Voucher reinforcement improves medication adherence in HIV-positive methadone patients: a randomized trial.

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Voucher Reinforcement Improves Medication Adherence in HIV-Positive Methadone Patients: A Randomized Trial

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Abstract

This clinical trial evaluated an intervention designed to improve medication adherence among HIV-positive methadone maintenance patients. After a 4-week baseline observation phase, eligible participants (N = 66) were randomly assigned to: (a) bi-weekly medication coaching sessions (comparison group) or (b) medication coaching plus voucher reinforcement for opening electronic medication caps on time (voucher group). The intervention was provided for 12 weeks, with a 4-week follow-up. Results indicated a clear impact of voucher reinforcement on medication adherence during the intervention period. Using the Medication Events Monitoring System (MEMS®) TrackCap, mean adherence among comparison and voucher reinforcement participants was 56% and 78%, respectively. Significant differences in change over time, favoring the voucher group, were found for all adherence measures: MEMS® adherence, MEMS® cap consecutive openings (i.e., longest duration of adherence), pill count adherence, and self-reported adherence. Differences between groups faded after vouchers were discontinued. Voucher reinforcement shows promise as a strategy to promote antiretroviral medication adherence.

Key words: randomized clinical trial, opioid use, contingency management, voucher reinforcement, methadone treatment, substance abuse treatment
Voucher Reinforcement Improves Medication Adherence in HIV-Positive Methadone Patients: A Randomized Trial

Adherence to human immunodeficiency virus (HIV) medications is essential to successful treatment outcomes. Illicit drug use is a significant barrier to adherence with prescribed highly active antiretroviral therapy (HAART), and drug use represents a challenge for the patient and their health care providers (Turner et al., 2001; Sollito et al., 2001). Research has demonstrated that HIV-positive drug users have difficulty adhering to complex HAART regimens (Batki & Ferrando, 1996; Freeman, Rodriguez, & French, 1996; Fogarty et al., 2002). Adherence to HAART has been associated with relative improvements in immunologic and virologic markers (Low-Beer et al., 2000; Paterson et al., 2000) and with less rapid progression to Acquired Immunodeficiency Syndrome (AIDS; Bangsberg et al., 2001). Because reducing the dose can contribute to the development of resistance to the medications (Carpenter et al, 1996), guidelines for antiretroviral therapy with protease inhibitors emphasize maintaining continuous drug administration at the optimal dosage level.

Contingency management may be an efficacious intervention for drug-using HIV patients with poor medication compliance. A significant body of work indicates that contingency management (CM) is an effective treatment for patients with substance use disorders, including those receiving methadone treatment (for example, Hall et al. 1977; Higgins et al. 1986; Calsyn et al. 1994). A variant of contingency management, voucher-based reinforcement therapy helps patients achieve and maintain abstinence from drugs by providing a voucher incentive for each drug-free urine sample. The voucher has monetary value and can be exchanged for goods and services consistent with the goals of treatment. Initially the value of the vouchers is low, but the
value increases with the number of consecutive drug-free urine specimens. This approach has been successful with methadone maintenance patients in encouraging sustained abstinence from cocaine (Silverman, Higgins, et al., 1996; Silverman et al., 2004) and opiates (Silverman, Wong, et al., 1996) as well as increasing full-day attendance at treatment (Jones, Haug, Silverman, Stitzer, & Svikis, 2001). More recently, Rigsby et al. (1999) demonstrated that monetary reinforcement (not vouchers), combined with structured training that provides cues about when to take medications, increases adherence to antiretroviral therapy.

In the present study we adapted the use of voucher-based reinforcement therapy to reinforce taking antiretroviral medications as prescribed. The study represents a novel application of CM as the first reported study to apply the use of voucher incentive therapy to HIV medication adherence. Voucher incentives were tested for their efficacy as behavioral reinforcement to increase patient adherence to antiretroviral medication-taking. We posited that, relative to the comparison group, participants randomly assigned to receive voucher incentives would show better medication adherence (measured by electronic medication cap openings, pill count, and self-report), as well as relative improvement in biological and behavioral measures of health (HIV-RNA levels, CD4+ count, and self-report).

