approached. Although patient partners were consulted to develop the recruitment strategy, they were not involved in recruiting participants.

Eligibility screening was conducted in clinic or by telephone by WS/JB. Table 1 summarizes eligibility criteria. Eligible participants screened in clinic also completed the Clinical HIV-associated Neuropathy Tool screening tool (CHANT), assessing subjective symptoms (foot pain and numbness) and objective signs (loss of vibration and ankle reflex) of neuropathy (Woldeamanuel et al., 2016). Positive CHANT and DN4 neuropathic pain interview screens together indicate 'probable' neuropathic pain (Finnerup et al., 2016). CHANT data were not used for eligibility, but to inform the feasibility of completing the CHANT during a routine visit versus a separate baseline assessment if a full-scale trial evaluating ACT OPEN is undertaken in the future.

TABLE 1 Trial Eligibility Criteria

Inclusion Criteria

- ≥18 years old and living with HIV
- Positive screen for peripheral sensory neuropathy (self-reported bilateral foot pain in a symmetrical distribution) (Woldeamanuel et al., 2016)
- Positive screen for neuropathic pain symptoms in the feet, indicated by a score of ≥ 3 on patient reported outcomes section of DN4 Neuropathic Pain Interview (Bouhassira et al., 2005, 2008)
- Pain present most days for ≥ 3 months
- Average past week pain intensity and interference of ≥ 4 on scale from 0 (no pain/interference) to 10 (pain as bad as you can imagine/unable to carry out any activities) (Von Korff et al., 1992; Zelman et al., 2005)
- At least moderate depression symptoms (≥10 on the PHQ-9) (Kroenke et al., 2001)

Exclusion Criteria

- Major surgery planned in next five months
- Inability to complete study in English
- Positive screen of self-reported alcohol or other substance misuse (excluding tobacco) in the past 3 months on the ASSIST-Lite (Ali et al., 2013)
- Severe depression symptoms (PHQ-9 score > 23/27)*
- Active suicidal ideation
- Any other severe (e.g. active psychosis, bipolar disorder) and poorly controlled psychiatric disorder judged to interfere with safely engaging in an online psychological treatment for pain management
- Changes to medications for pain or mood within the past six weeks

*A score of ≥ 20 has been suggested as a cut-off for severe depression on the PHQ-9 (Kroenke et al., 2001). However, the presence of pain overlaps with somatic items on the PHQ-9. Therefore, it was decided to raise the cut-off for severe depression to 23, which is one standard deviation above the mean score of patients attending specialty chronic pain treatment (Scott & McCracken, 2015).

2.4 | Sample Size

The initially planned sample was a total of 70 participants; this number was chosen as optimal for estimating the standard deviation of the outcome variable to calculate the sample size of an efficacy trial (Teare et al., 2014). With a total of 70 and 2:1 randomization, there would have been approximately 24 participants in the control group, which is above the suggested minimum of 12 per group (Julious, 2005). Given this was a feasibility trial and the recruitment rate unknown, we aimed for a minimum sample of 30 total in the situation where recruitment was lower than anticipated (Whitehead et al., 2016).

2.5 | Treatments

2.5.1 | ACT OPEN

The experimental treatment was ACT (Hayes et al., 2012; McCracken & Vowles, 2014) online for painful peripheral neuropathy in PLWH (ACT OPEN). A systematic review (Scott, Arkuter, et al., 2018), qualitative study (Scott et al., 2020) and consultation with community partners were used to tailor treatment to the needs of PLWH and painful peripheral neuropathy and to reduce potential participation barriers. Community partners provided feedback on treatment and study materials to increase acceptability, inclusivity and relevance to PLWH and chronic pain. Lack of Internet access was not an exclusion criterion and potential participants were told they could be loaned a wifi-enabled tablet if needed. ACT OPEN participants continued to receive standard medical care.

Treatment entailed 12 online sessions (45–60 min each) over 8 weeks. Two sessions were scheduled per week for six weeks, but there was flexibility such that participants were given two further weeks to complete any unfinished sessions. The system scheduled sessions so a maximum of two were completed per week to ensure participants had time to apply new strategies between sessions. Participants had to complete sessions in a set order, and they were not able to advance to a later session without completing the preceding one.

Following patient input, sessions contained quotations from PLWH and neuropathic pain (Scott et al., 2020), as well as brief videos and audio recordings which provided information about pain and guided participants through metaphors, experiential exercises, mindfulness practice, values clarification and goal-setting (Table S1). The order and content of sessions were designed so that participants were exposed to the three key processes of psychological flexibility – behaviour that is 'open, aware, and active/engaged' (Hayes et al., 2011) – in the early sessions. There were multiple strategies to promote these capabilities across sessions, and many sessions addressed multiple processes at once. This ensured that participants were exposed to core skills even if they did not complete all sessions. Participants were also given a hard copy workbook summarizing sessions, as suggested by patients during our development work. The complete workbook is in the Supplementary Materials.

ACT OPEN was therapist-supported (Andersson, 2016). The therapists (WS and BG) were clinical psychologists with experience providing ACT for pain and online delivery. Participants were asked to respond to questions assessing their treatment experiences and goals during each session. They were informed that their therapist could provide feedback through secure in-site written messages, brief telephone calls (10–30 min) or both. This flexibility of support was offered in response to varying preferences for support delivery identified during qualitative interviews and community partner feedback.

