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Feasibility and safety of extended-release naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial

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ABSTRACT

Background and aims HIV-infected people with substance use disorders are least likely to benefit from advances in HIV treatment. Integration of extended-release naltrexone (XR-NTX) into HIV clinics may increase engagement in the HIV care continuum by decreasing substance use. We aimed to compare (1) XR-NTX treatment initiation, (2) retention and (3) safety of XR-NTX versus treatment as usual (TAU) for treating opioid use disorder (OUD) and/or alcohol use disorder (AUD) in HIV clinics. **Design** Non-blinded randomized trial of XR-NTX versus pharmacotherapy TAU. **Setting** HIV primary care clinics in Vancouver, BC, Canada and Chicago, IL, USA. **Participants** Fifty-one HIV-infected patients seeking treatment for OUD ($n = 16$), AUD ($n = 27$) or both OUD and AUD ($n = 8$). **Measurements** Primary outcomes were XR-NTX initiation (receipt of first injection within 4 weeks of randomization) and retention at 16 weeks. Secondary outcomes generated point estimates for change in substance use, HIV viral suppression [HIV RNA polymerase chain reaction (pcr) < 200 copies/ml] and safety. **Findings** Two-thirds (68%) of participants assigned to XR-NTX initiated treatment, and 88% of these were retained on XR-NTX at 16 weeks. In comparison, 96% of TAU participants initiated treatment, but only 50% were retained on medication at 16 weeks. Mean days of opioid use in past 30 days decreased from 17.3 to 4.1 for TAU and from 20.3 to 7.7 for XR-NTX. Mean heavy drinking days decreased from 15.6 to 5.7 for TAU and 12.5 to 2.8 for XR-NTX. Among those with OUD, HIV suppression improved from 67 to 80% for XR-NTX and 58 to 75% for TAU. XR-NTX was well tolerated, with no precipitated withdrawals and one serious injection-site reaction. **Conclusions** Extended-release naltrexone (XR-NTX) is feasible and safe for treatment of opioid use disorder and alcohol use disorder in HIV clinics. Treatment initiation appears to be lower and retention greater for XR-NTX compared with treatment as usual (clinicaltrials.gov NCT01908062).

Keywords Alcohol, extended-release naltrexone, HIV, injection drug use, opioid-related disorders, randomized clinical trial.

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INTRODUCTION

Opioid and alcohol use disorders are common in HIV-infected individuals and contribute to gaps in the HIV care continuum [1–3]. Untreated opioid and alcohol use disorders are associated with decreased receipt of anti-retroviral therapy (ART) [3,4], decreased ART adherence [5,6], decreased HIV viral suppression [7,8] and decreased survival [9].

Treatment of substance use disorders can increase engagement in HIV care [10,11], potentially narrowing gaps in the HIV care continuum by improving linkage to care, receipt of ART, retention in care and HIV viral suppression. Opioid agonist therapy with methadone [12]

and sublingual buprenorphine/naloxone (BUP/NX) [13] for the treatment of opioid use disorder (OUD) improves HIV outcomes [11,14–16]. US HIV treatment guidelines recommend opioid agonist therapy for engaging people who inject drugs in HIV treatment [17]. Access to opioid agonist therapy, however, is suboptimal due to a shortage of waivered buprenorphine providers [18] and, in the case of methadone, federal prohibitions in the United States on office-based treatment. Patient acceptance of and retention on opioid agonist therapy is limited, due in part to frequent dosing requirements for both medications.

Pharmacotherapy for alcohol use disorders (AUD) is uncommon in HIV clinics, but is associated with decreased HIV RNA levels in alcohol-dependent, HIV-infected Veterans treated with oral naltrexone in addiction treatment settings [19]. Oral naltrexone's effectiveness, both for OUD and for AUD, is also limited by patient acceptability and daily dosing requirements.

Long-acting opioid antagonist treatment with extended-release naltrexone (XR-NTX) is effective in treating OUD [20–23] and AUD [24,25]. XR-NTX is a deep muscle injection that lasts 28 days, eliminating the need for daily dosing. Integration of XR-NTX for treatment of AUD into primary care clinics decreases alcohol use [26], but less is known about its use for treatment of OUD in primary care. XR-NTX also offers an alternative to agonist therapy for some HIV-infected patients who prefer a non-narcotic treatment option or once-monthly dosing. Given its long duration of action, XR-NTX has the potential to facilitate engagement in the HIV care continuum for patients with opioid and/or alcohol use disorder (OUD/AUD), but has not been tested in HIV clinics.