Method

Study Design

The study was a two-arm randomized controlled experiment conducted from April 2001 through March 2004 and included a 4-week baseline phase, a 12-week intervention phase in which participants were randomized to receive or not receive voucher incentives, and a 4-week follow-up phase.
Research Participants and Settings

Clinical Settings

Participants were recruited from among HIV-positive patients enrolled in methadone maintenance treatment at two urban clinics in San Francisco, California: The San Francisco General Hospital Opiate Treatment Outpatient Program (OTOP) and Bay Area Addiction Research and Treatment (BAART), Market Street Clinic. OTOP, a hospital-based program supported by the San Francisco Department of Public Health, provides substance abuse, medical, and psychiatric treatment to approximately 600 opioid-dependent patients. Nearly 33% of OTOP patients are HIV-positive. BAART, a private network of twelve clinics in five California counties, offers substance abuse treatment and medical care. The BAART Market Street Clinic provides services to 600 patients, with 10% diagnosed as HIV-positive. Throughout the study, patient confidentiality was maintained with regard to medication adherence, substance use, and other risk behaviors so that standard care at the methadone clinic was not affected by study participation.

Inclusion and Exclusion Criteria

The 66 adult participants met the following criteria for study participation: (a) enrolled in outpatient methadone maintenance treatment, (b) HIV antibody seropositive as indicated by clinic records, and (c) prescribed an antiretroviral medication for treatment of HIV/AIDS for at least 1 month, evidenced by prescription or prescription bottle. Participants were excluded from the study if they were: (a) participating in other adherence-improvement research or clinical programs or (b) living in a controlled environment that dispensed residents’ HIV medications.

Recruitment and Intake Procedures

Recruitment and Screening. The University of California, San Francisco Institutional Review Board approved all study procedures. A recruitment flyer was distributed to clinics and
counselors, who encouraged interested patients to contact the research staff. Research staff met with potential participants in a private room and administered a screening form assessing whether inclusion/exclusion criteria were met.

*Intake.* After screening, the research interviewer administered a written informed consent process, explaining that throughout the study, medication adherence results would not be given to the methadone clinic staff. The intake assessment battery was then administered, and in a second session the participant completed a diagnostic research interview, typically within 1 week of intake.

**4-Week Baseline Phase**

After study intake procedures, participants were enrolled in a 4-week baseline observation phase to record adherence to HAART medications, in preparation for the clinical trial.

*Assignment of Electronic Medication-Cap.* At the beginning of the baseline phase participants received a standard plastic vial with a MEMS® (Medication Event Monitoring System) TrackCap for one of their HAART medications (e.g., protease inhibitor, nucleoside analog reverse transcriptase inhibitor, or non-nucleoside reverse transcriptase inhibitor). For patients taking multiple medications, the one with the most frequent pill-taking schedule or the one that was determined as most difficult to take was selected as the target.

*Medication Coaching.* The medication coaching intervention included 10 strategies to improve adherence and was adapted from an approach used in the Adult AIDS Clinical Trials Group. The role of a medication coach was to provide support with the medication regimen and to work in partnership with the client to improve medication adherence. Participants met with a registered nurse or trained research assistant who provided medication coaching. The medication coach assessed current antiretroviral medications prescribed for the patient and generated a personalized schedule, taking into account lifestyle variations in sleep and eating
patterns. Medication coaching occurred once during the baseline phase and then every two weeks through participants' 20 weeks in the study. As a general guideline, the baseline meeting assessed the client’s current medication-taking habits, whereas sessions in the intervention phase built skills needed for improved medication adherence, and the follow-up meetings promoted future adherence. An intervention manual (Haug, Sorensen, Gruber, Lollo, & Roth., under review) describes the medication coaching and other interventions of the study.

**Bi-Weekly Assessments with Research Assistants.** During baseline, participants met with a research assistant twice per week to provide results of medication-cap openings. The visits were scheduled to coincide with the patient’s methadone dosing days. At each session the patient had an opportunity to view the display of medication-cap openings recorded since the last visit with the research assistant, following the feedback protocol used by Rigsby et al. (2000). The first interview of the week lasted 10-15 minutes per client and involved downloading information on medication-cap opening, counting pills remaining in the patient’s prescription bottle, and asking patients to provide self-report of medication adherence and side effects. The second appointment of the week simply downloaded information on medication-cap openings and usually lasted no more than 5 minutes. At the end of the 4-week baseline phase the research assistant assessed the participant’s interest in continuing in the clinical trial phase of the study, reassessed eligibility criteria, and recruited eligible participants.

