Published in final edited form as:

Drug Alcohol Depend. 2020 November 01; 216: 108230. doi:10.1016/j.drugalcdep.2020.108230.

Abstinence-reinforcing contingency management improves HIV viral load suppression among HIV-infected people who use drugs: A randomized controlled trial.

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Abstract

Background: HIV-infected people who use drugs (PWUD) have poor HIV outcomes. Few studies tested interventions to improve HIV outcomes among PWUD. Abstinence-reinforcing contingency management (CM) reduces drug use and could also improve HIV outcomes.

Methods: From 2012–2017, we conducted a randomized controlled trial testing whether a 16-week abstinence-reinforcing CM intervention improved HIV viral load (VL) among HIV-infected adults using opioids or cocaine. In the CM intervention, drug-free urines led to escalating value of vouchers (\$2.50–\$80/voucher, \$1320 total maximum). In intention-to-treat mixed-effects linear and logistic regression analyses, we examined whether the CM intervention improved log₁₀ VL (primary outcome), abstinence and antiretroviral adherence (secondary outcomes).

Results: Thirty-seven participants were randomized to the CM intervention and 36 to control. Median age was 49.2 years; most were male (61.6%) and non-Hispanic black (46.6%). In CM (vs. control) participants, mean reduction in log₁₀ VL was greater (–0.16 log₁₀ VL copies/mL per 4-week period; 95% CI: –0.29 to –0.03, p<0.05). Over 16 weeks, CM participants had a mean

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Contributors: COC designed the study, oversaw study implementation, oversaw analyses, and drafted the manuscript. NLS and JHA guided the study design, study implementation, and analytic approach. JJJ, RG and MRS oversaw data collection. MZ guided the analytic approach, conducted analyses and drafted portions of the manuscript. MH guided the study design, and analytic approach. MB guided the analytic approach and conducted analyses. All authors helped to interpret findings and approve of the.

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Conflict of Interest: No conflicts declared.

reduction of 0.64 copies/mL in log₁₀ VL greater than control participants. The CM intervention was not significantly associated with abstinence or adherence.

Conclusions: This is the first study to demonstrate improvements in HIV VL via an abstinence-reinforcing CM intervention. Because the CM intervention did not significantly affect abstinence or adherence, the mechanism of its effect is unclear. To end the HIV epidemic, innovative strategies must address individuals with poor HIV outcomes. Abstinence-reinforcing CM may be one potential strategy to improve HIV outcomes among a select group of PWUD.

Keywords

contingency management; opioids; cocaine; HIV; viral load suppression; abstinence; antiretroviral adherence

1. Introduction

Despite dramatic advances in HIV treatment, compared with other risk groups, HIV-infected people who use drugs (PWUD) continue to have poorer HIV outcomes (Malta et al., 2008, 2010; Cohen et al., 2004; Ding et al., 2005; Pulvirenti et al., 2003; Sharpe et al., 2004). With suboptimal HIV treatment and poorly controlled HIV infection, PWUD have great potential to transmit HIV to their drug-using and sexual partners, with serious public health consequences. For PWUD, drug treatment can mitigate poor outcomes, as drug treatment is associated with better HIV outcomes (Palepu et al., 2006; Spire et al., 2007). Thus, given poor HIV-related health outcomes experienced by PWUD, and better HIV outcomes associated with drug treatment, PWUD with HIV may benefit from drug treatment interventions.

Although numerous studies demonstrate poor HIV outcomes among PWUD, relatively few studies have tested interventions to improve HIV outcomes specifically in this population (Altice et al., 2007; Berg et al., 2010; Lucas et al., 2010; Metsch et al., 2016; Purcell et al., 2004; Solomon et al., 2014; Sorensen et al., 2007). Interventions among HIV-infected PWUD can improve adherence to antiretrovirals (ARVs) (Altice et al., 2007; Berg et al., 2010; Purcell et al., 2004; Rigsby et al., 2000; Rosen et al., 2007; Sorensen et al., 2007), but continued drug use can inhibit their ability to improve adherence substantially enough to achieve viral load (VL) suppression (Berg et al., 2010; Rigsby et al., 2000; Sorensen et al., 2007). It is unlikely that PWUD will achieve and maintain VL suppression unless ongoing drug use is addressed (Arnsten et al., 2002). Despite this, few studies specifically examine whether an intervention that aims to reduce active drug use is efficacious in improving HIV outcomes (Altice et al., 2011; Lucas et al., 2010; Metsch et al., 2016; Solomon et al., 2014).