The CTN-0055 CHOICES pilot study aims were to compare (1) treatment initiation, (2) treatment retention in pharmacotherapy, (3) treatment retention in counseling and (4) safety of XR-NTX versus treatment as usual (TAU) for treatment of patients with OUD/AUD in HIV clinics. The overall purpose of the study was to inform development of a multi-site comparative effectiveness trial of XR-NTX versus TAU in HIV clinics for improving engagement in the HIV care continuum.

METHODS

Design

The CTN-0055 CHOICES study (clinicaltrials.gov NCT01908062) was an open-label, randomized, pilot trial of XR-NTX versus treatment as usual (TAU) for treatment of OUD/AUD in HIV-infected patients. The study was conducted under the direction of the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) and approved by Institutional Review Boards at Oregon Health and Science University and pilot sites.

Setting

Study pilot sites (a) provided HIV primary care and had (b) sufficient potential participants to achieve study enrollment goals, (c) providers willing to be trained in the use of XR-NTX for management of OUD/AUD, (d) prior experience participating in research studies, (e) the capacity to prescribe ART to participants regardless of CD4 count and (f) access to addiction counseling services as part of usual care. Two large outpatient HIV clinics were selected as study pilot sites: the Ruth M. Rothstein CORE Center in Chicago, IL and the John Ruedy Immunodeficiency Clinic (IDC) at St Paul's Hospital in Vancouver, BC.

Participants

Participants were recruited during HIV clinic visits and through clinic-affiliated outreach programs between June 2014 and March 2015, with the last follow-up in August 2015. Prospective participants completed a brief prescreening questionnaire requiring verbal consent for assessment for appropriateness for screening (e.g., HIV-infected, wanting to decrease opioid and alcohol use, and interest in study participation), and then provided written consent to complete full screening. NIDA set the pilot enrollment target of 50 participants within 12 months to demonstrate feasibility of enrollment. Failure to enroll 50 participants within 12 months would have been considered evidence that a scale-up trial was not feasible.

Eligible HIV-infected participants (1) met DSM-5 criteria for moderate or severe OUD/AUD and (2) were willing to be randomized to XR-NTX or TAU, (3) willing to establish or continue ongoing HIV care at the site, (4) willing to initiate or continue ART, regardless of CD4 count, (5) aged at least 18 years, (7) able to provide written informed consent, (8) able to communicate in English and (9) if female, willing to take measures to avoid becoming pregnant. Potential participants were excluded for (1) disabling or terminal medical illness, (2) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than five times the upper limit of normal, (3) prothrombin time with international normalized ratio (INR) > 1.5 or platelet count $< 100\,000$, (4) known allergy or sensitivity to naloxone, naltrexone, polylactide-co-glycolide, carboxymethylcellulose or other components of the diluents, (5) anticipated surgery during study participation, (6) chronic pain requiring ongoing opioid analgesics, (7) pending legal action, (8) currently pregnant or breastfeeding, (9) body habitus that precludes safe intramuscular injection of XR-NTX, (10) receiving methadone or buprenorphine maintenance therapy in the past 4 weeks, (11) having taken an investigational drug in another study, (12) an electrocardiograph (ECG) finding

that, in the judgment of the study clinician, precludes safe study participation, or (13) having received treatment with XR-NTX for OUD/AUD during the past 3 months.

Intervention

Eligible participants were randomized in a 1 : 1 ratio via computer-generated randomized allocation by an independent NIDA data management contractor to receive non-blinded XR-NTX versus TAU, with blocking by site. Participants assigned to XR-NTX underwent medically supervised withdrawal, as needed. A urine drug screen (UDS) negative for opioids, including buprenorphine and methadone, followed by a negative naloxone challenge, was required prior to the first dose of XR-NTX. Naloxone used for challenge is an off-label use. Participants received XR-NTX (Vivitrol®) 380 mg intramuscular injection, provided by the manufacturer, and injected by the study clinician at treatment initiation and at 4, 8, and 12 weeks, in alternating gluteal muscles (total 16 weeks treatment exposure). Participants assigned to TAU were prescribed the local standard of care for OUD and AUD in their communities. All participants were referred to local counseling resources and attended monthly medical management appointments with treating providers. Research visits occurred every 4 weeks for collection of blood and urine samples, safety and other study assessments.

