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Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: a randomized controlled trial*

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Abstract

Objective—To determine if directly observed antiretroviral therapy (DOT) is more efficacious than self-administered therapy for improving adherence and reducing HIV viral load (VL) among methadone-maintained opioid users.

Design—Two-group randomized trial.

Setting—Twelve methadone maintenance clinics with on-site HIV care in the Bronx, New York.

Participants—HIV-infected adults prescribed combination antiretroviral therapy.

Intervention—24 weeks of DOT.

Main outcomes measures—Between group differences at 4 assessment points from baseline to week 24 in: (1) antiretroviral adherence measured by pill count, (2) VL, and (3) proportion with undetectable VL (< 75 copies/ml).

Results—Between June 2004 and August 2007, we enrolled 77 participants. Adherence in the DOT group was higher than in the control group at all post-baseline assessment points; by week 24 mean DOT adherence was 86% compared to 56% in the control group ($p < 0.0001$). Group differences in mean adherence remained significant after stratifying by baseline VL (detectable versus undetectable). In addition, during the 24-week intervention, the proportion of DOT participants with undetectable VL increased from 51% to 71%.

Conclusions—Among HIV-infected opioid users, antiretroviral DOT administered in methadone clinics was efficacious for improving adherence and decreasing VL, and these improvements were maintained over a 24-week period. DOT should be more widely available to methadone patients.

Keywords

Directly observed therapy; HIV; medication adherence; methadone; randomized trial

* A set of tables corresponding to figures 2-5 provide detailed information on data presented (e.g., sample sizes, means, standard deviations, proportions), and can be found in the supplementary materials by accessing the online version of this paper at doi:xxx/j.drugalcdep.xxx . . .

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1. INTRODUCTION

Though deaths among persons with AIDS have decreased with combination antiretroviral therapy, death rates among drug users have decreased less markedly (Tang et al., 2008). Disproportionately worse HIV treatment outcomes among drug users compared to non-drug users have been attributed partly to poor medication adherence (Arnsten et al., 2002; Malta et al., 2008). Though many adherence-improving interventions exist, few have focused specifically on drug users.

Programs providing directly observed therapy (DOT) for tuberculosis have been shown to improve medication adherence and clinical outcomes, and to reduce the incidence of drug resistance (Chaulk and Kazandjian, 1998; Weis et al., 1994). Since these same goals apply to HIV treatment, it is reasonable to extend the DOT model to antiretroviral therapy for HIV, particularly among populations at risk for non-adherence (Lanzafame et al., 2000; Mitty et al., 2002; Ford et al., 2009). Antiretroviral DOT programs have been successfully implemented in community settings using outreach workers (Altice et al., 2004; Behforouz et al., 2004; Khanlou et al., 2003; Ma et al., 2008; Mitty et al., 2005; Wohl et al., 2006), and in settings with infrastructures allowing frequent contact, such as prisons (Babudieri et al., 2000; Kirkland et al., 2002), housing facilities (Tinoco et al., 2004), and methadone clinics (Clarke et al., 2002; Conway et al., 2004; Lucas et al., 2004). While these studies have demonstrated feasibility and acceptability, few have examined efficacy using randomized designs, and none has evaluated methadone clinic-based DOT in a randomized trial.

Methadone clinics provide a promising infrastructure for DOT because federal regulations mandate that patients receive their daily methadone dose at one clinic, and the majority of doses are directly observed by nurses. However, providing co-located substance abuse treatment and HIV medical care is challenging because addiction medicine and HIV care are usually provided by specialists who may not have expertise in both fields. Though co-located medical care and methadone treatment improves outcomes among patients with tuberculosis, HIV, and Hepatitis C (Batki et al., 2002; Gourevitch et al., 2007; Litwin et al., 2009; Mauss et al., 2004), current payment policies promote segregation of substance abuse treatment and HIV care.

Support for Treatment Adherence Research through Directly Observed Therapy (STAR*DOT) was a randomized controlled trial designed to test the efficacy of directly observed antiretroviral therapy (DOT) provided on-site in methadone clinics. Our objective was to determine if DOT is more efficacious than self-administered antiretroviral therapy for improving adherence and reducing HIV viral load (VL) among methadone-maintained drug users. We hypothesized that at the end of the 24-week intervention period, participants in the DOT intervention group would have higher adherence and lower VL than participants in the treatment as usual (TAU) control group.