**Monetary Compensation.** All participants were compensated for completing scheduled assessments and other research activities: $10 for intake assessments; $10 for the Diagnostic Interview Schedule (DIS); $8 for MEMS cap assignment; $2 for each twice weekly download interviews (40 interviews); $2 for each weekly “survey” interview (20 interviews); $2 for each medication coach visit (10 visits); $10 for each monthly blood draw (6 blood draws); $3 for each
monthly urine sample (6 urine samples); and $10 for final return of the MEMS cap. The maximum amount paid to participants was $256.00.

Selection for Clinical Trial and Random Assignment. At the end of the 4-week baseline phase the study team reviewed the patients’ eligibility for the intervention phase of the study. Participants were not eligible for the clinical trial if their records indicated more than 80% medication adherence during the baseline phase, as measured by the medication-cap openings. Ineligible participants were debriefed about the study, explained that they were excluded because of high medication adherence, and provided with additional adherence resources.

Eligible participants were randomly assigned to receive vouchers or a comparison intervention according to a computer-generated list, with assignment stratified by baseline CD4 lymphocyte count (i.e., greater than or equal to 200 cells/UL versus less than 200 cells/UL). The stratification variable was selected because more medically compromised patients were likely to have more severe medical problems during the study; the cut point represented the level that defined AIDS as the study began. The research assistant, who had been blind to the future group assignment, opened a sealed envelope of assignments generated by the project statistician.

12-Week Intervention Phase

Voucher Intervention. In this intervention, participants who opened medication caps as scheduled received vouchers that were exchangeable for goods and services consistent with the participant’s treatment goals. Vouchers were provided to participants for each dose of their target HIV medication that was taken as prescribed. Specifically, MEMS® confirmed when the medication cap was opened, and reinforcement was provided if the interval was 2 hours plus or minus the scheduled dosing time.

During the intervention phase, each participant met twice weekly with a research assistant, for a total of 24 visits. At these visits, participant earnings were calculated based on the level of
adherence demonstrated. They could exchange the voucher immediately for goods/services or leave it at the clinic to accumulate for higher-value items at a later time.

The fixed-ratio schedule reinforced consistency in taking the medications. The behavioral units and voucher values were based on the researchers’ experience with a pilot study and on research reinforcing drug-free urine samples in methadone maintenance (Silverman, Wong, et al., 1996, Silverman, Higgins, et al., 1996). Each participant received a voucher for the number of medication doses taken as scheduled. On Day 1 of the schedule, each participant could earn up to $1 per day (e.g., $.50 per dose for medications taken twice daily). If any dose was not taken within the scheduled timeframe, a voucher was not earned for that dose, and the voucher value for the subsequent dose began at the starting value (e.g., $.50 per dose for medications taken twice daily).

A key feature of the protocol was that the value of a voucher increased for each consecutive day that all medications were taken on time but was reset to the original amount when a medication was not taken on time. In the first five days the participant had opportunity to earn $1.40 more with each successive day if all doses were taken as scheduled. If a dose was not taken on schedule, earnings reverted to the initial level of $1 per day. This earnings increase for consecutive doses taken within schedule continued until Day 6. From Day 6 on, the increase for taking all doses within schedule was $.20 per day (from $7.00 for Day 7 to $7.20 for Day 8, etc.). On any day a participant did not take a dose on schedule, the earnings level reset at $1 per day with the subsequent $1.40 per day increase for each day of consecutive doses taken on schedule. After two weeks of consecutive adherence, the highest level previously earned could be reinstated, with increases by $.20 per day for each consecutive day of doses taken on schedule. A participant could earn as much as $1172.40 in vouchers if he/she took all medication doses as scheduled through the 12-week intervention period.
Comparison Intervention. At the beginning of the trial, patients in the comparison condition did not receive vouchers. Several of the first eight comparison participants, however, expressed dissatisfaction with their treatment relative to the voucher participants, and two of them discontinued study participation for that reason. To promote retention in the comparison group, and to reinforce attendance at scheduled interviews, the project implemented a fishbowl lottery modeled described Petry and Martin (2002).