Abstinence-reinforcing contingency management (CM) (financial incentives contingent on drug-free urine) leads to reduction in illicit opioid and cocaine use (Giuffrida and Torgerson, 1997; Griffith et al., 2000; Higgins et al., 2000; Lussier et al., 2006; Prendergast et al., 2006; Preston et al., 2000, 2002; Schottenfeld et al., 2005; Silverman et al., 1996a, 1996b, 1998, 2004). Due to the success of abstinence-reinforcing CM, other studies have used CM to optimize HIV outcomes (Bassett et al., 2015; El-Sadr et al., 2017; Farber et al., 2013; Metsch et al., 2016; Rigsby et al., 2000; Rosen et al., 2007; Silverman et al., 2019; Solomon

et al., 2014; Sorensen et al., 2007). Of seven randomized trials that tested the effect of CM interventions on HIV outcomes, three reinforced ARV adherence (Rigsby et al., 2000; Rosen et al., 2007; Sorensen et al., 2007), one reinforced VL suppression (Silverman et al., 2019), one reinforced linkage to HIV care and VL suppression (with two separate CM interventions) (El-Sadr et al., 2017), and two reinforced several different behaviors including attending patient navigation sessions, HIV clinic visits, HIV blood tests, ARV initiation, VL suppression, substance use disorder treatment, or drug-free lab tests (Metsch et al., 2016; Solomon et al., 2014). One non-randomized pre-post study also examined a CM intervention that reinforced VL suppression (Farber et al., 2013). Of the randomized trials, three led to significant improvements in VL—one that reinforced ARV adherence, and two that reinforced VL suppression (El-Sadr et al., 2017; Rosen et al., 2007; Silverman et al., 2019). Of these three studies, none specifically targeted HIV-infected PWUD; however, the study samples included 18–63% of people with histories of injection drug use. The three studies that targeted HIV-infected PWUD did not find significant improvements in VL (Metsch et al., 2016; Solomon et al., 2014; Sorensen et al., 2007); in two studies, the primary outcomes were not VL, but instead time to ARV initiation and adherence.

To our knowledge, we are not aware of any published study examining whether an abstinence-reinforcing CM intervention affects HIV outcomes. Because abstinence-reinforcing CM that focuses on drug use behaviors reduces drug use, and less drug use is associated with better HIV outcomes (Kapadia et al., 2008; Palepu et al., 2006; Sambamoorthi et al., 2000; Spire et al., 2007), it is possible that abstinence-reinforcing CM that focuses on drug use behaviors may extend to improving HIV outcomes as well. Therefore, in a randomized controlled trial, we tested the efficacy of an abstinence-reinforcing CM intervention on improving VL among HIV-infected adults with opioid or cocaine use disorder, who were receiving opioid agonist treatment for opioid use disorder, and who were actively using opioids or cocaine. We hypothesized that compared to control participants, participants randomized to the CM intervention would have improved VL (primary outcome), along with improved abstinence and ARV adherence (secondary outcomes). This study was among the first to test whether CM that focuses on reinforcing one behavior (achieving abstinence) leads to improved outcomes from another related behavior (reducing VL).

2. Methods

2.1 Setting:

The study took place at the Albert Einstein College of Medicine/Montefiore Medical Center's (Einstein/Montefiore) Clinical Research Center or drug treatment centers in the Bronx, NY. Montefiore is a large urban medical center consisting of four hospitals, four emergency departments, six drug treatment centers, a hospital-based HIV clinic, and over 20 community clinics. Collectively, among the ambulatory treatment sites, over 4200 HIV-infected patients receive primary care and over 4400 patients receive drug treatment. Of patients receiving HIV or drug treatment at Montefiore, the vast majority are black or Hispanic and have Medicaid.

This study was approved by the Institutional Review Board at Einstein/Montefiore and was registered in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01376570) (Identifier: [NCT01376570](https://clinicaltrials.gov/ct2/show/study/NCT01376570)).

2.2 Participants:

Participants were recruited from June 15, 2012 to January 23, 2017 from Montefiore and the general public. Recruitment strategies included: 1) Montefiore staff informing potential participants about the study and assisting with referrals, 2) letters to Montefiore patients informing them about the study, 3) flyers and brochures in Montefiore sites and surrounding community-based organizations, 4) participant incentives to recruit peers, and 5) advertisements in newspapers.