2. METHODS

2.1 Design and setting

Patients were randomly assigned to one of two antiretroviral treatment groups: DOT or TAU. The trial was conducted in a network of twelve methadone clinics administered by the Division of Substance Abuse (DoSA) at the Albert Einstein College of Medicine and Montefiore Medical Center in the Bronx, New York. These affiliated clinics provide care for approximately 3,500 opioid-dependent patients, of whom 10-15% is HIV-infected. A detailed description of study procedures has been described previously (Berg et al., 2009).

2.2 Participants

Patients were eligible for inclusion if they: were HIV-infected and prescribed antiretroviral therapy; received HIV treatment at their methadone clinic or a closely affiliated site; attended the methadone clinic 5 or 6 days per week (hereafter, 5 or 6 day pick-up schedule); were on a stable dose of methadone for 2 weeks prior to baseline; and were genotypically sensitive to their prescribed antiretroviral regimen. Eligibility was not based on antiretroviral treatment experience, current drug use, or antiretroviral adherence. Participants were excluded if they were: (1) unable to provide informed consent; (2) monolingual Spanish speakers; (3) currently receiving antiretroviral DOT; or (4) if their primary HIV care provider did not agree to their trial participation.

2.3 Recruitment and randomization

Research staff recruited patients from clinic waiting areas using a brief survey that assessed HIV status and current antiretroviral therapy. If patients consented, blood was drawn for genotypic resistance testing and a baseline visit was scheduled. Prior to baseline, the study medical director (KMB) verified eligibility by reviewing medical records, conferring with the patient's HIV provider, and confirming genotypic sensitivity to prescribed medications.

Random-number tables were used to allocate subjects. Randomization was stratified by antiretroviral experience (versus naïve), and by once-daily (versus twice-daily) dosing. We randomized by blocks within each of these four strata.

2.4 DOT intervention

Participants randomized to the DOT intervention received one dose of their antiretroviral medications at the same time that they received their daily methadone. Antiretroviral medications were stored in weekly pill trays composed of seven removable single dose pillboxes. Clinic nurses dispensed and observed ingestion of both methadone and antiretroviral medications at the usual methadone dispensing locations. Non-observed antiretroviral doses included evening doses for participants on twice-daily regimens, Saturday doses for participants on 5-day pick-up schedules, and Sunday doses for all participants. In these instances, participants were given enough single-dose antiretroviral pillboxes or “take home doses” to last until their next methadone clinic visit. Participants were asked to return these pillboxes to the nurses at their next visit, whether or not they had taken the pills.

During the 24-week intervention, the study medical director phoned in prescriptions to a designated community pharmacy. HIV providers were asked to suspend writing prescriptions for DOT participants during the intervention period, and to contact the study medical director if a participant changed medications.

2.5 TAU control

Participants in the TAU group received antiretroviral prescriptions from their regular HIV provider, and self-administered their antiretroviral medications.

2.6 Resources available to both DOT and TAU participants

After completion of the baseline visit, all study participants were referred for adherence counseling, which was provided in each DoSA clinic by paraprofessional counselors (Cooperman et al., 2007). DOT and TAU participants attended a similar number of counseling visits (3.33 for DOT versus 4.92 visits for TAU; $p=0.11$).

2.7 Visit schedule and data collection

The visit schedule for all participants included a baseline visit followed by 8 weekly visits and 4 monthly visits (i.e., weeks 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24). Baseline survey data were collected using Audio Computer-Assisted Self-Interview (ACASI) technology. ACASI allows participants to read questions on a computer screen while simultaneously listening to the questions through headphones, and has been shown to improve reporting of stigmatized behaviors (DesJarlais et al., 1999; Macalino et al., 2002; Mizuno et al., 2007).

2.8 Main outcome measures

2.8.1 Adherence—For DOT participants, pills remaining in the pill trays were counted weekly. We assumed that unreturned take-home pillboxes contained pills that had not been ingested.

Pill counts for TAU participants occurred at all study visits. To increase the accuracy of pill counts, interviewers documented activities that would alter the pill count adherence rate, including: receipt of a prescription refill, ingestion of pills from another source, or loss of any pills (details available from authors).

For TAU participants, in addition to pill counts, we assessed adherence using the Medication Event Monitoring Systems (MEMS), in which a computerized cap is placed on a medication bottle and records each opening as a presumptive dose. We monitored either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor. Because pill counts were not performed on the monitored medication we calculated adherence rates in two ways: using pill counts alone, and combining data from both pill counts and MEMS.