The fishbowl lottery awarded small ($1-$2) and large prizes (approximately $80). For each completed research visit, the participant had the opportunity to pick a number from the fishbowl. Participants had a 1 in 3 chance of winning a small prize (snacks, soaps, lotions, nutritional drinks, socks, etc.) and a 1 in 350 chance of winning a large prize (TV, VCR, microwave, stereo). As part of implementing the fishbowl lottery, the researchers polled participants to determine their preferences for the prize selection, and during the study participants were asked what prizes they wanted to have replenished. Comparison group attendance improved after fishbowl implementation (Veluz et al., 2003). Specifically, the attrition rate dropped from 25% to 0%, and the total number of missed interviews decreased from an average of 4.38 to 0.47.

4-Week Follow-up Phase

During the 4-week follow-up phase, vouchers were discontinued, but visits with the medication coach continued. All participants continued to meet with the research assistant and download MEMS® results. To promote retention in both study groups, the fishbowl lottery continued in weeks 17-20 in the comparison group and was initiated in the voucher group, rewarding participants’ attendance to research visits with the opportunity to draw a number from a bowl of small and large prizes.

Baseline Measures
Addiction Severity Index (ASI; McLellan et al., 1992) is a semi-structured clinical interview that measures psychosocial problems in seven domains of functioning: medical, employment, alcohol, drug, legal, family/social and psychiatric.

Beck Depression Inventory–II (BDI-II; Beck, Steer, & Brown, 1996) is a widely used, 21-item measure of severity of depressive symptoms in the past 2 weeks.

Computerized Diagnostic Interview Schedule–IV (CDIS-IV; Robins et al. 1995) is a structured interview yielding diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition; DSM-IV; American Psychiatric Association, 1994). The current study administered only the Mood and Substance Abuse/Dependence Modules.

Outcome Measures

Medication Event Monitoring System V TrackCap (MEMS®; Aprex, Inc.) is a measure of medication adherence that uses a medication cap containing a microelectronic chip to record bottle opening dates and times. These data are downloaded to a computer using a communicator device and PowerView® software (Aardex Ltd.) that stores the information in a database. In this study, we monitored one selected HAART medication. This measure was the primary outcome measure of adherence (i.e., percent observed openings/percent expected), as research has shown it to be more sensitive than other methods (Arnsten et al., 2001; McNabb et al., 2003). On-time MEMS® cap openings were expressed as the percentage of scheduled dosing times when the cap was opened “on-time,” defined as taking place in a 4-hour window (2 hours before or after) around the scheduled dosage time. We used MEMS® records to calculate both on-time openings and longest documented period of continuous on-time openings (or longest duration).

Medication Adherence and Side Effects Questionnaire (adapted from Chesney et al., 2000) is a self-report of patient’s adherence for the previous day and the past 3 days for each medication
in the current regimen. The measure also includes questions about medication side effects and was administered weekly throughout the study.

*Pill Count* was completed for the one selected HAART medication—-at baseline to reflect the initial stock, then weekly to track adherence, and after refills to account for new pills added to the bottle. We deduced the number of pills taken, which was divided by the number of pills the patient was expected to take based on their medication regimen. In the few cases where the calculation exceeded 100%, it was capped at 100.

*Medical Outcomes Study Short-Form* (MOS SF-36; Ware, 1996) is a 36-item self-administered instrument that evaluates health-related quality of life in eight dimensions, including: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, mental health, and reported health transition. It provides two summary measures; a Mental Health Summary Scale and a Physical Health Summary Scale, which were utilized as the primary outcome measures of self-reported health. The SF-36 was administered monthly (baseline, weeks 4, 8, 12, 16, and 20).

*Urine Toxicology Screen.* Specimens were collected monthly and analyzed by Quest Diagnostics, Inc. (formerly Unilab Corporation) using Enzyme Multiplied Immunoassay Technique (EMIT), and positive screens were re-analyzed using Thin-layer Chromatography (TLC). Reported results included alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine, however, only cocaine and opiates were examined in the current report.

