Study Protocol and Statistical Analysis Plan

Title of the study: Nurse-Led Community Health Worker Adherence Model in 3HP Delivery Among Homeless Adults at Risk for TB Infection and HIV (3HP-LTBI)

NCT Number: NCT03702049

Document Date: January 2, 2024

Procedures

Recruitment, Informed Consent, and Compensation

A well-trained RN and CHWs visited shelters and informed residents frequenting the sites about the study. Approved flyers were posted, and informational session presentations were given by the staff in the lobbies of the shelters where residents and visiting homeless awaited services. After informed consent was administered, a brief 2-minute structured questionnaire, which assessed TB history, followed. All potentially eligible participants were escorted to our community-based partner clinic in Skid Row and were tested with a blood assay using QuantiFERON-TB Gold Plus, a tuberculin skin test alone, or a combination of screening with the tuberculin skin test followed by the QuantiFERON-TB Gold Plus, as well as other routine testing (i.e., liver function and HIV tests). LTBI-positive homeless adults were escorted back to the clinic and completed a CXR to rule out active TB.

Following a subsequent clinic visit, all eligible participants were cleared for 3HP treatment for LTBI and were administered a second informed consent, followed by a 60-minute questionnaire that assessed general health and psychosocial and behavioral variables. All participants were paid $3 for the screening questionnaire and, if eligible, $5 for further laboratory tests at the clinic and $20 for the completion of baseline measures.

RN/CHW LTBI Program Training and Competency Evaluation

Upon development of the intervention protocol, the RN/CHW team was trained to deliver the 3HP LTBI intervention. The team was composed of a research RN and four part-time CHWs. CHWs were selected because they were formerly homeless adults who had transitioned out of homelessness, had excellent social skills, were positive role models, and had knowledge of the community and culture of homelessness. During the research team training, each member completed human subjects and Health Insurance Portability and accountability Act of 1996 (HIPAA) training, quizzes evaluating knowledge, baseline and follow-up questionnaire administration and mock training, and case studies of PEH with corresponding discussions. After the research leadership team introduced all content and knowledge that were assessed verbally using discussions, role play, and teach-back methods, the RN/CHW team was evaluated by the primary investigator and research investigators using a comprehensive competency checklist.

Development of RN/CHW 3HP LTBI Weekly Operations, Fidelity Monitoring, and Oversight

During the study implementation, a weekly operations and fidelity report on Research Electronic Data Capture was used to track outreach (e.g., flyer distribution, recruitment, information sessions, and screening), participant clinic appointments (e.g., laboratory tests, CXRs, and purified protein derivative test/CXR test result), physician clearance,

daily monitoring, weekly activities, and sessions. On a daily basis, the RN/CHW team reported to the research investigators and project coordinator. Every week, the research team went over the weekly operations, discussed, and evaluated research study progress. Based on these reports, concerns that arose during intervention implementation were addressed using constant evaluation and brainstorming, and creative approach to mitigating further challenges was discussed.

Intervention: RN/CHW Intervention Delivery

Each CHW was assigned seven to eight participants. At a mutually convenient time, the RN/CHW team met weekly with participants, under the direction of the RN, and assessed any side effects before the next dose. If none, the CHW provided directly observed treatment in a screened and private area. After the first dose of 3HP treatment, CHW conducted weekly one-on-one, 20-minute case management sessions over 12 weeks, where detailed information was provided about the program, along with coaching support to identify personal values and goals participants set for themselves. Education about TB and LTBI, its dangers, and the need for support to counteract the barriers of drug and alcohol use and mental health issues to 3HP medication completion was provided. Participants were encouraged to apply the problem-solving model to different hypothetical situations that served as triggers to engage in substance use and so forth. Progress was reviewed in overcoming barriers to medication adherence and appointment keeping.

The team also provided health and social service referrals (e.g., physical, mental health, substance treatment, and housing) and regularly tracked (detailed searching) participants who missed a 3HP dose. This tracking process was explained during the consenting process. If the participant failed to meet the team for the next dose, the team would begin making calls to reconnect based upon the locator information provided by the participant. This process occurred when a dose was missed on a specific date or a follow-up appointment was missed. Based on guidelines, participants who received 11 of 12 doses over 16 weeks were considered completers. Those who had a gap of >4 weeks between doses were noncompleters and were encouraged to restart the treatment.

Historical Control Group

In our comparison group, the historical control was provided the 3HP LTBI treatment to PEH attending a clinic. As a result of an outbreak in the Skid Row area of Los Angeles in 2014, the county investigated and screened 727 homeless adults. Over two thirds of the sample participants were between the ages of 35 and 54 years, whereas the remainder were 55 years and older. Three quarters of the sample participants were equally distributed as Black or Hispanic, whereas 13% were White and 2% were Asian. Among the 727 screened, 159 (21.8%) were LTBI positive, and 107 (67.3%) were recommended for 3HP treatment. Among the 56 who initiated treatment, 37 (66%) completed treatment.