2.8.2 HIV viral load—We collected blood for quantifying HIV viral load at baseline and weeks 8, 16, and 24. Plasma viral load was quantified using the VERSANT HIV-1 bDNA 3.0 assay (Bayer, Tarrytown, NY). Virologic outcomes were: (1) median VL ($\log_{10}$ copies/ml), and (2) proportion of participants with undetectable VL (<75 copies/ml). We also measured CD4+ T lymphocyte count using the BD FACSCount system (BD Biosciences, San Jose, CA).

2.9 Additional variables

2.9.1 Self-reported adherence—Baseline self-reported adherence with each antiretroviral medication was assessed using standard questions (Chesney et al., 2000). We calculated adherence as the pills taken divided by pills prescribed during the prior week, and dichotomized self-reported adherence at 100% (Simoni et al., 2006).

2.9.2 Drug and alcohol use—We used the Recent Drug Abuse Survey to assess drug and alcohol use during the 30 days prior to baseline (Arnsten et al., 2002; Berg et al., 2004). In addition, urine was collected at every research visit for toxicology testing using the EMIT procedure (Siemens Healthcare Diagnostics, Deerfield, IL).

2.10 Statistical analyses

2.10.1 Assessment periods—Using an intent-to-treat approach, we examined the effect of DOT on pill count adherence during four assessment periods: baseline to week 4 (“week 4”), weeks 5 to 8 (“week 8”), weeks 9 to 16 (“week 16”), and weeks 17 to 24 (“week 24”). To examine the effect of the intervention on VL, we compared the two study groups at baseline and at weeks 8, 16, and 24.

2.10.2 Pill counts—We modified pill count adherence rates that were <0% or >100% according to the following rules. Since pill count adherence rates could be negative if participants added pills to a bottle but did not remove any pills, we considered all negative pill count adherence rates to represent 0% adherence. Pill count adherence rates >100% might occur if participants mistakenly took extra pills. We decided this scenario was plausible, but should reasonably occur no more than twice weekly, and therefore considered all pill counts between 100% and 120% to represent 100% adherence. Finally, if pill count adherence rates were >120%, we imputed new values for those data points by averaging five randomly drawn imputed values based on the mean and standard deviation from the same participant. Four percent of pill count adherence rates were <0, 77% were between 0 and 100, 9% were between 100 and 120, and 10% were >120%. Missing pill count data were not included in analyses.

Final pill count adherence rates were derived by first computing the mean pill count adherence rate for all the antiretroviral medications in the participant's regimen. We then computed the mean pill count adherence rate for all time points in the assessment period (e.g., week 8 pill count adherence represents the mean of pill count adherence rates at weeks 5, 6, 7, and 8).

In addition, we created a composite adherence rate for each participant by calculating a weighted average accounting for the number of pills in the regimen that were counted during pill counts and the number that was monitored by MEMS. Using the composite adherence rate did not change the results, we therefore present pill count adherence only.

2.10.3 Baseline comparisons—To check randomization, we used Chi-square tests and Wilcoxon Rank Sum tests as appropriate.

2.10.4 Intervention effect—We fit the repeatedly measured outcomes of pill count adherence and VL using a mixed-effects linear model, which included an intervention effect (DOT vs. TAU), a time effect, and an intervention by time effect, all of which were considered fixed. Time was entered as a discrete variable and the covariance matrix of the error term was assumed to be unstructured to account for within-subject correlations. Subsequently, based on the mixed-effects model, contrasts representing the intervention effect across the time points were constructed and tested at a two-tailed significance level of 0.05. In addition, we calculated mixed effects logistic regression to determine the odds of achieving viral suppression for DOT participants compared to TAU participants. Analyses were conducted using SAS, version 9.1 (SAS Institute; Cary, NC).

3. RESULTS

3.1 Baseline characteristics

From June 2004 to August 2007, we screened 3,231 potential participants. Of these, 97 were eligible and 77 enrolled. The retention rate at 24 weeks was 84% (Figure 1).

The sample was 53% male, 45% Hispanic and 40% Black, with a mean age of 47. All participants were antiretroviral experienced, and 45% had undetectable baseline VL. The majority (70%) was prescribed twice-daily antiretroviral regimens. The median duration of methadone treatment was 10 years [interquartile range (IQR) 5-16] and the median methadone dose was 125 mg (IQR 90-180). At baseline, 55% had urine toxicology results consistent with cocaine use, and 31% with non-methadone opioid use. All measured characteristics, including self-reported antiretroviral adherence and VL, were similar between groups (Table 1).