2.2.1 Inclusion criteria included: 1) at least 18 years old, 2) English or Spanish fluency, 3) HIV-infected, 4) currently taking ARVs for at least 16 weeks, 5) self-reported imperfect (<100%) adherence to ARVs in the four weeks prior to enrollment, 6) most recent VL within the previous nine months >40 copies/mL while prescribed ARVs and at least 16 weeks from the time of the initial ARV prescription, 7) (a) opioid use disorder and currently enrolled in a methadone maintenance treatment program or prescribed buprenorphine for at least three months or (b) cocaine use disorder, 8) (a) self-reported cocaine or heroin use in the prior month or (b) misuse of prescription opioid analgesics in the prior month, 9) at least one urine toxicology test positive for opiates, oxycodone, or cocaine during the 4-week Run-In Period. Eligibility criteria 3, 4, 6, and 7 were confirmed by medical records, criterion 5 was based on the response to a standardized single-item question (Berg et al., 2012), and criterion 8 based on responses to questions from two different standardized questionnaires (Knisely et al., 2008; McLellan et al., 1992).

Consistent with other CM studies, we included a Run-In Period to: 1) ensure participants were actively using opioids or cocaine via objective biological measures (urine drug tests), 2) ensure that participants would be likely to complete the majority of research visits given our study protocol of 44 research visits, and 3) establish a baseline VL measured immediately prior to the Intervention Period.

2.2.2 Exclusion criteria included: 1) inability to give informed consent, 2) inability to follow the research protocol (e.g., visits twice weekly), 3) current chronic pain syndrome that requires prescription opioid analgesics for one or more months, 4) unstable health, defined as hospitalized three or more times in the previous six months, 5) missing more than half of the research visits during the 4-week Run-In Period, including missing the first or last visit.

2.3 Research visits

Research visits occurred from June 2012 to August 2017, and occurred twice weekly (Monday/Thursday or Tuesday/Friday) during the 4-week Run-In Period and 16-week Intervention Period. Visits occurred every two weeks during the 8-week Post-Intervention Period. Participants received \$35 for completing monthly visits (which included questionnaires, and blood and urine tests), \$5 for completing all other visits (which included urine tests only), and round-trip subway/bus fare card (worth \$5) for all visits.

To further incentivize attendance at research visits among all study participants, particularly those randomized to the control group, we implemented a Fishbowl Prize System. At the completion of each visit, participants had the opportunity to choose one ticket from the fishbowl. Of the 100 tickets in the fishbowl, 1 was a large prize (\$50 gift card), 10 were medium prizes (\$10 gift card), and 33 were small prizes (granola bar, small bag of chips, \$2.50 subway/bus fare card, or bottle of juice). This strategy has improved attendance at research visits in prior CM studies, particularly for those in the control group (Haug and Sorenson, 2006; Petry and Martin, 2002; Sorensen et al., 2007).

2.4 Experimental design and assigned groups: contingency management (CM) vs. performance feedback (control)

After obtaining informed consent, reviewing medical records, and completing visits in the Run-In Period, eligible participants were randomized 1:1 to the CM (intervention) group or the performance feedback (control) group. Randomization was computer-generated, in blocks with randomly permuted sizes of 4–8 participants, and stratified according to cocaine use and recruitment site (Montefiore's drug treatment centers, Montefiore's HIV clinic, other).

2.4.1 Contingency Management (CM) intervention—The 16-week CM intervention consisted of participants receiving vouchers exchangeable for goods or services contingent on achieving abstinence, defined as urine free of opiates (not including buprenorphine or methadone), oxycodone, and cocaine. When the urine was free of opiates, oxycodone, and cocaine, participants were categorized as abstinent and received a voucher. If participants had evidence of opiates, oxycodone, or cocaine in their urine, missed a research visit, or were unable to provide urine, they were considered non-abstinent and did not receive a voucher. The value of the vouchers increased with continued evidence of abstinence. Specifically, the voucher for the first drug-free urine was worth \$2.50, and with each subsequent drug-free urine, the voucher value increased by \$2.50 (e.g. the second voucher was worth \$5.00, the third voucher worth \$7.50, etc.). When participants had urines with cocaine, opiates, or oxycodone, the value of the voucher was reset back to baseline (e.g. \$2.50). However, after four subsequent consecutive drug-free urine samples (two weeks of abstinence), the voucher value was re-established at the level that the participant had achieved previously. The maximum possible earnings for achieving continued abstinence over the 16-week intervention period was \$1320. Participants redeemed their voucher earnings at their discretion and chose from gift cards or subway/bus fare cards that ranged in value from \$2.50 to \$50. Many aspects of our CM intervention were similar to other CM studies (e.g., duration of intervention; visit frequency; value, escalation, and resetting of vouchers; amount of maximal possible earnings) (Griffith et al., 2000; Haug and Sorensen, 2006; Lussier et al., 2006; Prendergast et al., 2006; Roll et al., 1996; Rosen et al., 2007; Schottenfeld et al., 2005; Silverman et al., 1996a, 1996b; Sorensen et al., 2007). In addition, because our CM intervention focused on HIV VL suppression, and because a reduction in VL of 1.0 log₁₀ is expected within 4 weeks of full adherence to a sensitive ARV regimen (Panel on Antiretroviral Guidelines for Adults and Adolescents), our 16-week intervention is sufficient time for a significant reduction in VL to occur and be detected.