Therapists provided feedback tailored to individual responses; therefore, feedback content was not manualized. The main functions of therapist feedback were to motivate continued treatment engagement, build the therapeutic alliance, identify instances of psychologically flexible/inflexible responding, and help participants become more sensitive to the impacts of their responses. As an example, for a participant who practiced a new ACT-based strategy while experiencing pain, the therapist feedback might have included the following: praise for engaging in this behaviour alongside validation of the discomfort of doing so; acknowledgement that this behaviour is an example of responding with openness; and, a question asking the participant to reflect on what they noticed as a result of approaching the pain differently. Therapist feedback was also used to monitor progress on valued goals.

To initiate treatment, a phone call was arranged to identify participants' preferences for receiving therapist support, discuss website practicalities, and identify and plan for treatment barriers. A few participants preferred for this information to be communicated by email. Participants were informed that their therapist would respond to messages within 24 (work week) to 72 hr (over the weekend). Additional phone calls were prompted by the therapist based on identifying a need for further support, such as to manage difficulties experienced during treatment. Phone calls were scheduled at a mutually convenient time. A final phone call was offered after session 12 to review progress and make a plan to maintain this; alternately, this could be discussed via messaging if preferred.

2.5.2 | Waitlist control

Waitlist participants received standard medical care at the discretion of their HIV clinicians and general practitioners for five months. Control participants had access to ACT OPEN, as above, after completing the five-month assessment. A waitlist control was chosen as there was no clearly credible active/attention control in this context. In the context of few legitimate available alternatives, a waitlist control in which participants continued to receive standard medical care was chosen to pragmatically (Ford & Norrie, 2016) investigate the addition of ACT OPEN.

2.6 | Assessment

Self-report questionnaires were completed online (https://www.onlinesurveys.ac.uk) or by post at baseline and two- and five-months post-randomization (unless otherwise

specified). Participants received £10 gift vouchers for each assessment. Control participants completed questionnaires after completing ACT OPEN (7-months post-randomization) and received £5 for this. At baseline, participants answered demographic, medical history and pain symptom (DN4, self-report (Bouhassira et al., 2005, 2008)) questions.

2.6.1 | Primary Feasibility Measures

Recruitment and Retention

The number of referrals, and eligible, consenting and randomized participants were recorded. The number of participants who completed baseline and follow-up assessments was also recorded.

Treatment completion

Therapists recorded ACT OPEN session completion. Treatment completion was defined as completing ≥ 8/12 sessions; this proportion was previously used to define treatment completers in a full-scale RCT of online ACT for pain (Trompetter et al., 2014). Completion of 8 ACT OPEN sessions exposes participants to the core ACT processes of 'openness, awareness and engagement' (Hayes et al., 2011). We expected 70% of participants would complete treatment as a feasibility indicator, based on previous studies (Scott, Chilcot, et al., 2018; Trompetter et al., 2014).

Treatment Credibility and Satisfaction

At baseline, participants completed the six-item Treatment Credibility and Expectations Questionnaire (CEQ; current Cronbach's $\alpha = 0.89$). Participants rated their beliefs and feelings about ACT OPEN on a 9-point scale after reading a brief treatment summary (Devilly & Borkovec, 2000). CEQ items were reworded to assess expected improvements in limitations due to pain (Smeets et al., 2008). Higher CEQ subscale scores indicate greater credibility (items 1–3) and expectancy (items 4–6; range each subscale: 3–27). An example credibility item is, "At this point, how logical does the therapy offered to you seem?" (1, not at all logical to 9, very logical). An example expectancy item is, "At this point, how much do you really feel that the therapy will help to reduce your limitations due to chronic pain?" (1, not at all to 9, very much) (Devilly & Borkovec, 2000; Smeets et al., 2008). In a previous chronic pain RCT in which CBT was superior to a waitlist control and comparable to physiotherapy, mean CBT credibility and expectancy ratings were 19.2 ($SD = 3.7$) and 15.4 ($SD = 4.4$), respectively (Smeets et al., 2008).

Participants completed the 8-item Client Satisfaction Questionnaire (CSQ-8) (Nguyen et al., 1983) at 2- (whole sample) and 7-months (waitlist). Participants rated items from 1–4. Each item has slightly different response options. Higher total CSQ scores indicate greater satisfaction (range: 8–32; current $\alpha = 0.90$). An example item is, "To what extent has our programme met your needs?" (rated from 1: None of my needs have been met, to 4: Almost all of my needs have been met). In a previous RCT demonstrating the efficacy of online ACT for pain compared to expressive writing, the mean ACT CSQ rating was 24.7 ($SD = 4.0$) (Trompetter et al., 2014).

Participants made a single global impression of change (PGIC) rating using a 7-point scale from 1 (very much improved) to 7 (very much worse) (Farrar et al., 2001; Guy, 1976; Scott & McCracken, 2015). Participants completed the PGIC at 2- and 5-months (whole sample) and 7-months post-randomization (waitlist).

Participants were asked if they shared ACT OPEN materials with others. Participants answered open-ended questions to describe the most and least helpful ACT OPEN features, adverse events and suggest improvements. Adverse events were also captured by recording relevant information provided during follow-up assessments and/or therapist communication.

Data Completeness

The number of individual questionnaires with missing data was recorded.

2.6.2 | Secondary Feasibility Outcomes

Secondary outcomes were pain intensity and interference (Brief Pain Inventory) (Cleeland & Ryan, 1994), the impact of pain on work and social functioning (Work and Social Adjustment Scale; WSAS) (Cella et al., 2011; Mundt et al., 2002), depression symptoms (PHQ-9) (Kroenke et al., 2001), number of analgesic medications, healthcare visits, and other treatments for pain, and pain acceptance (Chronic Pain Acceptance Questionnaire; CPAQ-8) (Fish et al., 2010; McCracken et al., 2004). See Table S2 for psychometric details of secondary outcome measures.