*Weight* (lbs.) was measured on a physician mechanical balance beam scale at baseline and at 20-week follow-up.

*Plasma HIV-1 RNA* (viral load) was quantified from monthly blood draws using the Quantiplex bDNA Assay Version 3.0 (Bayer Corp), which has a dynamic range of 75 - 500,000
copies/ml. A decrease of at least .5 in log10 viral load is considered consistent with improvement and not within the range of lab error.

*CD4(+) lymphocyte counts* (a type of white blood cells or T-cells vital to immune function) were obtained at baseline, weeks 12 and 20 from blood samples sent to the hematology section of San Francisco General Hospital clinical laboratories.

**Attrition from Screening and Sample Characteristics (Figure 1)**

A total of 181 people were screened during a 31-month recruitment period. Out of those screened, 103 were eligible. Attrition from screening to consent was 16%, with 86 people enrolling in the study and beginning the baseline phase. Reasons for ineligibility were: n = 7 did not have sufficient clinic records to indicate that they were HIV antibody seropositive, n = 36 were not being prescribed an antiretroviral medication for treatment of HIV/AIDS for at least one month, n = 9 were participating in other adherence-improvement research or clinical programs, n = 5 were living in a controlled environment that dispensed residents’ HIV medications and n = 21 were ineligible due to other reasons (i.e., too ill, incarcerated, psychiatric impairment). Of the 86 participants who began the baseline phase, 66 were randomized and began the intervention phase. Reasons for not being randomized appear in Figure 1.

Attrition from the study during the intervention and follow-up phases was minimal. For the analysis of the primary outcomes, 28 of 32 (87.5%) of the comparison condition and 32 of 34 (94%) of the voucher condition provided data. At the end of the follow-up phase, the respective retention percentages were 81% and 91%. Of participants who dropped out of the intervention and follow-up phases, n = 1 was discharged from the methadone maintenance program, n = 4 dropped out due to group assignment or time commitment, n = 2 discontinued HAART medications, and n = 2 died.

**Data Analysis**
For the adherence measures collected weekly or more, the response analyzed was constructed by taking the mean of all assessments within each of the baseline, intervention, and follow-up phases. Measures assessed only monthly (i.e., SF-36, plasma HIV-1 RNA levels, drug screens) and CD4 counts were not averaged across assessment points, but instead individual data points were used. The main analysis was a mixed-effects ANOVA model estimated via maximum likelihood by Proc MIXED in SAS version 9.1.3 with treatment condition, assessment phase and the interaction of the two as effects in the model and Kenward-Roger's adjustment to the degrees of freedom (Kenward & Roger, 1997). The interaction term tested whether the change across phases differed between the conditions. The viral RNA level, which displayed both an abundance of values below the level of detection and skew in the detected levels, was tested using a two-part model (Tooze, Grunwald, & Jones, 2002) using all assessment points as an outcome and also using the two baseline phase assessments (weeks 0 and 4) as covariates. In the two-part model, one of the parts modeled the presence versus absence of detectable viral levels and the second part modeled the mean of the log of those levels above detection.

Results

A total of 66 study participants were randomized to the two treatment conditions; comparison (n = 32) and voucher (n = 34). Table 1 displays summary statistics of the participants at study intake. The majority were heterosexual men and women who were unemployed and had limited income, with an average age of 43 years and taking an average dose of 80mg of methadone when they entered the study. The mean BDI-II score at baseline was 19.7 (SD = 11.05), indicative of moderate depression, and 32 of 63 (51%) assessed participants met the criteria for lifetime major depressive episode. The most frequent antiretroviral medications prescribed to participants included nelfinavir, lopinavir, lamivudine and zidovudine combination, and nevirapine. Participants from the two clinical settings were compared, revealing no differences in
background characteristics; consequently the clinics were combined in outcome analyses.

Participants in the two clinics did not differ.

**Primary Outcomes**

Means of the primary outcomes by phase and treatment condition are presented in Table 2 and Figures 2-5. As participants were randomized to the intervention, comparisons at baseline were not tested (Senn, 1994).