2.4.2 Performance Feedback (control condition)—To match attention between the two groups, participants in the control group had the same number of scheduled visits and a similar type of interaction with the research team as participants in the CM group. Participants in both groups received real-time feedback with informational slips of paper indicating results of urine tests. This feedback also provided congratulation messages when urines were drug-free, or encouraging messages to stop using opioids and/or cocaine when urines were not drug-free. The control group did not receive vouchers based on results of the urine tests. Similar performance feedback control conditions have been employed in prior CM studies.

2.5 Data sources and collection

2.5.1 Blood tests: VL and CD4 count—At visits every 4 weeks, blood samples were collected for HIV VL measurements initially via VERSANT® HIV-1 RNA 3.0 Assay (bDNA), then via Montefiore's central lab. CD4 count was measured at baseline initially by the FACS® Multiset™ System (Becton Dickinson and Co.), then via Montefiore's central lab.

2.5.2 Urine toxicology tests—Participants provided observed urine specimens at all research visits. Urine temperature was tested to assess validity of the specimen. Urine was immediately tested for cocaine, opiates, oxycodone, methadone, and buprenorphine using the RapidTox7 from American Bio Medica (results were positive/negative for each substance). While methadone and buprenorphine were measured to confirm treatment of opioid use disorder, the absence or presence of methadone and buprenorphine were not included in our definition of abstinence. As mentioned above, for the CM intervention, abstinence was defined as urine free of opiates, oxycodone, and cocaine.

2.5.3 Questionnaires—At visits every 4 weeks, research staff administered questionnaires using Audio Computer-Assisted Self-Interview (ACASI) technology. The ACASI system displayed each question on a computer monitor while playing an audio recording of the question. Participants entered responses directly on the computer. Variables measured included sociodemographic and clinical characteristics. Sociodemographic variables included: age, gender (male, female, transgender), race/ethnicity (Hispanic, non-Hispanic black, non-Hispanic other), and education. Clinical characteristics included: duration of HIV-infection, history of Hepatitis C Virus infection, alcohol and drug use (McLellan et al., 1992; Saunders et al., 1993) (current substance use in the previous 30 days [opioids, cocaine, cannabinoids, benzodiazepines], ever and current injection drug use), and depression symptoms (Radloff, 1977).

2.5.4 Medical records—Research staff reviewed medical records to confirm eligibility prior to the Run-In Period. With oversight from a physician, a trained research assistant conducted data extraction from medical records. Variables included HIV status, ARVs prescribed, methadone and buprenorphine treatment including doses and duration.

2.6 Outcome measures

Our primary outcome was HIV VL, analyzed as a continuous measure ($\log_{10}$ copies/ml). Secondary outcomes included abstinence and adherence. Abstinence was defined as having drug-free urine (no opiates, oxycodone, and cocaine) and analyzed dichotomously. Adherence was self-reported and measured as the proportion of ARVs taken over the previous three days (Chesney et al., 2000).

2.7 Analyses

We first reviewed and summarized data using descriptive summaries and graphical analyses to ensure that values were within appropriate ranges, to check for the presence of outliers and abnormal values, and to verify that the distributions of measures meet the assumptions of statistical tests. Using chi square tests, Fischer exact tests, or Wilcoxon rank sum tests, we examined whether the CM and control groups differed on potential confounding variables identified a priori (age, gender, race/ethnicity, education, baseline drug use, methadone and buprenorphine doses and duration, and depression symptoms). Because no variables significantly differed between groups, we did not include these variables in our analytic models. In our primary analysis, we used the intention-to-treat approach analyzing all observed data. To understand the intervention effect, we also conducted secondary analyses using a per-protocol approach. In the per-protocol approach, participants who completed at least half of all visits during the Intervention Period were considered to have received an adequate “dose” of the intervention or control condition and were included in the analyses. Those who completed less than half of the Intervention Period visits were excluded from analyses.