Measures

The main independent variable was treatment assignment (XR-NTX versus TAU). Primary outcomes included (1) patient self-report of acceptance of opioid antagonist therapy and willingness to participate in a trial of XR-NTX versus TAU, (2) participant recruitment rate (number randomized per month per site), (3) treatment initiation (receipt of at least one dose of XR-NTX or other medication-assisted TAU within 4 weeks of randomization) and (4) retention on treatment (percentage of

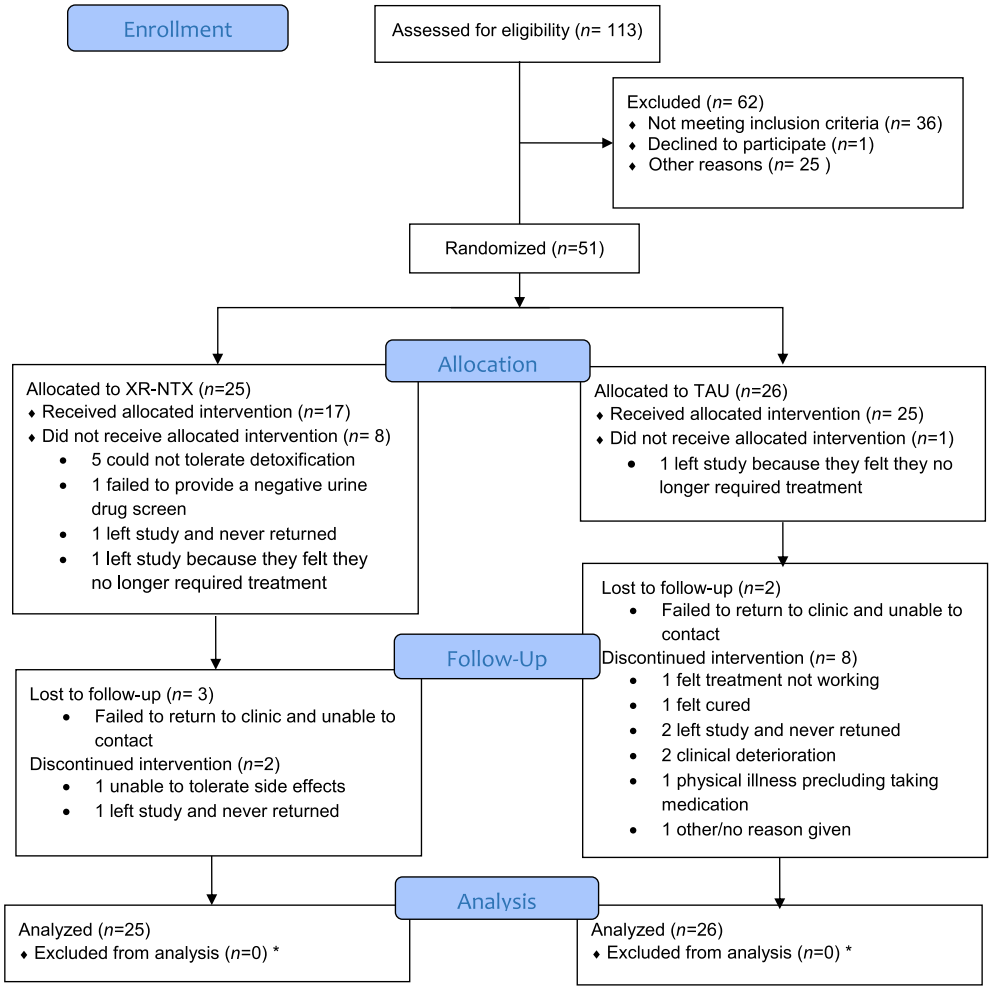

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. [Colour figure can be viewed at wileyonlinelibrary.com]

assigned treatment received over 16 weeks, among those initiating treatment). Secondary outcomes, measured at 16 weeks, included change in past 30-day opioid and alcohol use [Addiction Severity Index (ASI)-lite self-report, urine toxicology screening and urine ethylglucuronide testing] and HIV-1 RNA viral suppression (plasma HIV-1 RNA pcr < 200 copies/ml). Adverse events and XR-NTX injection site reactions were monitored at each research visit. Other patient safety measures included change in AST and ALT, fatal and non-fatal opioid overdose, and precipitated opioid withdrawal due to XR-NTX. Socio-demographic data was assessed by self-report. All data were entered into a centralized database managed by an independent data management center.