*Medication Adherence.* Results indicated clear improvement in medication adherence in the voucher group from baseline (Phase 1) through the intervention (Phase 2). The mean percent of MEMS® adherence did not differ in the baseline period, averaging 51%. During the intervention period the voucher participants averaged 78% MEMS® adherence, while the comparison participants showed 56%, \( p < .0001 \). Significant intervention condition-by-assessment interaction effects were found for all four of the adherence measures; MEMS® adherence \( (F(2, 187) = 5.11, p = .0069) \), MEMS® longest duration of on-time openings \( (F(2, 179) = 9.34, p = .0001) \), pill count adherence \( (F(2, 190) = 4.06, p = .0187) \), and self-reported adherence \( (F(2, 192) = 3.43, p = .0345) \). As Figure 2 illustrates, adherence declined during the 4-week baseline. During the Intervention phase (Weeks 5-16), the voucher participants quickly exceeded the comparison condition in their on-time MEMS® cap openings, and they continued through the 12-week intervention. In the last 3 weeks of the intervention (14-16), there was a decrease in performance. This pattern is characteristic of the voucher reinforcement intervention, as participants realize that they do not have sufficient remaining time to build up to large rewards for conducting the desired behavior (Kenneth Silverman, personal communication). During the Follow-up phase, the voucher reinforcement was discontinued, and the groups converged again. During the follow-up period, the voucher participants averaged 66% on-time openings, the non-voucher participants 53%. \( (p = .07) \).
Health Measures. No significant effects for condition or change over time were seen in the three measures of health: HIV-1 RNA levels, CD4 lymphocyte count, SF-36 Physical Component summary scale, or for weight at the end of the study.

Drug Use. Similarly, no significant differences between groups were found in the results of the urine toxicology screens for opiate or cocaine use, with anywhere from 32% to 47% of participants testing positive for opiates and 47% to 63% testing positive for cocaine at any one of the six assessment points where urine samples were tested.

Secondary Analyses

No significant differences were observed for the summary side effects measure. On examination of the residuals from the statistical model, one participant had markedly greater residual values than the others. After confirming that the entered data matched the original instrument (consistently high side effects were reported at all assessments), we re-estimated the model for this variable without that one person. The p-value for the effect measuring change over time went from $p = .06$ to $p = .02$ indicating a significant decrease in reported side effects for both conditions. The most commonly reported side effects by participants were: fatigue/loss of energy (60%), pain, numbness, tingling (52%), muscle/joint aches (50%), fever, chills, sweat (49%), bloating/gas (48%), and loss of appetite (47%). The other two effects of treatment condition and the interaction in the model remained non-significant.

Viral load was significantly associated with the percentage of medication-cap openings at Week 4 ($r = -0.27$, $p = .03$), Week 8 ($r = -0.43$, $p = .0006$) and Week 20 ($r = -0.37$, $p = .005$). At Week 16 the correlation was negative ($r = -.26$) but not statistically significant ($p = .0518$). The negative sign indicates that the greater the level of MEMS® adherence, the lower the viral load. No statistically significant similar relationships were found with the CD4 count or the SF-36 Physical Health summary scale.
Voucher participants could have earned $1172.40 if they adhered perfectly to the medication regimen over 12 weeks. One participant achieved this perfect adherence, but the mean earning was $378.47 (31% of that possible), which was still significantly more than the comparison group would have earned if they had been receiving vouchers for their MEMS® cap openings ($154.36) ($t = 4.14, df = 64, p = 0.0001).

Discussion

This study assessed whether participation in voucher reinforcement was associated with improved HIV medication adherence in methadone maintenance patients. Relative to the comparison group, participants randomly assigned to receive voucher reinforcement showed better medication adherence, measured by MEMS®, pill count, and self-report. Differences faded after the voucher contingencies were removed. Relative improvement did not appear in biological and behavioral measures of health, although viral load was significantly and negatively associated with the percentage of on-time MEMS® openings.

The results provide preliminary support for the development of voucher reinforcement as a strategy to improve medication adherence among HIV-positive methadone maintenance patients. Voucher reinforcement was associated with a difference in opening of medication caps from 56% to 78%. Thus this study builds upon randomized trials of voucher reinforcement aimed at decreasing drug use (Jones et al., 2001; Silverman, Higgins, et al., 1996; Silverman, Wong, et al., 1996; Silverman et al., 2004) as well as the application of behavioral approaches to improve adherence to HIV medication regimens (Rigsby et al., 1999). Specifically, this study extends these findings, indicating that voucher reinforcement can be applied successfully to reinforcing adherence to medications in HIV-positive methadone maintenance patients.