Our primary analysis examined whether the intervention effect (CM vs. control) was associated with change in $\log_{10}$ VL over the 16-week Intervention Period. We used mixed-effects linear regression analyses (SAS, PROC MIXED) to examine intervention and time main effects as well as intervention-by-time interactions. We also conducted a series of pre-specified secondary analyses. In one analysis, we examined the durability of effect on VL by including the 8-week Post-Intervention Period in the analysis. In other analyses, we separately examined abstinence and adherence as dependent variables using mixed-effects logistic and linear regression models, respectively; we did not include time or a time-by-intervention interaction terms in these models. To fully understand the CM intervention effect on VL, we also used a single mixed effect linear regression model that included the intervention, time, time-by-intervention, abstinence, and adherence to predict log VL. Finally, for missing data, we conducted multiple imputations (n of imputations=2000) using Markov Chain Monte Carlo imputation methods. We then conducted mixed effect linear or logistic regression analyses for each imputed data set and pooled the results into a single final result using Rubin’s method (Rubin, 1987).

To provide a visual depiction of the differences between the CM and control groups over the entire study period, we created Figure 2 by calculating mean $\log_{10}$ VLs and 95% confidence intervals at research visits every 4 weeks. We similarly created Figure 3 by calculating the percentage of participants with abstinent urine drug tests at all 44 research visits, and Figure 4 by calculating the mean self-reported adherence at research visits every 4 weeks. We used

observed raw data to create these figures, and not modeled data that take repeated measures by individual participants into account.

2.7.1 Power analyses—Our study was designed to achieve 80% power to detect a moderate effect size (Cohen's $d=0.35$) on VL suppression between CM and control groups, with an anticipated sample size of 202, a 15% attrition rate, and an intra-class correlation of $\log_{10}$ VL of 0.7. We did not power our study based on secondary outcomes, abstinence and adherence. As described below, although we enrolled 236 participants, only 73 were ultimately eligible for randomization.

3. Results

Of the 1,437 unique individuals screened, 236 enrolled in the study (see Figure 1). Of the 1201 excluded individuals, the most common reasons were: not HIV-positive (40.4%); no current cocaine, heroin, or opioid misuse (17.7%); taking chronic opioid analgesics for pain (14.0%); and perfect (100%) adherence in the previous 4 weeks (12.3%). Of the 236 enrolled individuals, 118 were ineligible after medical record review (104 had undetectable VLs), 18 were ineligible after the Run-In Period, 17 were lost to follow-up prior to randomization, 8 declined further participation, and 1 was invalid due to research staff error.

Of the final sample of 73 participants, 37 were randomized to the CM group and 36 to the control group. Participants' median age was 49.2 years, and most were male (61.6%) and non-Hispanic black (46.6%) (see Table 1). There were no significant differences in sociodemographic or clinical characteristics between participants in the two groups. Of the 3,212 total scheduled visits among the 73 randomized participants, 2,161 (67.3%) were completed. Of the 2,336 scheduled visits during the Intervention Period, 1,528 (65.4%) were completed, with no difference in the proportion of completed visits between those in the control versus CM group (63.8% vs. 67.1%, $p=0.09$). At the 3212 scheduled visits, 481 (15.0%) of urine toxicology tests were negative for opiates, oxycodone, and cocaine (missed visits were counted as positive urine toxicology tests). Of these 481 tests, 244 (50.7%) were positive for methadone or buprenorphine, while negative for opiates, oxycodone and cocaine. These 244 urine toxicology tests were from 25 participants, all of whom received methadone or buprenorphine treatment. Of the 37 participants randomized to the CM group, of all vouchers received, the median total value was \$5.00 (IQR=\$0-\$40.00), the mean total value was \$84.93 (SD=\$226.75), and range was \$0-\$952.50. Twelve participants earned \$0, and nine earned \$50 or more.

In the primary intention-to-treat analysis, compared with the control group, the mean reduction in $\log_{10}$ VL during each 4-week time point during the Intervention Period in the CM group was significantly greater ($-0.16 \log_{10}$ VL copies/mL per 4-week period; 95% CI: -0.29 to -0.03 , $p<0.05$). Thus, over the entire 16-week Intervention Period, the CM group had a mean reduction of 0.64 copies/mL in $\log_{10}$ VL greater than the control group. In Figure 2, we present the observed mean $\log_{10}$ VL results by group. When examining the durability of the CM intervention by including the 8-week Post-Intervention Period in the analysis, the difference in $\log_{10}$ VL between the control group and CM group no longer

remained significant ($-0.07 \log_{10}$ copies/mL per 4-week period; 95% CI: -0.15 to 0.02 , $p=0.12$).