2.7 | Feasibility criteria

A full-scale RCT of ACT OPEN was regarded as feasible if: 1) 70 participants were recruited and randomized; 2) 80% of participants were retained at the first follow-up (at 2-months post-randomization); 3) 70% of participants completed at least 8/12 treatment sessions; 4) ACT OPEN treatment credibility and satisfaction were comparable to scores in previous trials of CBT/ACT for pain (Smeets et al., 2008; Trompetter et al., 2014); and 5) at least small between-groups effect sizes were observed on secondary outcomes.

2.8 | Data Analysis

Descriptive statistics were computed to characterize the sample and examine primary feasibility outcomes. Due to small numbers, comparisons between follow-up assessment completers and non-completers and treatment completers and non-completers were not undertaken using statistical testing. Responses to open-ended treatment experience questions were analysed using content analysis.

Secondary outcome data were used to estimate between-groups effects. Given the feasibility aims, significance testing was not undertaken as the sample size was not informed by an a priori power calculation. The estimates of efficacy were interpreted in terms of the width of the 95% confidence intervals (CIs) for the between-group effect. Continuous outcomes were analysed using intention-to-treat (ITT) linear mixed effects regression models with maximum likelihood estimation, assuming data missing at random. Random intercepts accounted for the repeated measures nature of the data. The models included treatment group, time, a group-by-time interaction and the baseline score for the relevant outcome as covariates. The estimated mean differences at each follow-up from the models were used to compute Hedge's g (corrected for small sample) with 95% CIs; values of 0.20, 0.50 and 0.80 were considered small, medium and large, respectively (Cohen, 1988).

For count outcomes, mixed effects negative binomial regression equations were conducted. Covariates were included as described above. For these models, incidence rate ratios (IRRs) and 95% CIs were computed as the measure of effect size. A sensitivity analysis testing missing data assumptions involved re-running analyses using baseline observation carried forward imputation (BOCF).

3 | RESULTS

3.1 | Primary Feasibility Outcomes

3.1.1 | Recruitment and Participant Characteristics

Figure 1 displays the CONSORT diagram. One hundred and thirty-three participants were referred (July 2018 to May 2019); 57 were interested and eligible (42.9%, CI = 34.5–51.3). Thirty-eight participants consented, completed baseline questionnaires and were randomized (25 to ACT OPEN, 13 to waitlist). Thus, the recruitment rate was 28.6% (CI = 20.9–36.3).

The sample was comprised predominantly of men (76.3%) and white participants (65.8%), with a mean age of 55.9 (*SD* = 5.8) years (Table 2). Participants had longstanding HIV (mean = 22.9 years, *SD* = 8.9) and self-reported neuropathic pain (mean = 11.4 years, *SD* = 8.2). In addition to peripheral neuropathic pain, 39.5% reported widespread pain. On average, participants reported moderate levels of pain intensity and interference, and moderately-severe depression symptoms (Kroenke et al., 2001; Zelman et al., 2005).

3.1.2 | Trial Retention, Treatment Completion and Data Completeness

Of 25 ACT OPEN participants, 19 (76%, CI = 59.3–92.7) and 17 (68%, CI = 49.7–86.3) completed 2- and 5-month assessments, respectively. Of 13 control participants, 12 (92.3%; CI = 77.8–100.0) and 10 (76.9%, CI = 54.0–99.8) were retained at 2- and 5-months. The combined retention was 31 (81.6%, CI = 69.3–93.9) and 27 (71.1%, CI = 56.7–85.5) participants at 5- and 5-months.

Seventeen of 25 participants randomized to ACT OPEN were treatment completers (68.0%, CI = 49.7–86.3). The median number of sessions completed in this group was 12 (interquartile range (IQR) =9). Ten waitlist participants completed the 5-month assessment and were subsequently offered ACT OPEN; seven (70.0%; CI = 41.6–98.4) of these were treatment completers (median sessions completed = 11, IQR = 9). Taken together, 24/35 participants offered ACT OPEN (68.6%, CI = 53.2–84.0) completed treatment with a median of 12 sessions (IQR = 9). The number of sessions completed among treatment non-completers was 0 ($n = 5$), 1 ($n = 2$), 2 ($n = 1$), 4 ($n = 2$), and 5 ($n = 1$). Reasons for non-completion were: struggling with other health problems ($n = 4$); managing pain okay ($n = 2$); struggled to use website ($n = 2$); no Internet (Wi-Fi-enabled tablet not provided as went abroad; $n = 1$); bereavement ($n = 1$); no reason given ($n = 1$).

Participants primarily received support through a mix of messaging and telephone calls (number of calls, median: 1, range: 0–3; four participants opted for messages only). Phone calls were principally utilized at the start and end of treatment. Calls that occurred as participants were completing the online sessions were spread across different sessions with no clear pattern to the timing of these. The average therapist support time across messages and calls was 2 hr and 14 min (*SD*: 42 min, range: 55 min to 3 hours and 40 min). No participant was supported entirely by phone.