Statistical analysis

We used descriptive statistics to report participant characteristics and the four primary feasibility outcomes. We assessed differences in primary outcomes by treatment assignment using χ^2 tests for categorical variables and *t*-tests for continuous variables. Secondary outcomes are reported with descriptive statistics. Participants were analyzed as members of the treatment arm to which they were assigned for all outcomes (i.e., intent-to-treat design).

RESULTS

Research assistants pre-screened 113 individuals, 100 of whom were eligible for screening (Fig. 1). The most common reasons for exclusion at pre-screening were current buprenorphine or methadone maintenance treatment and chronic pain requiring ongoing opioid analgesics. Of 78 participants consented for screening, 51 were randomized (45.1% of pre-screened; 65% of screened). The most common causes for exclusion during screening were serious medical, psychiatric or substance use disorder. Three eligible participants declined randomization.

Forty-three per cent of randomized participants were women, 47% black, 45% disabled and 61% had a high school education or greater (Table 1). Mean age was 46 [standard deviation (SD) = 10] years. Twenty-seven participants (53%) had only AUD, 16 (31%) had only OUD and eight (16%) met DSM-5 criteria for both OUD

Table 1 Participant characteristics overall, and by treatment group.

Characteristic	*TAU (n = 26)*	*XR-NTX (n = 25)*	*Total (n = 51)*
Female gender	*8 (31%)*	*14 (56%)*	*22 (43%)*
Age, mean (SD)	*45 (12)*	*47 (8.8)*	*46 (10)*
Hispanic ethnicity	*3 (12%)*	*1 (4%)*	*4 (8%)*
Race			
Black/African American	*12 (46%)*	*12 (48%)*	*24 (47%)*
White	*9 (35%)*	*4 (16%)*	*13 (26%)*
Other	*5 (19%)*	*9 (36%)*	*14 (27%)*
Education completed			
< High school	*8 (31%)*	*12 (48%)*	*20 (39%)*
High school/GED	*7 (27%)*	*8 (32%)*	*15 (29%)*
≥ Some college	*11 (42%)*	*5 (20%)*	*16 (32%)*
Married or living with partner	*2 (8%)*	*6 (24%)*	*8 (16%)*
Employment			
Working now	*4 (15%)*	*3 (12%)*	*7 (14%)*
Looking for work, unemployed	*6 (23%)*	*5 (20%)*	*11 (22%)*
Disabled	*10 (38%)*	*13 (52%)*	*23 (45%)*
Other	*6 (23%)*	*4 (16%)*	*10 (20%)*
Substance use disorder			
Opioid use disorder alone	*9 (35%)*	*7 (28.0%)*	*16 (31%)*
Alcohol use disorder alone	*14 (54%)*	*13 (52%)*	*27 (53%)*
OUD + AUD	*3 (11%)*	*5 (20%)*	*8 (16%)*
ASI drug score	*0.37 (SD = 0.33)*	*0.44 (SD = 0.39)*	*0.41 (SD = 0.36)*
ASI alcohol score	*0.33 (SD = 0.32)*	*0.41 (SD = 0.32)*	*0.37 (SD = 0.32)*
Baseline CD4 count, mean (SD)	*564 (246)*	*683 (418)*	*620 (339)*
Baseline ART, n *(%)*	*25 (96%)*	*23 (92%)*	*48 (94%)*
Baseline HIV viral suppression, n *(%)*	*21 (81%)*	*20 (80%)*	*41 (80%)*

TAU = treatment as usual; XR-NTX = extended-release naltrexone; SD = standard deviation; GED = general educational development; AUD = alcohol use disorder; OUD = opioid use disorder; ASI = Addiction Severity Index; ART = anti-retroviral therapy.

and AUD. Participant characteristics were generally balanced across these groups, although women comprised 37% of those with AUD only, 56% of those with OUD only and 38% of those with both OUD and AUD ($P = 0.44$). Participants with OUD alone, and those with OUD and AUD were combined for the analysis; therefore, 24 participants (47%) were classified as having OUD with or without AUD and 27 (53%) were classified as having AUD alone. Ninety-four per cent of participants were prescribed ART and 80% had HIV viral suppression at baseline, with a mean CD4 cell count of 620 (SD = 339).