3.2 Between group differences in adherence

Adherence over time is presented in Figure 2a. At all assessments, adherence in the DOT group was higher than in the TAU group. During the trial, adherence in the DOT group remained high while adherence in the TAU group fell to lower levels. The difference in adherence between DOT and TAU participants increased from 12% at week 4 to 30% at week 24.

When we examined adherence over time after stratifying by baseline VL, the DOT intervention remained efficacious for improving adherence among participants with both detectable and undetectable baseline VL (Figure 2b). Among those with detectable VL, the difference in adherence between DOT and TAU increased by 26% (from 8% at week 4 to 34% at week 24), while among those with undetectable VL, the adherence difference increased by 13% (from 15% at week 4 to 28% at week 24). Further, the three-way interaction among intervention, baseline VL, and time was not significant ($p=0.51$), suggesting that the significance of the DOT intervention effect among the entire sample was not driven by participants with detectable baseline VL. Finally, we examined the efficacy of the DOT intervention after stratifying by baseline CD4 count (≤ 350 vs. > 350 cells/mm³), and found that rates of achieving viral suppression in each study arm were independent of baseline CD4 count (data not shown).

3.3 Between group differences in viral load

Over the 24-week period, VL in the DOT group decreased 0.52 log₁₀ copies/ml (from 2.74 to 2.22 log₁₀ copies/ml), while VL in the TAU group remained relatively stable (Figure 3a).

When we examined VL over time after stratifying by baseline VL, the DOT intervention was efficacious for reducing VL only among participants with detectable baseline VL (Figure 3b). Among DOT participants with detectable baseline VL, the decrease in VL was 1.07 log₁₀ copies/ml, and 47% became undetectable by week 24.

A similar proportion of participants in both groups had undetectable VL at baseline (51% for DOT and 42% for TAU; $p=0.42$). After baseline, the proportion of participants with undetectable VL was significantly higher in the DOT group than the TAU group at all assessment points (Figure 4). At week 24, the odds of having undetectable VL were 3-fold greater for DOT than TAU participants [$OR_{\text{unadj}} = 3.1$ (95% confidence interval 1.1-5.4)]. Further, among TAU participants with undetectable baseline VL, the proportion that remained undetectable decreased to 92% at week 16 and 79% at week 24. Therefore, among TAU participants with undetectable baseline VL, 21% became detectable during the course of the 24-week trial.

4. DISCUSSION

Among antiretroviral-experienced adults taking methadone for opioid dependence, 24-weeks of DOT was more efficacious for improving adherence and lowering VL than self-administered antiretroviral medications. Using an intent-to-treat approach, adherence in the DOT group was significantly higher at all assessment points than adherence in the TAU group. During the 24-week trial, participants in the DOT group maintained high adherence, while adherence among participants in the TAU group dropped. Further, while there was no change in VL in the TAU group, VL decreased by 0.5 log₁₀ copies/ml in the entire DOT group, and by 1.07 log₁₀ copies/ml among DOT participants with detectable baseline VL. Despite similar proportions of participants in both groups with undetectable VL at baseline (51% DOT, 42% TAU), at week 24 this proportion increased to 71% in the DOT group and did not change in the TAU group. In fact, among TAU participants with undetectable baseline VL, 21% experienced viral rebound. While several DOT studies have reported

decreases in VL (Altice et al., 2007; Conway et al., 2004; Lucas et al., 2006; Macalino et al., 2007) and modest improvements in self-reported adherence (Altice et al., 2007; MA et al., 2008; Pearson et al., 2007), ours is one of the few DOT trials to report improvements in objectively measured adherence at multiple time points.

Unlike most DOT programs, we enrolled participants with both detectable and undetectable baseline VL (Goggin et al., 2007). To examine the effect of DOT among those with undetectable baseline VL, who are often not considered DOT candidates, we stratified analyses by baseline VL (detectable versus undetectable). We found that the DOT intervention significantly improved adherence even among participants with undetectable baseline VL.

The decrease of 0.52 log₁₀ copies/ml we found among the entire DOT group is less than that found in other DOT studies. In addition to our trial participants having a lower baseline log VL (2.81 copies/ml) than those in other DOT studies (Lucas et al., 2006; Macalino et al., 2007; Wohl et al., 2006), another explanation for this modest VL decrease is the inclusion of participants with undetectable baseline VL. While the proportion of DOT participants with viral suppression increased from 51% to 71% during the trial, almost half (47%) the DOT participants with detectable baseline VL achieved viral suppression. Our finding of a three-fold increase in the odds of viral suppression at trial end among DOT participants compared to TAU participants is consistent with the work of both Altice et al and Lucas et al, who reported similar results among samples of drug users (Altice et al., 2007; Lucas et al., 2004). Taken together, these data strongly suggest that DOT is an effective intervention for achieving viral suppression, the ultimate goal of HIV treatment, among drug using populations.