In the present study the adherence differences faded after the voucher contingencies were removed. In short, the voucher intervention did not build long-lasting adherence habits that
endured without reinforcement, and the results may speak to the desirability of a longer intervention. Recently Silverman et al. (2004) demonstrated that reinforcing contingencies can retain their effectiveness over periods as long as a year if continuously applied. The contingencies used in the present study may have greater effectiveness in a longer trial and more opportunity to improve participants' health. Furthermore, this kind of intervention could be applied to address medication adherence issues among patients with diseases such as tuberculosis or hepatitis C, which involve time-limited medication regimens.

The improvements in medication adherence were not sufficient to produce changes in health. The lack of differences may reflect a limitation of the intervention, in that improved adherence was still not at the 95% level that may be necessary for the medications to suppress viral load. Also, the intervention phase lasted only 12 weeks, the sample size of the trial was relatively small, and a larger, multi-site trial might uncover significant differences in measures of health.

Urine drug screens to detect use of opiates or cocaine also indicated no differences between intervention conditions. This result is not surprising, since the voucher incentives reinforced medication cap openings rather than abstinence from illicit drugs. Future research could devise more complex reinforcement schedules to address both medication-taking and drug use.

Ability to generalize from this study is restricted by study limitations that may be addressed in future research. These included the use of rigorous exclusion criteria, in a process that started with 181 possible participants and ended with 66 in the clinical trial. We note that use of the MEMS® was necessary to reinforce medication cap opening but was awkward for many patients, who preferred use of "medisets" that put their medications in compartments to be taken at times indicated. A computerized mediset would be a useful addition to the adherence promotion armamentarium. Further, the study did not observe actual medication-taking, but rather measured the opening of medication bottle caps. Perhaps practitioners in clinical settings
could be more flexible in selecting participants, which could yield more robust results. In particular, 36 potential participants were screened out because they had not been on antiretroviral medications for a month before the trial began, and patients new to HIV medications may be ideal for mounting clinical adherence interventions. Additionally, the level of the reinforcement was guided by what had been accomplished in the work of studies that were reinforcing abstinence from substance use rather than medication adherence, and future study would benefit by testing reinforcement ratios and sizes that are designed specifically for medication adherence. We must also note that there are broader solutions to non-adherence, such as educating patients about treatment, working with patients to improve practical life supports, treating co-occurring psychiatric disorders that prevent optimal adherence to medications and simplifying medication regimens (see Gathe, 2003).

The longer-term outcomes and cost-outcomes of the intervention are unknown. We are gathering information on the cost of the interventions and the service utilization of participants, in order to address some of these issues in the future.

This study successfully applied the voucher reinforcement approach to adherence to medications for HIV/AIDS. Voucher participants improved their adherence relative to a medication-coaching comparison group. The intervention had limited efficacy in that it did not improve physical health of participants. Future studies may explore a longer-term intervention, higher cash values for vouchers, and larger sample sizes.
References


Table 1. Participant Characteristics by Group Assignment.