Feasibility

Patient acceptance of opioid antagonist therapy

Patients being approached for study participation were interested in XR-NTX treatment. Prospective study participants ($n = 113$) were asked about their interest in cutting back or quitting substance use and their willingness to participate in a trial of XR-NTX during pre-screening. Ninety-eight per cent of 60 prospective participants interested in reducing opioid use and 99% of 82 prospective participants interested in reducing alcohol use were definitely or maybe willing to consider enrolling in a clinical trial of XR-NTX.

Rate of participant recruitment

Fifty-one of 113 pre-screened individuals (45.1%) were randomized. The trial achieved 155% actual versus expected randomizations, reaching randomization targets 4 months ahead of schedule. The study enrolled a mean 3.2 participants per month per site (1.5 and 1.7 participants per month per site for OUD and AUD, respectively).

Treatment initiation

Overall, 68% of participants assigned to XR-NTX initiated treatment within 4 weeks of randomization compared with 96% of those assigned to TAU ($P = 0.011$) (Table 2). XR-NTX initiation was greater for those with AUD-only compared with those with OUD (92 versus 42%, $P = 0.011$). TAU participants with OUD ± AUD ($n = 12$) primarily received office-based buprenorphine/naloxone (84%). Pharmacotherapy for TAU participants with AUD ($n = 14$) consisted of oral naltrexone (50%), gabapentin (29%), acamprosate (14%) and disulfiram (7%). Among participants with OUD, TAU pharmacotherapy exceeded XR-NTX initiation (100 versus 42%, $P = 0.002$), but among those with AUD only, pharmacotherapy initiation was comparable (93 versus 92%, $P = 1.00$). The leading reason for not initiating XR-NTX was inability to tolerate opioid detoxification (Fig. 1).

Table 2 Treatment initiation and retention.

	Treatment initiation within 4 weeks			
	Total (n = 51)	*AUD alone (n = 27)*	*OUD ± AUD (n = 24)*	*P-value (AUD versus OUD)*
TAU (n = *26)*	*25/26 (96%)*	*13/14 (93%)*	*12/12 (100%)*	*1.00*
XR-NTX (n = *25)*	*17/25 (68%)*	*12/13 (92%)*	*5/12 (42%)*	*0.011*
Total (n = *51)*	*42/51 (82%)*	*25/27 (93%)*	*17/24 (71%)*	*0.066*
P-*value (TAU versus XR-NTX)*	*0.011*	*1.00*	*0.002*	–
	Retention on pharmacotherapy at 16 weeks			
	Total (n = 41)	*AUD alone (n = 24)*	*OUD ± AUD (n = 17)*	*P-value (AUD versus OUD)*
TAU-MAT (n = *24)*	*12/24 (50%)*	*6/12 (50%)*	*6/12 (50%)*	*1.00*
XR-NTX (n = *17)*	*15/17 (88%)*	*10/12 (83%)*	*5/5 (100%)*	*1.00*
Total (n = *41)*	*27/41 (66%)*	*16/24 (67%)*	*11/17 (65%)*	*0.896*
P-*value (TAU versus XR-NTX)*	*0.018*	*0.190*	*0.100*	–
	Retention in counseling at 16 weeks			
	Total (n = 34)	*AUD alone (n = 19)*	*OUD ± AUD (n = 15)*	*P-value (AUD versus OUD)*
TAU-counseling (n = *17)*	*6/17 (35%)*	*2/7 (20%)*	*4/10 (40%)*	*1.00*
XR-NTX (n = *17)*	*15/17 (88%)*	*10/12 (83%)*	*5/5 (100%)*	*1.00*
Total (n = *34)*	*21/34 (62%)*	*12/19 (63%)*	*9/15 (60%)*	*0.851*
P-*value (TAU versus XR-NTX)*	*0.004*	*0.040*	*0.040*	–

TAU = treatment as usual; XR-NTX = extended-release naltrexone; AUD = alcohol use disorder; OUD = opioid use disorder; MAT = Medication-Assisted Treatment.