Enrolling patients with undetectable baseline VL into DOT trials is relatively uncommon, and our ability to examine the effect of the intervention in this group is unique. Though VL did not change significantly in the TAU group, 21% of TAU participants with undetectable baseline VL experienced viral rebound. The effect of DOT on viral suppression among participants with undetectable baseline VL has been examined by Altice et al who also found that among those with undetectable baseline VL, more DOT than standard care participants maintained viral suppression (Altice et al., 2007). These results suggest that DOT is efficacious in preventing virologic failure among participants who are already meeting clinical goals.

Though evidence in support of antiretroviral DOT programs is mounting, important questions still remain. In particular, the minimally efficacious dose of DOT is unclear. Because of differences in antiretroviral dosing and methadone pick-up schedules the proportion of observed antiretroviral doses in our trial varied from 86% among participants on once-daily regimens with a 6 day/week methadone pick-up schedule to 36% among participants on twice-daily regimens with a 5 day pick-up schedule. Among drug users in a community-based DOT program, Altice et al found that adherence was significantly higher with observed than unobserved medication doses, suggesting that a greater number of observed doses may improve outcomes (Altice et al., 2004). In contrast, Lucas et al found that in a methadone clinic based DOT program, the percent of observed doses was not associated with virologic failure, suggesting that even minimal participation in a DOT program may improve outcomes (Lucas et al., 2007). The effect of DOT programs on adherence with unobserved, or “take-home”, doses merits further research.

Despite ongoing research, little is known about the optimal target population for antiretroviral DOT programs, and this has important cost implications. Our intervention was efficacious among participants who had been HIV-infected for a median of 13 years and

were all antiretroviral experienced. Despite long-term opioid replacement therapy with high-doses of methadone, over half was using cocaine at baseline, and approximately one third was using non-methadone opioids. These findings support the recommendation that DOT should be offered to all methadone maintained patients, regardless of active drug use. To better understand the potential benefit of DOT to drug users, future research should examine the effect of DOT on active versus former drug users, and the efficacy of DOT for reducing substance use.

Our study has several important strengths. First, HIV providers made all clinical decisions and we did not restrict antiretroviral dosing regimens. Second, frequency and duration of research visits were the same in each group, minimizing the risk of attention bias. Lastly, the DOT intervention utilized existing methadone resources. The main difference between our trial and a program without additional funding was the specially prepared pill trays for observed and take-home antiretroviral doses. Ad hoc DOT occurs in our clinics for non-HIV medications (e.g., benzodiazepines), and in these cases nurses dispense daily doses directly from patients' medication bottles, which are stored in the clinic. Nonetheless, the cost effectiveness of DOT programs remains an open question (Goldie et al., 2003).

Limitations to generalizability should be noted. First, because our trial was conducted in a network of methadone clinics with fully integrated onsite HIV care, the feasibility and efficacy of DOT in methadone clinics with off-site medical care is unknown. In addition, we only enrolled patients who attended the methadone clinic at least 5 days per week limiting our ability to extend our results to patients who attend clinic less frequently.

These findings have important policy implications. HIV care and substance abuse treatment must be further integrated before DOT can be widely implemented in methadone clinics. Though this model would be most effective if methadone treatment programs had on-site HIV care, antiretroviral DOT could be achieved through close partnerships between HIV clinics and substance abuse treatment programs. For example, with coordination among off-site HIV specialists, community pharmacies, and methadone clinic staff, antiretroviral medications could be delivered directly to methadone clinics and then dispensed by methadone clinic nurses as observed doses. Lastly, to increase the feasibility of methadone based DOT programs, efforts to provide on-site HIV care in methadone clinics should be aggressively pursued. Allowing higher reimbursement rates for treatment of HIV is one step towards this goal, and could increase the number of existing methadone clinics capable of providing DOT.