In the per-protocol analysis during the Intervention Period (including only participants who completed at least half of their study visits), VL findings were similar to the intention-to-treat analysis. In addition, in the per-protocol analysis examining durability (including only participants who completed at least half of their study visits and including the 8-week Post Intervention Period), compared with the control group, the mean reduction in $\log_{10}$ VL in the CM group was significantly greater ($-0.10 \log_{10}$ copies/mL per 4-week period; 95% CI: -0.19 to -0.01 , $p<0.05$). In other analyses using imputed missing data, findings remained similar.

When using the intention-to-treat approach to examine abstinence and adherence during the Intervention Period, compared to the control group, the CM group had no significant difference in achieving abstinence (OR=1.13, 95% CI: -0.10 to 2.36 , $p=0.07$) or difference in adherence (2.3% adherence, 95% CI: -12.9% to 17.5% , $p=0.76$). However, when using a per-protocol approach, the CM group had a significantly greater odds of achieving abstinence (OR=1.35, 95% CI: 0.03 to 2.68 , $p<0.05$), with no difference in adherence (2.6% adherence, 95% CI: -15.1% to 20.2% , $p=0.78$). In Figures 3 and 4, by group, we present observed abstinence and mean adherence results, respectively.

To understand how the CM intervention, abstinence, and adherence simultaneously affect VL during the Intervention Period, when including them into a single model, the CM intervention and adherence were significantly associated with log VL (for CM intervention vs. control: $-0.15 \log_{10}$ copies/mL per 4-week period; 95% CI: -0.28 to -0.03 , $p<0.05$; for every 10% increase in adherence: $-0.03 \log_{10}$ copies/mL over the 16-week Intervention Period, 95% CI: -0.06 to -0.007 , $p<0.05$), while abstinence was not associated with log VL (for every 10% increase in abstinence: $-0.003 \log_{10}$ copies/mL over the Intervention Period, 95% CI: -0.06 to 0.05 , $p=0.91$).

4. Discussion

In this randomized controlled trial of HIV-infected adults who had opioid or cocaine use disorder, were receiving opioid agonist treatment for opioid use disorder, and who were actively using opioids or cocaine, our abstinence-reinforcing contingency management intervention improved HIV viral load. In intention-to-treat analyses, the improvement in VL diminished after the CM intervention ceased; however, in per-protocol analyses, VL improvement remained durable. Furthermore, while our CM intervention significantly improved abstinence in the per-protocol analysis, the CM intervention did not improve abstinence or ARV adherence in intention-to-treat analyses.

To our knowledge, this is the first study to demonstrate improvements in HIV VL via a CM intervention that focuses on reinforcing abstinence from drugs. Our study incrementally advances the science related to contingency management, drug use, and HIV. Most studies that examine abstinence-reinforcing CM interventions focus on drug-related outcomes. Of the randomized trials that tested the effect of CM interventions on HIV outcomes, the CM

interventions have focused mainly on reinforcing ARV adherence, VL suppression, or HIV clinic visit attendance (El-Sadr et al., 2017; Metsch et al., 2016; Rigsby et al., 2000; Rosen et al., 2007; Silverman et al., 2019; Solomon et al., 2014; Sorensen et al., 2007). Of these studies, three led to significant improvements in VL, though none specifically targeted HIV-infected PWUD or employed an abstinence-reinforcing CM intervention (El-Sadr et al., 2017; Rosen et al., 2007; Silverman et al., 2019). The three studies that targeted HIV-infected PWUD did not find significant improvements in VL (Metsch et al., 2016; Solomon et al., 2014; Sorensen, et al., 2007).

Our study is unique in that our CM intervention, which focused on reinforcing abstinence rather than adherence or VL, improved VL. Rather than focusing our CM intervention on the HIV outcome itself, we chose to target our CM intervention on drug use, a critical mediator of achieving optimal HIV outcomes. Our decision was based on both our clinical experiences and a body of literature demonstrating strong associations between drug use, drug treatment, and HIV outcomes (Malta et al., 2008; Arnsten et al., 2002; Cohen et al., 2004; Lucas et al., 2010; Altice et al., 2011). While several studies have shown associations between drug use and HIV outcomes, and others have shown associations between drug treatment and HIV outcomes, few randomized controlled trials have tested interventions that aim to reduce drug use as a vehicle to improve HIV outcomes. Other studies have similarly focused financial incentives on behaviors that are not directly focused on HIV, but rather on structural factors or behaviors that are more proximal in the causal pathway with regards to acquiring HIV infection (Baird et al., 2012; de Walque et al., 2012; Pettifor et al., 2016). For example, because lack of education and economic dependence on men is an important risk factor for HIV infection in women in low income countries, two studies tested financial incentives for school attendance among adolescent school girls in low income countries (Baird et al., 2012; Pettifor et al., 2016). These studies had mixed findings—one study found financial incentives led to lower prevalence of HIV infection while the other did not.