All but one TAU participant received pharmacotherapy for OUD/AUD treatment.

Treatment retention

Of those initiating treatment (n = 41), 88% were retained on XR-NTX at 16 weeks compared with 50% retention on TAU pharmacotherapy (Table 2). All but one participant who initiated XR-NTX received all four possible doses without treatment interruption. Treatment retention was higher for XR-NTX than TAU pharmacotherapy, both for those with AUD (83 versus 50%, P = 0.190) and those with OUD (100 versus 50%, P = 0.100). Similarly, retention in counseling was higher for XR-NTX than TAU overall (88 versus 35%, P = 0.004), and regardless of AUD (83 versus 20%, P = 0.040) and OUD (100 versus 40%, P = 0.040) status.

Secondary outcomes

Point estimates of secondary outcomes were collected to inform a potential large-scale trial and not powered for hypothesis testing (Table 3). Among participants with OUD, the mean number of days of opioid use and the percentage of UDS positive for opioids decreased in both treatment arms. Among participants with AUD, the mean number of days of drinking to intoxication and the percentage of UDS positive for urine ethylglucuronide decreased in both treatment groups.

Overall, 48 of 51 (94.1%) participants were receiving ART at baseline (Table 3). Two of the three participants not prescribed ART at baseline were prescribed ART during study participation. The single participant who was not prescribed ART by 16 weeks was an HIV elite suppressor (HIV RNA pcr < 200 copies/ml without ART) and declined ART initiation. Overall, 80% of participants had HIV viral suppression at baseline, and 84% were suppressed at 16 weeks. Among those with OUD, HIV viral suppression increased from 67 to 80% for XR-NTX and from 58 to 75% for TAU. Among those with AUD only, HIV viral suppression changed from 92 to 82% for XR-NTX and from 100 to 100% for TAU.

Safety

Fourteen participants experienced a total of 29 adverse events (38% mild, 55% grade 2 moderate and 7% severe). The majority (62%) were not related to study treatment. Leading adverse events were gastrointestinal disorders (11 participants) followed by psychiatric disorders/insomnia (three participants) and nervous system disorders, such as headache and migraine (three participants). Two serious adverse events occurred: one suicidal ideation and one ankle fracture, both of which led to inpatient admissions. Neither were related to study treatment. Four participants receiving XR-NTX experienced a total of seven injection site reactions. In three participants, reactions were mild and self-limited and XR-NTX was continued. One participant developed a delayed hypersensitivity reaction to XR-NTX [27] and switched to oral naltrexone. There were no precipitated withdrawals.

Table 3 Secondary outcomes.

	TAU		*XR-NTX*	
	Baseline	*16 weeks*	*Baseline*	*16 weeks*
Opioid use				
Mean days of opioid use in past 30 days[a]	*17.3 (SD = 13.14)* n = *12*	*4.1 (SD = 5.43)* n = *11*	*20.3(SD = 12.29)* n = *12*	*7.7 (SD = 11.32)* n = *11*
UDS positive for opioids[a]	*9 (75.0%)* n = *12*	*7 (58.3%)* n = *12*	*9 (75.0%)* n = *12*	*4 (40.0%)* n = *12*
Alcohol use				
Mean days of alcohol use in past 30 days[b]	*15.6 (SD = 9.95)* n = *14*	*5.7 (SD = 8.40)* n = *12*	*12.5 (SD = 11.02)* n = *13*	*2.8 (SD = 3.05)* n = *12*
Urine ethylglucuronide positive, n *(%)*[b]	*7 (50.0%)* n = *14*	*4 (30.8%)* n = *14*	*6 (54.5%)* n = *13*	*3 (25.0%)* n = *13*
HIV outcomes				
Prescribed ART[c]	*25 (96.2%)* n = *26*	*26 (100%)* n = *26*	*23 (92.0%)* n = *25*	*24 (96.0%)* n = *25*
HIV viral suppression[c]	*21 (80.8%)* n = *26*	*20 (87.0%)* n = *23*	*20 (80.0%)* n = *25*	*17 (81.0%)* n = *21*

[a]Among participants with opioid use disorder retained at 16 weeks. [b]Among participants with alcohol use disorder retained at 16 weeks. [c]Among all participants completing study assessments. TAU = treatment as usual; XR-NTX = extended-release naltrexone; SD = standard deviation; UDS = urine drug screen; ART = anti-retroviral therapy.