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<tr>
<td>Opiate (positive urine screen)</td>
<td>35</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Cocaine (positive urine screen)</td>
<td>53</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.0 (7.84)</td>
<td>42.6 (7.29)</td>
<td>43.3 (7.55)</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>21.6 (12.54)</td>
<td>17.8 (8.99)</td>
<td>19.7 (11.05)</td>
</tr>
<tr>
<td>ASI Medical Composite</td>
<td>0.6 (0.32)</td>
<td>0.6 (0.31)</td>
<td>0.6 (0.31)</td>
</tr>
<tr>
<td>ASI Drug Composite</td>
<td>0.2 (0.11)</td>
<td>0.2 (0.11)</td>
<td>0.2 (0.11)</td>
</tr>
<tr>
<td>ASI Psychiatric Composite</td>
<td>0.5 (0.29)</td>
<td>0.4 (0.27)</td>
<td>0.4 (0.28)</td>
</tr>
<tr>
<td>Variable</td>
<td>% Voucher (n = 34)</td>
<td>% Comparison (n = 32)</td>
<td>% Total Sample (N = 66)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Methadone dose (mg.)</td>
<td>85.4 (30.7)</td>
<td>73.3 (34.14)</td>
<td>79.8 (32.62)</td>
</tr>
<tr>
<td>SF-36 Physical Health Summary</td>
<td>24.6 (1.2)</td>
<td>24.3 (1.51)</td>
<td>24.5 (1.36)</td>
</tr>
<tr>
<td>SF-36 Mental Health Summary</td>
<td>22.1 (1.88)</td>
<td>23.0 (1.93)</td>
<td>22.5 (1.94)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (copies)</td>
<td>4209.4 (13416.21)</td>
<td>22324.9 (90107.45)</td>
<td>12984.1 (63569.24)</td>
</tr>
<tr>
<td>CD4+ (cells/UL)</td>
<td>301.71 (197.51)</td>
<td>298.8 (230.35)</td>
<td>300.3 (211.81)</td>
</tr>
</tbody>
</table>

*aMale-to-female

*bSelf-reported as homeless (8%) or living in room/hotel/motel (31%)
Table 2. Means (and Standard Deviations) of Primary Outcomes by Study Phase and Treatment Condition.

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Baseline Phase (Weeks 0-4)</th>
<th>Intervention Phase (Weeks 5-16)</th>
<th>Follow-up Phase (Weeks 17-20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Voucher</td>
<td>Comparison</td>
<td>Voucher</td>
</tr>
<tr>
<td>MEMS Cap On-time Openings (% adherence, SD)</td>
<td>50.1 (17.21)</td>
<td>51.9 (19.99)</td>
<td>77.6 (17.49)</td>
</tr>
<tr>
<td>Longest String of On-time Openings (M, SD)</td>
<td>3.6 (3.25)</td>
<td>4.4 (2.68)</td>
<td>21.1 (16.74)</td>
</tr>
<tr>
<td>Pill count (% adherence, SD)</td>
<td>70.5 (20.92)</td>
<td>79.1 (1879)</td>
<td>85.9 (11.42)</td>
</tr>
<tr>
<td>Self-Report (% adherence, SD)</td>
<td>75.0 (22.40)</td>
<td>75.9 (24.97)</td>
<td>87.3 (13.98)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (copies) (M, [Median])</td>
<td>8885.0 [57]</td>
<td>21063.3 [0]</td>
<td>6880.4 [0]</td>
</tr>
<tr>
<td>CD4+ (cells/UL) (M, SD)</td>
<td>301.7 (197.51)</td>
<td>298.8 (330.35)</td>
<td>302.4 (194.29)</td>
</tr>
<tr>
<td>SF-36 Physical Health (M, SD)</td>
<td>36.1 (9.46)</td>
<td>35.6 (11.02)</td>
<td>39.7 (8.69)</td>
</tr>
<tr>
<td>Opioid (% positive, SD)</td>
<td>47</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>Cocaine (% positive, SD)</td>
<td>50</td>
<td>63</td>
<td>55</td>
</tr>
</tbody>
</table>
Figure 1. Recruitment, Random Assignment, and Retention of Study Participants.

- **Completed screening** (n = 181)
  - Excluded (n = 78)
  - Dropped out (n = 17)

- **Enrolled in study**
  - 4-week Baseline (n = 86)
    - Adherence > 80% (n = 8), Illness (n = 1), Not interested (n = 7), Clinic discharge (n = 2), Another adherence study (n = 1), Physician recommendation (n = 1)

- **Randomized** (n = 66)
  - Comparison (n = 32)
  - Voucher Incentives (n = 34)
    - Completed 12-week control (n = 28)
    - Completed 12-week intervention (n = 32)
    - Completed 4-week follow-up (n = 26)
    - Completed 4-week follow-up (n = 31)
Figure 2. Medication Adherence: Weekly On-Time Medication-Cap Openings
Figure 3. Medication Adherence: Weekly Pill Count
Figure 4. Medication Adherence: Weekly Self-Report
Figure 5. Longest Duration of Medication Adherence: On-time Consecutive Medication-Cap Openings by Phase.