Instruments

In this study, the primary dependent variable was completion of a 12-dose 3HP LTBI treatment compared to a historical, clinic-based control group that obtained 66% completion among homeless adults. Secondary outcome variables included an assessment of decline over time of the mental health symptoms of depression and anxiety and the drug use score and problematic alcohol use.

Independent Variables

Sociodemographic factors included age, gender, race/ethnicity, country of birth, and housing history (e.g., own/living with family or friends; shelter, street, living with family, friends).

General health was measured using five items from the general health perceptions subscale of the RAND 36-Item Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992). Participants responded to five statements, such as “my health is excellent” or “I expect my health to get worse,” with response options ranging from “true” to “definitely false” and end points 100, 75, 50, 25, and 0, with several items reverse scored. A total score was determined by calculating the average, where higher scores of 80+ were termed as “more favorable,” scores of 60–80 were termed as “favorable,” and scores of <60 were termed as “less favorable” perception of health. For this measure, Cronbach’s α = .78.

Social support was measured using the Medical Outcome Study Social Support Survey (Sherbourne & Stewart, 1991), a 19-item instrument that assesses availability of social support and includes four subscales: emotional/informational support (eight items, α = .95), tangible support (four items, α = .94), positive support (three items, α = .98), and affectionate support (three items, α = .96). Participants respond on a 5-point Likert scale, ranging from 1 (*none of the time*) to 5 (*all of the time*), with higher scores indicating more social support. We have thus labeled the scores as *high* (75+), *moderate* (25–74), and *low* (<25) social support. An overall support index was also calculated (α = .98).

Primary Dependent Variables

3HP Treatment Completion

As further clarified in the data analysis section, treatment completion was calculated by totaling the number of doses completed by each individual, with completion defined as 11 of 12 doses. The percentage of treatment completion was calculated using 95% confidence intervals.

Secondary Outcome Variables

Drug use score and problematic alcohol use, as well as the mental health symptoms of depression and anxiety, were assessed to observe the effect on the primary outcome of treatment completion, as well as the decline over time, and constitute secondary

outcomes of this study. These variables were of critical importance as they are historically considered significant barriers to treatment completion.

Drug use score and problematic alcohol use were measured using the Texas Christian University (TCU) Drug Screen 5 (Institute of Behavioral Research, 2020), a 17-item measure that screens for mild to severe substance use disorder per the Diagnostic and Statistical Manual for Mental Disorders (5th Edition). Participants indicated either “yes” or “no” responses to substance dependency questions and frequency of drug use based on a 5-point scale from 1 (*never*) to 5 (*daily*). The TCU Drug Screen 5 is scored on a point system, ranging from 0 to 11. Participant scores correspond to the number of symptoms endorsed by the participant and the severity of substance use disorder, including mild disorder (2–3 points), moderate disorder (4–5 points), or severe disorder (6 or more points). Problematic use of alcohol and specific drugs was defined as self-identified as being a problem (TCU Item 12) or daily consumption. For this measure, Cronbach’s α = .89.

Depression was assessed using the Center for Epidemiological Studies Depression Scale–Revised, a 10-item measure used to screen for depression (Eaton et al., 2004). This scale assesses depressive symptoms using a 4-point Likert scale that reflects the frequency of a symptom in the past week, ranging from 0 (*rarely* or *none of the time*) to 3 (*most of the time*). Example items include “I was bothered by things that do not usually bother me,” “I felt depressed,” and “I felt fearful.” Responses are summed (range: 0–30); a total score above 10 indicated depression. Reliability was good (Cronbach’s α = .79).

Anxiety was measured using the Generalized Anxiety Disorder-7, a seven-item self-report instrument used to screen and assess for anxiety, using a 4-point Likert scale ranging from 0 (*not at all*) to 3 (*nearly every day*; Spitzer et al., 2006). Example items include “worrying too much about different things,” “trouble relaxing,” and “not being able to control worrying.” Scores were summed and ranged from 0 to 21. The severity of anxiety was determined with cutoff scores of 5 (*mild anxiety*), 10 (*moderate anxiety*), and 15 (*severe anxiety*). In this study, reliability was very good (Cronbach’s α = .87).

Statistical Analysis

Descriptive statistics, including frequency and percentages, were computed for all variables. We assessed reliability of psychosocial scales used in our study by estimating Cronbach’s alpha. Our primary outcome was 3HP treatment completion, defined as completing 11 of 12 3HP doses. We estimated this outcome by dividing the number of participants with treatment completion by the total eligible participants and calculated the 95% confidence intervals using the scoring method. The lower bound of the 95% confidence limit was compared to 66% historical completion to assess successful improvement. We used mixed-effects models to account for within-participant correlation across time for the secondary outcomes of changes in drug use severity, anxiety, and depression scores.

For each model, the secondary outcome was specified as the dependent variable, time point as an ordinal independent variable, and subject identification as the random

variable. We also investigated the changes in problematic use of alcohol (binary outcome, yes vs. no) over time by fitting a generalized estimating equation to account for repeated measures over time for each subject. R v4.0.2 packages Hmisc, gee, and lme4 were used for analysis (R Core Team, 2020).