While our study was not powered to detect changes in our secondary outcomes (abstinence and adherence), we were surprised to find that the mechanism of our CM intervention was not as we had expected. We anticipated that the CM intervention would improve abstinence, abstinence would improve ARV adherence, and ARV adherence would improve VL. In secondary analyses, our CM intervention significantly improved abstinence only in our per-protocol analysis, and not in our intention-to-treat analysis. Our CM intervention also did not significantly improve adherence. When including our CM intervention, abstinence, and adherence in a single model to predict VL, both the CM intervention and adherence independently predicted VL, but abstinence did not. Therefore, it is not entirely clear how the CM intervention led to a reduction in VL. One explanation of our findings is that the CM intervention reduced opioid or cocaine use, but not to full abstinence. When we examined self-reported number of days of heroin use and cocaine use, compared to the control group, the CM group reported less days of heroin use and cocaine use (data not shown). In preclinical studies, cocaine use promotes viral replication; thus, a reduction in cocaine use could directly impact VL without achieving abstinence or changing adherence. Because our study was powered to detect a change in VL (primary outcome) and not abstinence and adherence (secondary outcomes), and because the sample size randomized to the CM intervention or control groups was much smaller than the sample enrolled (which was the

target sample size), it is possible that our findings reflect limited power to detect changes in abstinence and adherence.

Despite VL improvement during the 16-week Intervention Period, once the CM intervention ceased during the Post-Intervention Period, improvement in VL diminished. This finding of diminished improvement in outcomes after CM interventions cease is common among CM studies, and often a critique of CM interventions. It is possible that CM interventions might be more effective in sustaining behavior change if paired with psychosocial support to help individuals recognize positive health changes and support them to find ways to maintain positive health behaviors over time.

One unexpected observation of our study was the number of HIV-infected individuals who had suppressed VLs, despite reporting active illicit opioid or cocaine use and imperfect (<100%) ARV adherence. Of the 236 participants enrolled, 104 (44%) were subsequently excluded from the study because they had suppressed VLs documented in their medical records. And, this number does not take into account those who were actively using drugs with 100% adherence. In addition, of the participants with non-suppressed VLs prior to enrolling, nearly half (44%) had suppressed VLs at the end of the Run-In Period. During the study period from June 2012 to August 2017, several new ARVs were approved by the US Food and Drug Administration. Over this time frame, ARV regimens became even more potent and forgiving, facilitating optimal HIV outcomes despite active drug use and imperfect adherence. Our observation questions the relevance of prior studies showing poor HIV outcomes in PWUD, particularly when they are in drug treatment and taking today's ARV regimens. It also suggests that for PWUD who are receiving drug treatment and HIV treatment, they may no longer need additional interventions to enhance their HIV outcomes, and that our CM intervention is appropriate for a small select group of PWUD.

Our study has limitations. As mentioned above, our study enrolled a select population of HIV-infected PWUD in New York City, where drug and HIV treatment are widely available and where there is a long history of treating HIV-infected PWUD. Thus, our findings have limited generalizability. Our CM intervention was a time- and resource-intensive intervention, with visits occurring twice weekly for 16 weeks. Therefore, implementation of an intervention like this would need to be limited to a select population in specific settings with frequent visits (e.g. opioid treatment programs). While our control condition was matched for attention, we did not utilize vouchers that were not contingent on abstinence. Although we defined abstinence as urine free of opiates, oxycodone, and cocaine, which are commonly misused substances, we did not measure or include all opioids in our definition of abstinence. Our target sample size was 202; we enrolled 236 but only randomized 73 due to many participants unexpectedly meeting further exclusion criteria. Thus, our study was not fully powered, which may have affected our ability to find significant differences in secondary outcomes.