Mean AST and ALT were unchanged between screening and 16 weeks, overall and by treatment group (AST = 32.3–32.2 for TAU and 36.8–38.8 for XR-NTX; ALT = 33.0–30.8 for TAU and 35.0–40.1 for XR-NTX). Two participants (3.9%) reported at least one opioid overdose during the study: one assigned to TAU with two non-fatal overdoses; one assigned to XR-NTX with one non-fatal overdose prior to initiating XR-NTX. There were no fatal overdoses.

DISCUSSION

Creative solutions for improving engagement in HIV care for patients with substance use disorders are needed urgently. The current study demonstrates that integration of XR-NTX into HIV clinics was feasible and safe for the treatment of OUD/AUD. These findings support the need for a multi-site trial to assess the capacity of integrated addiction treatment in HIV clinics to improve engagement and retention in the HIV care continuum.

After being informed of the pros and cons of opioid antagonist therapy, nearly all prospective participants who were interested in cutting back opioid and/or alcohol use were willing to consider participating in a clinical trial of XR-NTX. The high willingness to consider opioid antagonist therapy was probably influenced by the fact that these people were being approached by a research assistant from a clinical trial for which they hoped to qualify. One pilot site independently surveyed 657 community-based people who injected opioids to assess willingness to try XR-NTX, as part of its site application process [28], 52% of whom expressed willingness to receive XR-NTX for treatment of OUD. Daily heroin injection was associated with increased willingness to try XR-NTX [odds ratio (OR) = 1.53, 95% confidence interval (CI) = 1.02, 3.12] [28] Together, these data call into question the common clinical assumption that people with OUD would not be interested in treatment with an opiate receptor blocker.

Nearly all participants assigned to TAU initiated pharmacotherapy, as did those assigned to XR-NTX with AUD only. Fewer than half of participants with OUD initiated XR-NTX within 4 weeks of randomization, and pharmacodynamics may have played a role. Because naltrexone's binding affinity at the opioid mu receptor exceeds that of full or partial opioid agonists, naltrexone initiation requires patients to be opioid-free in order to avoid precipitated withdrawal. Medically supervised withdrawal from opioids is required typically for people with OUD, and this may take several weeks, depending on the severity of physical dependence and methods used (i.e., buprenorphine taper versus non-opioid medication withdrawal support). The CTN-0055 CHOICES study randomized participants prior to detoxification and provides a benchmark for XR-NTX treatment initiation in community-dwelling outpatients with OUD. Both of the two clinical trials of XR-NTX for OUD that led to Food and Drug Administration (FDA) approval required successful residential detoxification prior to randomization and did not report treatment initiation rates [20,22].

Another reason for lower XR-NTX initiation rates may have been the study's conservative requirements for a UDS negative for all opioids, including buprenorphine. Providers were generally encouraged to avoid use of buprenorphine or methadone for detoxification unless the participant failed non-opioid detoxification, often resulting in a prolonged time from last use of illicit opioids to XR-NTX injection. In a recent pilot study, streamlined induction procedure using cross-tapered dosing of buprenorphine with escalating very low doses of oral naltrexone achieved 70% XR-NTX initiation at 8 days [29]. Similar protocols adapted for use in HIV clinics could improve XR-NTX initiation. Additional implementation studies are needed to identify ways to address barriers and maximize uptake of XR-NTX in outpatient settings.