Across assessments, questionnaires with the highest completion rates were: BPI, PHQ-9, WSAS and analgesic classes (93.5%–100% of participants completed). The CEQ (71.0%–79.0%) and CSQ (77.0%) had the lowest completion. On the CEQ, item 3 ("How confident would you be in recommending this treatment to a friend with the same

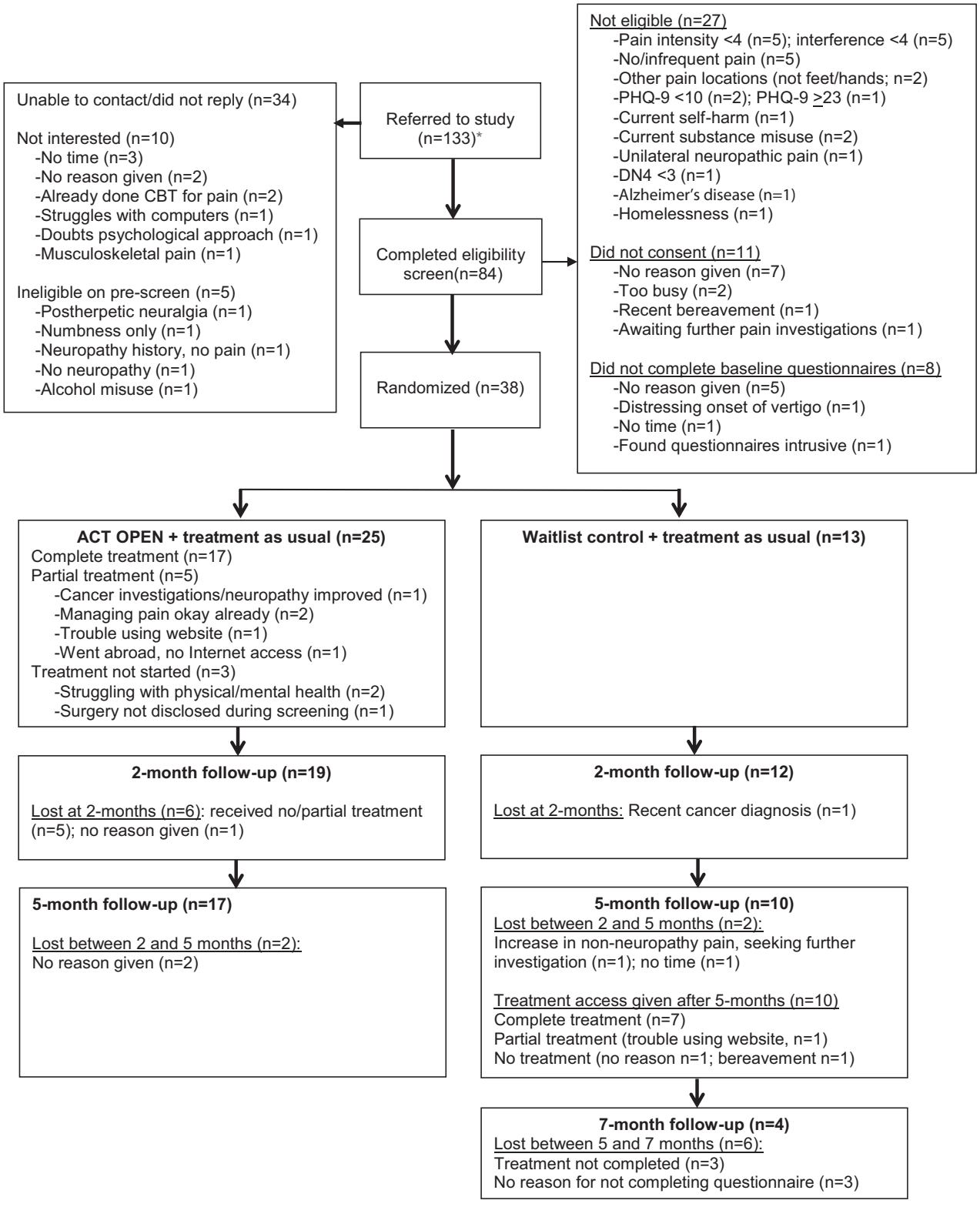

FIGURE 1 CONSORT Flow Diagram. *Note: Clinician referrals ($n = 105$), re-contacted from previous studies ($n = 26$), reponded to advertisement in clinic ($n = 2$)

problems?") had the most missing responses (23.7%). On the CSQ, item 4 ("If a friend were in need of similar help, would you recommend this treatment to him or her?") had the most missing responses, along with items 5 and 8 (each 36.8% missing).

3.1.3 | Treatment Credibility and Satisfaction and Adverse Events

Mean ACT OPEN credibility and expectancy ratings were 18.1/27 ($SD = 3.9$) and 18.0/27 (4.2), respectively. Mean