5. Conclusions

In this randomized controlled trial of HIV-infected people who use drugs, compared with a control condition, our 16-week abstinence-reinforcing CM intervention significantly

improved HIV VL. However, the CM intervention did not significantly improve abstinence or ARV adherence. Despite the advances made in HIV treatment, to end the HIV epidemic, innovative strategies must address individuals who continue to have poor HIV outcomes. Health departments and payors could consider abstinence-reinforcing contingency management as one potential strategy to improve HIV VL among a select group of people who use drugs.

Acknowledgements:

We thank all study participants for participating in the study. We also are grateful to all study staff for their help in implementing the study.

Role of funding source: The funding source had no role in study design, analyses, results, or interpretation or dissemination of findings. final manuscript.

Funding: This work was supported by the National Institute of Health (R01DA032110, K24DA036955, P30AI124414, R25DA023021, K08DA043050).

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Highlights

- Abstinence-reinforcing contingency management (CM) improved HIV viral load (VL).
- The mechanism of CM's effect on VL is not completely understood, as CM did not significantly affect abstinence or adherence. In addition, while CM and adherence were significantly associated with VL, abstinence was not.
- CM's median amount was \$5.00 and led to improvements in HIV VL.
- When CM ceased, the improvement in HIV VL diminished.

Figure 1.
CONSORT flow diagram.

Figure 2.
Mean log₁₀ HIV viral load by contingency management (CM) versus control groups during the Run-In, Intervention, and Post-Intervention Periods.

Figure 3.

Abstinence from opiates, oxycodone and cocaine by contingency management (CM) versus control groups during the Run-In, Intervention, and Post-Intervention Periods.

Figure 4.
Mean adherence rate by contingency management (CM) versus control groups during the Run-In, Intervention and Post-Intervention Periods.

Table.

Characteristics of 73 study participants by randomized condition

Characteristic	Total	Abstinence-reinforcing contingency management	Control condition
	(N=73) n (%)	(N=37) n (%)	(N=36) n (%)
Sociodemographic characteristics			
Age, mean years $\pm$ SD	49.2 $\pm$ 7.3	50.5 $\pm$ 7.1	47.8 $\pm$ 7.3
Male sex	45 (61.6)	23 (62.2)	22 (61.1)
Race/Ethnicity			
Hispanic	21 (28.8)	13 (35.2)	8 (22.2)
Non-Hispanic black	34 (46.6)	16 (43.2)	18 (50.0)
Education < high school	30 (41.1)	15 (40.5)	15 (41.7)
Median annual income (US dollars, IQR)	9600 (2000, 12,000)	9000 (2000, 13,000)	9800 (3500, 12,000)
Clinical characteristics			
Depression symptoms ^a	47 (64.4)	25 (67.6)	22 (61.1)
History of Hepatitis C Virus infection	31 (43.7)	16 (43.2)	15 (44.1)
Years of HIV infection			
<5 Years	5 (7.0)	2 (5.4)	3 (8.8)
5–9 Years	37 (52.1)	20 (54.1)	17 (50.0)
10 years	29 (40.9)	15 (40.5)	14 (41.2)
HIV viral load (VL) ^b			
Median Log VL (copies/mL)	2.00	2.00	2.00
Undetectable VL	30 (44.1)	15 (41.7)	15 (46.9)
Median CD4 count ^b (cells/mm ³)	239	239	254
Substance use in the previous 30 days ^b			
Opioids	21 (28.8)	8 (21.6)	13 (36.1)
Cocaine	56 (76.7)	29 (78.4)	27 (75.0)
Cannabinoids	31 (42.5)	20 (54.1)	11 (30.6)
Benzodiazepines	9 (12.3)	5 (13.5)	4 (11.1)
Ever injected drugs	25 (34.3)	10 (27.0)	15 (41.7)
Currently injecting drugs	12 (16.4)	6 (16.2)	6 (16.7)
Current methadone treatment	32 (43.8)	15 (40.5)	17 (47.2)
Current buprenorphine treatment	5 (6.9)	4 (10.8)	1 (2.8)
Hazardous alcohol use ^c	17 (23.9)	8 (21.6)	9 (26.5)

^aScore of >16 on the Clinical Epidemiological Study of Depression (CESD) Scale^bValues are from the end of the Run-In Period^cScore of >9 on the Alcohol Use Disorder Identification Test (AUDIT)

Missing data (n): Age (2), Sex (2), Education, (2), Race/Ethnicity (2), Depression symptoms (2), History of HCV infection (2), Years of HIV infection (2), HIV viral load (2), CD4 count (2), Opioids (2), Cocaine (3), Cannabinoids (2), Benzodiazepines (2), Ever injected drugs (2), Currently injecting drugs (2), Hazardous alcohol use (2).

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