Most (88%) participants who initiated XR-NTX received all four doses over 16 weeks. The high retention rate among participants with OUD (100%) exceeds that reported in two previous clinical trials of XR-NTX for OUD conducted in specialty addiction treatment settings. In a US-based study, 68% of participants with OUD were retained on XR-NTX at 8 weeks [20] In a study conducted in Russia among people with no other pharmacotherapy options for OUD, 57.9% were retained on XR-NTX at 24 weeks [22]. Similarly, the high retention rate among participants with AUD (82%) exceeds that reported in a large trial of XR-NTX for AUD (62.5% retention and receipt of all doses of XR-NTX at 24 weeks) [24] and a demonstration study of XR-NTX for AUD in primary care (62% retained in treatment at 12 weeks) [26]. The high rate of retention on XR-NTX in CTN-0055 may be related to XR-NTX treatment integration into HIV clinics where participants receive ART in a patient-centered medical home model. Further implementation research is required to explore contributors to XR-NTX retention, particularly for individuals less engaged in HIV primary care.

Given the small number of participants enrolled to assess feasibility, the pilot study was not powered for hypothesis testing of secondary HIV or substance use outcomes. The study's secondary analyses must be regarded as hypothesis-generating only, and need to be validated in a fully powered study. Nevertheless, XR-NTX decreased use of opioids and, to a lesser degree, alcohol in this intent-to-treat analysis, consistent with previous studies demonstrating its effectiveness for treating OUD/AUD [22,24]. Greater retention on XR-NTX compared with TAU suggests that greater treatment exposure for longer follow-up periods may indeed improve long-term substance use outcomes that mediate improved HIV outcomes. The

majority of participants were already prescribed ART at baseline, consistent with expansion of universal ART coverage in these cities. HIV viral suppression was consequently high at baseline, with the exception of participants with OUD, who experienced an increase in the percentage suppressed at 16 weeks. Future trials testing the ability of XR-NTX to improve engagement and retention in HIV care should also consider sustained viral suppression at 12 months, retention in HIV care and mortality risk as outcomes.

XR-NTX was safe for use in HIV clinics. XR-NTX injections were generally well tolerated, apart from one participant who experienced a delayed hypersensitivity reaction, due probably to the microspherule drug delivery mechanism [27]. Unchanged liver enzymes levels are consistent with recent studies supporting the lack of hepatotoxicity in patients receiving XR-NTX and led to removal of the previous FDA black box hepatotoxicity warning [19,21,30].

The current study should be interpreted in view of several limitations. First, the pilot trial was not powered to assess XR-NTX effects on HIV outcomes. The study's successful demonstration of HIV clinic integration feasibility merits development of a fully powered, multi-site trial designed to assess the effect of XR-NTX on HIV care engagement, retention, HIV viral suppression and mortality risk. Secondly, the short-term nature of a pilot study precluded assessment of continued use of XR-NTX and opioid overdose risk after the 16-week treatment period. Future trials should include follow-up periods that determine the proportion of participants who continue on XR-NTX treatment covered by health-care insurance and the long-term risk of opioid overdose among those participants who choose not to continue opioid antagonist therapy. Thirdly, pilot HIV clinics were chosen partly on the basis of their previous successes in implementation, as evidenced by high rates of pharmacotherapy initiation among those assigned to TAU that are probably atypical of many other HIV clinics. HIV clinics with less implementation experience should be included in a multi-site scale-up trial and may demonstrate larger differences between XR-NTX and TAU for substance use and HIV outcomes. Finally, study results should not be interpreted as supporting XR-NTX replacement of opioid agonist therapy for OUD, which has more than 40 years of data supporting its safety and effectiveness. XR-NTX should be viewed, rather, as a potential addition to an expanding menu of effective treatment options that can be tailored to patient preferences.

In conclusion, the CTN-0055 CHOICES randomized trial demonstrates that XR-NTX treatment of OUD/AUD is acceptable, feasible and safe for integrating into HIV clinics. The findings underscore the need for a multi-site trial to test the potential of XR-NTX for improving engagement in the HIV care continuum. Use of long-acting addiction pharmacotherapies such as XR-NTX may improve the capacity for HIV-infected patients with substance use disorders to engage more effectively in HIV treatment and close gaps in the HIV care continuum. Such interventions are needed urgently to achieve the UNAIDS 90–90-90 target (90% diagnosed, 90% treated with ART and 90% with HIV viral suppression) by 2020.

Declaration of interests

D. McCarty served as the Principal Investigator on research service agreements with Alkermes, Inc. and Purdue Pharma. The other authors have no disclosures or conflicts.

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