TABLE 2 Baseline demographics and scores on study variables

	ACT OPEN Mean (*SD*) or *n* (%)	Waitlist Control Mean (*SD*) or *n* (%)	Total sample Mean (*SD*) or *n* (%)
Gender			
Men	20 (80.0)	9 (69.2)	29 (76.3)
Women	5 (20.0)	4 (30.8)	9 (23.7)
Age (years)	55.80 (5.65); $n = 25$	56.00 (6.22); $n = 13$	55.87 (5.77); $n = 38$
Sexuality			
Men who have sex with men	16 (64.0)	9 (69.2)	25 (65.8)
Heterosexual	7 (28.0)	2 (15.4)	9 (23.7)
Missing	2 (8.0)	2 (15.4)	4 (10.5)
Ethnicity			
White	17 (68.0)	8 (61.5)	25 (65.8)
Black	8 (32.0)	3 (23.1)	11 (28.9)
Mixed	0 (0)	2 (15.4)	2 (5.3)
First language			
English	18 (72.0)	10 (76.9)	28 (73.7)
Language other than English	7 (28.0)	2 (15.4)	9 (23.7)
Missing	0 (0)	1 (7.7)	1 (2.6)
Living status			
Alone	11 (44.0)	7 (53.8)	18 (47.4)
With partner/children/relatives	12 (48.0)	6 (46.2)	18 (47.4)
Missing	2 (8.0)	0 (0)	2 (5.3)
Level of education			
Entry level/GCSEs	6 (24.0)	2 (15.4)	8 (21.1)
A-levels	3 (12.0)	3 (23.1)	6 (15.8)
Foundation degree	2 (8.0)	0 (0)	2 (5.3)
Undergraduate	11 (44.0)	5 (38.5)	16 (42.1)
Postgraduate	2 (8.0)	1 (7.7)	3 (7.9)
Missing	1 (4.0)	2 (15.4)	3 (7.9)
Work status			
Employed	5 (20.0)	4 (30.8)	9 (23.7)
Unemployed	14 (56.0)	7 (53.8)	21 (55.3)
Student	1 (4.0)	0 (0)	1 (2.6)
Retired	3 (12.0)	2 (15.4)	5 (13.1)
Missing	2 (8.0)	0 (0)	2 (5.3)
HIV duration (years)	22.53 (10.24); $n = 20$	23.61 (6.05); $n = 11$	22.91 (8.88); $n = 31$
Most recent CD4 count			
<200	3 (12.0)	0 (0)	3 (7.9)
<350	1 (4.0)	1 (7.7)	2 (5.3)
<500	5 (20.0)	2 (15.4)	7 (18.4)
≥500	12 (48.0)	7 (53.8)	19 (50.0)
Missing	4 (16.0)	3 (23.1)	7 (18.4)
Most recent viral load			
Undetectable	24 (96.0)	12 (92.3)	36 (94.7)
Detectable	1 (4.0)	0 (0)	1 (2.6)
Missing	0 (0)	1 (7.7)	1 (2.6)

(Continues)

TABLE 2 (Continued)

	ACT OPEN Mean (*SD*) or *n* (%)	Waitlist Control Mean (*SD*) or *n* (%)	Total sample Mean (*SD*) or *n* (%)
On ART			
Yes	25 (100.0)	13 (100.0)	38 (100.0)
Neuropathic pain duration (years)	12.31 (7.85); $n = 21$	9.93 (8.83); $n = 12$	11.44 (8.16); $n = 33$
Neuropathic pain symptoms (DN4i)	5.32 (1.44); $n = 25$	5.15 (1.28); $n = 13$	5.26 (1.37); $n = 38$
CHANT positive (participants screened in clinic only)	5/5	6/6	11/11
Widespread pain[b]			
Yes	10 (40.0)	5 (38.5)	15 (39.5)
No	15 (60.0)	8 (61.5)	23 (60.5)
Average pain intensity (BPI)	6.79 (2.29); $n = 24$	5.90 (1.68); $n = 13$	6.48 (2.11); $n = 37$
Pain interference (BPI)	6.99 (2.07); $n = 24$	7.27 (1.62); $n = 13$	7.09 (1.90); $n = 37$
Work and Social Adjustment (WSAS)	28.83 (10.74); $n = 23$	30.46 (7.83); $n = 13$	29.42 (9.71); $n = 36$
Depression (PHQ−9)	16.56 (5.38); $n = 25$	14.62 (5.58); $n = 13$	15.89 (5.45); $n = 38$
Number of classes of analgesic medications	2 (0–5); $n = 25$[a]	2 (0–4); $n = 13$[a]	2 (0–5); $n = 38$[a]
Number of healthcare visits (GP, A&E, other doctors)	1.5 (0–10); $n = 24$[a]	1 (0–5); $n = 11$[a]	1 (0–10); $n = 35$[a]
Number of other treatments accessed for pain	1 (0–4); $n = 23$[a]	2 (0–7); $n = 12$[a]	1 (0–7); $n = 35$[a]
Pain acceptance (CPAQ−8)	21.42 (9.70); $n = 22$	19.25 (6.89); $n = 12$	20.65 (8.76); $n = 34$
ACT OPEN treatment credibility (CEQ)			
Credibility subscale	18.44 (4.13); $n = 16$	17.55 (3.78); $n = 11$	18.07 (3.94); $n = 27$
Expectancy subscale	18.16 (4.15); $n = 19$	17.64 (4.43); $n = 11$	17.97 (4.19); $n = 30$

Note: All variables included in the table were self-reported by participants.

Abbreviation: BPI, Brief Pain Inventory; CEQ, Treatment Credibility and Expectations Questionnaire; CHANT, Clinical HIV-associated Neuropathy Tool; CPAQ-8, Chronic Pain Acceptance Questionnaire 8-item version; DN4, Douleur Neuropathique 4 Questions Interview (English version); PHQ-9, Patient Health Questionnaire--Depression; WSAS, Work and Social Adjustment Scale

[a]Median and range.

[b]Widespread pain in addition to peripheral neuropathic pain.

treatment satisfaction at 2-months was 25.9/32 (*SD* = 4.6) for ACT OPEN and 19.7/32 (*SD* = 2.5) for control participants. Seven ACT OPEN participants shared treatment materials with others (not in the trial).

On the 2-month PGIC, 31.6% (CI = 13.4–49.8) of ACT OPEN participants rated themselves as 'much improved' or 'very much improved' overall compared to 0% of control participants; at 5-months these values were 23.5% (CI = 7.0–40.2) for ACT OPEN and 10% (CI = 0.0–28.6) for control participants. At 2-months, two waitlist participants were 'minimally worse' and one 'much worse'; one waitlist participant rated 'minimally worse' at 5-months. No ACT OPEN participant reported any worsening on the PGIC during follow-ups.

The content analysis of open-ended treatment experience questions appears in Table S3. The most common "most helpful" aspects of ACT OPEN were space/time to reflect; (re-)engaging with mindfulness/meditation; user-friendly, well-structured and manageable sessions; and prompt/helpful therapist feedback. The most common "least helpful" aspects were the "hurried" frequency of sessions and repetition of some strategies. Three participants reported treatment was "challenging or stressful". One participant reported that low mood and pain were barriers to treatment completion.

Four adverse events were reported (2 ACT OPEN; 2 waitlist). One waitlist participant was diagnosed with cancer after baseline; this serious adverse event was unrelated to research procedures. One participant reported increased irritability while completing ACT OPEN which they attributed to altering antidepressant dose. Another reported a new onset of fever, fatigue and abdominal pain under investigation which interfered with starting ACT OPEN. Finally, one waitlist participant reported increased knee pain following the 2-month assessment, under further investigation.

3.2 | Secondary Feasibility Outcomes

For all continuous variables, treatment effect sizes favoured ACT OPEN and were typically small to moderate at both two- and five-months (Table 3). There was considerable uncertainty in the estimates with 95% CIs indicating the potential for true effects to range between small harms and large

TABLE 3 Between-groups effects on secondary outcome variables

Variable and Time	ACT OPEN Mean (SE; CI)[a]	Waiting list Mean (SE; CI)[a]	Hedge's g[b]/IRR (CI)	ACT OPEN BOCF Mean (SE; CI)[a]	Waiting list BOCF Mean (SE; CI)[a]	BOCF Hedge's g[b]/ IRR (CI)
Pain intensity						
2-months	5.85 (0.34; 5.16–6.52)	6.56 (0.45; 5.67–7.46)	0.32 (−0.34–1.00)	6.14 (0.28; 5.57–6.70)	6.90 (0.39; 6.13–7.67)	0.34 (−0.34–1.02)
5-months	5.12 (0.37; 4.38–5.85)	6.56 (0.46; 5.63–7.49)	0.65 (−0.05–1.34)	5.77 (0.28; 5.57–6.70)	6.77 (0.39; 6.01–7.54)	0.45 (−0.23–1.13)
Pain interference						
2-months	5.64 (0.36; 4.92–6.35)	7.00 (0.44; 6.12–7.87)	0.67 (−0.02–1.36)	5.94 (0.29; 5.36–6.52)	6.94 (0.40; 6.15–7.74)	0.49 (−0.19–1.17)
5-months	5.40 (0.37; 4.60–6.14)	7.04 (0.47; 6.09–7.98)	0.81 (0.11–1.50)	6.06 (0.29; 5.5–6.64)	7.03 (0.40; 6.24–7.82)	0.48 (−0.20–1.16)
Work/social function						
2-months	25.26 (1.50; 22.23–28.28)	30.00 (1.78; 26.40–33.60)	0.46 (−0.23–1.15)	26.30 (1.19; 23.91–28.69)	30.0 (1.58; 26.81–33.17)	0.36 (−0.33–1.05)
5-months	24.86 (1.52; 21.8–27.93)	31.08 (1.87; 27.31–34.85)	0.60 (−0.10–1.29)	26.21 (1.19; 23.80–28.60)	31.01 (1.58; 27.83–34.19)	0.46 (−0.23–1.15)
Depression						
2-months	12.09 (1.18; 9.71–14.46)	15.89 (1.48; 12.90–18.87	0.66 (−0.03–1.35)	13.00 (0.95; 11.10–14.90)	15.94 (1.32; 13.29–18.59)	0.51 (−0.17–1.19)
5-months	11.36 (1.23; 8.89–13.83)	15.05 (1.55; 11.93–18.18)	0.65 (−0.04–1.34)	12.81 (0.95; 11.11–14.90)	14.85 (1.32; 12.20–17.50)	0.36 (−0.32–1.04)
Pain acceptance						
2-months	27.25 (1.35; 24.50–30.00)	20.26 (1.68; 16.84–23.67)	−0.75 (−1.48 - −0.02)	25.26 (1.15; 22.94–27.58)	19.93 (1.56; 16.79–23.08)	−0.57 (−1.29–0.15)
5-months	23.50 (1.39; 20.68–26.31)	20.52 (1.81; 16.86–24.18)	−0.32 (−0.39–1.03)	22.49 (1.15; 20.17–24.81)	19.93 (1.56; 16.79–23.08)	−0.27 (−0.98–0.44)
No. analgesics						
2-months	2.33 (0.38; 1.58–3.08)	2.34 (0.31; 1.73–2.96)	0.99 (0.21; 0.66–1.49)	2.16 (0.28; 1.61–2.71)	2.22 (0.27; 1.69–2.76)	0.97 (0.16; 0.70–1.35)
5-months	2.31 (0.35; 1.63–2.99)	2.42 (0.31; 1.81–3.01)	0.96 (0.19; 0.65–1.40)	2.12 (0.26; 1.63–2.61)	2.22 (0.24; 1.74–2.70)	0.95 (0.14; 0.71–1.28)
No. health visits						
2-months	2.34 (0.46; 1.44–3.24)	1.65 (0.45; 0.77–2.53)	1.41 (0.48; 0.73–2.73)	2.20 (0.33; 1.57–2.87)	1.78 (0.38; 1.05–2.52)	1.24 (0.32; 0.76–2.05)
5-months	1.55 (0.39; 0.78–2.31)	1.46 (0.45; 0.57–2.34)	1.10 (0.43; 0.48–2.37)	1.68 (0.27; 1.14–2.21)	1.78 (0.34; 1.12–2.44)	0.94 (0.23; 0.58–1.52)
No. other treatments						
2-months	1.21 (0.33; 0.56–1.85)	1.14 (0.27; 0.61–1.67)	1.06 (0.39; 0.51–2.19)	1.18 (0.23; 0.74–1.63)	1.18 (0.21; 0.77–1.59)	1.0 (0.28; 0.58–1.73)
5-months	1.21 (0.28; 0.66–1.76)	1.75 (0.44; 0.88–2.61)	0.69 (0.24; 0.35–1.36)	1.21 (0.21; 0.80–1.61)	1.46 (0.31; 0.85–2.06)	0.83 (0.23; 0.48–1.41)

Abbreviations: CI, 95% confidence interval; IRR, Incidence rate ratio; SE, standard error.

[a]Adjusted means.

[b]Corrected for small sample size.

benefits. The BOCF analyses showed a similar pattern of effects and 95% CIs. For count outcomes, there was considerable uncertainty in the estimates of treatment effect and the 95% CIs indicated the potential for true effects to range between large harms and large benefits. This pattern was seen at both 2- and 5-months and in BOCF analyses.

Seven of 10 waitlist control participants offered ACT OPEN at five-months completed treatment. However, only four of these completed questionnaires following treatment completion. Given small numbers, these data are not presented.

4 | DISCUSSION

This study examined the feasibility of a full-scale RCT of online ACT for neuropathic pain in PLWH. Feasibility was demonstrated on three of five criteria: 1) 2-month follow-up retention; 2) ACT OPEN treatment credibility and satisfaction were comparable (within one half of a standard deviation) to scores reported for CBT/ACT in previous RCTs demonstrating the efficacy of these treatments for pain (Smeets et al., 2008; Trompetter et al., 2014); and 3) small to moderate between-groups effects favouring ACT OPEN on key outcomes were observed. The proportion of treatment completers (69%) was just below the a priori criterion (70%). However, the recruited sample was below the target of 70 participants. Taken together, these data suggest that further study of ACT OPEN is warranted for pain management in PLWH. A full scale RCT may be feasible with refinements to trial design to account for recruitment issues.

The specific focus on painful peripheral neuropathy may have limited recruitment into our trial. While neuropathic pain remains burdensome in PLWH (Ellis et al., 2010; Pillay et al., 2017; Wadley et al., 2011), its incidence may be decreasing with reduced use of neurotoxic ART (Pillay et al., 2019). Importantly, pain of any aetiology is also prevalent in this population (Merlin, Long, et al., 2018; Sabin et al., 2018). In addition to peripheral neuropathic pain, 40% of the current sample reported widespread pain, although data on specific chronic pain comorbidities (e.g., fibromyalgia) were not collected. Anecdotally, HIV clinicians at the recruitment sites frequently described the prevalence of chronic pain that was not neuropathic. Although there was a low frequency of participants excluded because their pain was not neuropathic, many patients with other types of pain were likely not referred to the study at all. In a 2018 pilot RCT of an in-person behavioural treatment for PLWH and any type of pain ($n = 44$), 57% and 77% of participants reported knee or low back pain, respectively, while only 43% reported symptoms suggestive of neuropathic pain (Merlin, Westfall, et al., 2018); a full-scale trial is now underway (https://clinicaltrials.gov/ct2/show/NCT03692611). Therefore, broadening eligibility to include PLWH with any type of chronic pain would facilitate recruitment for a larger trial of ACT OPEN. Possible moderation of the treatment effect by pain type could then be explored.

The ACT OPEN completion rate was 8% higher than a previous feasibility RCT of online ACT for chronic pain conducted at a tertiary care pain clinic (Scott, Chilcot, et al., 2018). Additionally, the completion rate was higher than earlier randomized (43%) (Evans et al., 2003) and non-randomized (35%) (Cucciare et al., 2009) trials of in-person CBT for pain in PLWH. We conducted interviews (Scott et al., 2020) and had input from community representatives to tailor treatment to the needs of PLWH and pain. Particularly for groups that are not adequately represented in pain research, involving people with lived experience in treatment development is important to ensure acceptability (Kuhajda et al., 2011; Thorn et al., 2018).

Two more recent pilot RCTs of behavioural treatments for HIV and pain in the US demonstrated higher mean/median sessions completed relative to total sessions than these earlier trials (Merlin, Westfall, et al., 2018; Uebelacker et al., 2016). The treatments in these trials appeared to offer greater flexibility of delivery and personalization of content than earlier trials. The flexibility of online delivery in the current trial may have likewise facilitated completion. At the same time, the online system required a standard order of sessions. A more advanced system could allow session order to be tailored to an individual's specific needs, determined through more frequent assessment; this might further increase treatment engagement. Most treatment non-completers either never engaged with the first session or stopped after the first few sessions. Several of these reported that other health or psychosocial challenges interfered with treatment. This may be difficult to mitigate in a trial without further excluding participants; however, in a clinical setting, delaying treatment while other issues are addressed may optimize successful engagement in ACT OPEN.

Our sample was primarily comprised of white participants despite recruiting from clinics that served a diverse population. This mirrors findings of underrepresentation of Black, Asian and Minority Ethnic participants in research more widely (Smart & Harrison, 2017). At least in part, the requirement to conduct the current study in English and online may have limited inclusion of a more diverse sample. Work is needed to investigate how to optimize the acceptability of and access to psychologically informed pain management in a diverse group of PLWH. Alongside the recruitment methods used in this study, a larger trial could focus on engagement with and recruitment from third sector organizations that specifically provide support for individuals with HIV from ethnic minority groups. Early engagement with such organizations could help identify and mitigate participation barriers in these groups and could build trust with the research team.

Further investigation of cross-cultural conceptualizations of pain and its management in PLWH is also needed.

Online delivery of ACT was chosen to increase flexibility and reduce the burden of attending treatment in-person. Given the threat to in-person clinics posed by the COVID-19 pandemic, services may increasingly rely on remote delivery (Eccleston et al., 2020). To ensure equity, services may need to fund patients' access to digital technology in some cases (Estacio et al., 2017). Considering patient preferences and complexity of need, in-person pain management delivery may still be required for a subgroup of patients. More work is needed to identify patients who are likely to engage with and benefit from different delivery options.

The magnitude of the point estimates for pain interference and depression in the current study are consistent with previous RCTs of online ACT for chronic pain compared to active and inactive controls (Buhrman et al., 2013; Lin et al., 2017; Scott, Chilcot, et al., 2018; Trompetter et al., 2014). The treatment effect estimates and confidence intervals for continuous outcomes in the current study suggest that the true effect may favour ACT OPEN, but do not exclude small harms. In contrast, effects for count-based healthcare use variables showed considerable uncertainty in either direction. A full-scale trial is required to precisely determine the treatment effect; pain interference would be an appropriate primary outcome based on the current data. An effect size of $d = 0.50$ has been identified as the typical minimally clinically important difference (MCID) for key patient-reported outcome measures in pain (Dworkin et al., 2008), which is consistent with the point estimates and upper confidence bounds for pain interference in our study. This MCID and the standard deviation for pain interference at 2-months can be used to calculate the sample size for a larger trial. The recruitment rate from the current study only applies to a future trial using 2:1 allocation. Although 2:1 allocation is less efficient than 1:1, the loss of efficiency is greater for smaller effects and/or samples. Under any plausible scenario the loss of efficiency is less than 10%. For example, with an MCID of $d = 0.50$ and a total sample of 150, 2:1 and 1:1 allocation ratios have approximately 80 and 85% power, respectively (~6% loss of efficiency).

Several limitations must be considered. The sample was small, limiting precision around the effect estimates. The number of participants for the waitlist control at 5-months ($n = 10$) was just below the recommended minimum per group ($n = 12$; Julious, 2005). In addition to the strategies identified to boost recruitment in a larger trial, a number of recruitment centres will be needed to increase participant numbers. Additionally, the use of a waitlist control may have biased the results through lack of participant blinding. Treatment effects may have also been inflated by including nonspecific effects of being treated (Cunningham et al., 2013; Hróbjartsson et al., 2014). The CEQ was not completed in relation to the waitlist control given variability in standard medical treatment. Therefore, differing treatment expectancies between groups may have accounted, in part, for the observed outcomes. Notably, while comparable to a previous CBT trial (Smeets et al., 2008), ACT OPEN expectancy ratings were not on the extreme end of the scale, as has been reported for expectancies for invasive pain treatments (i.e., surgery) (Haanstra et al., 2015). The reasonable yet modest ACT OPEN expectancy scores might suggest that ACT-specific components contribute to the treatment effect beyond non-specific factors alone. Nonetheless, in a larger trial, patient and clinician input could be drawn upon to describe standard medical treatment for rating CEQ items, which could then be controlled for. Lastly, several questionnaires had more than 10% missing data (e.g., CEQ and CSQ), which may have been due to participant fatigue, language difficulties or intentional non-response. Shortening the questionnaire pack may mitigate these challenges, in part, in a larger trial. Cognitive interviews could help to further understand item non-completion in this population.

To conclude, this study supports the potential feasibility of a full-scale trial to evaluate the impact of a remotely delivered version of ACT for PLWH and chronic pain. Broadening eligibility criteria is needed to ensure successful recruitment in a full-scale trial. Further consideration of procedures to ensure a larger trial includes a diverse sample is needed.

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CONFLICTS OF INTEREST

WS delivers ACT-based treatment for pain within the UK's National Health Service, delivers teaching on ACT, and has done consultancy work for Ampersand Health (no compensation received). MB has received travel and research grants from and has been an advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, Teva. MJL has received speaker and conference fees from Gilead Sciences, Inc and ViiV Healthcare, outside the submitted work. ASCR undertakes consultancy and advisory board work for Imperial College Consultants--in the last 24 months this has included remunerated work for: Abide, Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Asahi Kasei, Toray and Theranexus. ASCR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015 and from which payments continued until 2019. ASCR is named as an inventor on patents WO2005/079771 and WO2013/110945. All other authors have no conflicts of interest to declare that are relevant to the contents of this article.

AUTHOR CONTRIBUTIONS

WS, HIK, JJ, PC, ACdCW, ASCR and LMM contributed to the study conception and design. WS, JB, HIK, ASCR, MB, GM, FAP, LC, MJL and JL contributed to designing and carrying out recruitment procedures. Data collection was performed by WS, BJG, JB and ED. WS, JC and SN carried out data analyses. The first draft of the manuscript was written by WS. All authors discussed the results, commented on the manuscript and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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