In conclusion, this study adds to the literature on antiretroviral DOT programs by demonstrating efficacy of DOT in a randomized trial of antiretroviral experienced, methadone maintained patients, many with ongoing drug use. Future DOT trials should determine the optimal dose and duration of antiretroviral DOT for drug users. In addition, to inform allocation of resources, research efforts should focus on identifying the most appropriate target population from both a clinical and cost-effectiveness perspective. Our finding that DOT was efficacious in a sample that was heterogeneous regarding both baseline VL and drug use suggests that antiretroviral DOT programs have the potential to provide substantial clinical benefit to drug users on methadone for opioid dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
 Flow chart of study recruitment, enrollment, and completion.

Figure 2a.

Differences in mean pill count adherence rates by study arm at each assessment point during the 24-week intervention period. Precise estimates available in online supplementary materials.

DOT: directly observed therapy; TAU: treatment as usual

* $p < 0.01$, based on mixed effects model analysis.

Figure 2b.

Differences in mean pill count adherence rates by study arm at each assessment point during the 24-week intervention period, stratified by baseline viral load (≥ 75 copies/ml versus < 75 copies/ml). Precise estimates available in online supplementary materials.

DOT: directly observed therapy; TAU: treatment as usual; VL: viral load

* $p < 0.01$ for difference between DOT and TAU among participants with undetectable baseline VL.

† $p < 0.01$ for difference between DOT and TAU among participants with detectable baseline VL.

All p values based on mixed effects model analysis.

Figure 3a.

Differences in log₁₀ viral load by study arm at each assessment point during the 24-week intervention period. Precise estimates available in online supplementary materials.

DOT: directly observed therapy; TAU: treatment as usual; VL: viral load

*p < 0.01 based on mixed effects model analysis

Figure 3b.

Differences in $\log_{10}$ viral load by study arm at each assessment point during the 24-week intervention period, stratified by baseline viral load (≥ 75 copies/ml versus < 75 copies/ml). Precise estimates available in online supplementary materials.

DOT: directly observed therapy; TAU: treatment as usual; VL: viral load

* $p < 0.02$ for difference between DOT and TAU among participants with detectable baseline VL, based on mixed effects model analysis.

Figure 4.

Proportions of participants with undetectable viral load (<75 copies/ml) by study arm at each assessment point during the 24-week intervention period. Precise estimates available in online supplementary materials.

DOT: directly observed therapy; TAU: treatment as usual

Table 1

Baseline characteristics of the study sample

	Total (n=77)	Directly observed therapy (DOT) study arm (n=39)	Treatment as usual (TAU) study arm (n=38)	P value [*]
Sociodemographic characteristics				
Age, mean (sd)	47 (7)	45 (7)	49 (7)	0.05
Sex, n (%)				
Male	41 (53)	19 (49)	22 (58)	0.42
Race, n (%)				
White	10 (13)	5 (13)	5 (13)	0.70
Black	31 (40)	14 (36)	17 (45)	
Other	36 (47)	20 (51)	16 (42)	
Ethnicity, n (%)				
Hispanic	35 (45)	20 (51)	15 (39)	0.30
Non-Hispanic	42 (55)	19 (49)	23 (61)	
Education, n (%)				
Less than high school	38 (49)	19 (49)	19 (50)	0.89
High school (partial or completed)	20 (26)	11 (28)	9 (24)	
College (partial or completed)	19 (25)	9 (23)	10 (26)	0.74
Marital status, n (%)				
Married or living with partner	34 (44)	17 (44)	17 (45)	0.14
Widowed, separated or divorced	22 (29)	8 (20)	14 (37)	
Single	21 (27)	14 (36)	7 (18)	
Employment status, n (%)				
Employed	2 (3)	1 (3)	1 (3)	1.00
Unemployed or unable to work, n (%)	75 (97)	38 (97)	37 (97)	
Insurance, n (%) [†]				
Medicaid	69 (90)	33 (85)	36 (95)	0.26

	Total (n=77)	Directly observed therapy (DOT) study arm (n=39)	Treatment as usual (TAU) study arm (n=38)	P value [*]
Medicare	16 (21)	10 (26)	6 (16)	0.40
Private insurance	6 (8)	3 (8)	3 (8)	1.00
Antiretroviral regimen and HIV clinical characteristics				
Self-reported seven-day antiretroviral adherence [†]				
100%, n (%)	55 (72)	25 (66)	30 (79)	0.20
<100%, n (%)	21 (27)	13 (34)	8 (21)	
Median duration of HIV infection, years (IQR)	13 (9-17)	12 (8-15)	15 (10-18)	0.09
Duration of antiretroviral therapy, n (%) [§]				
<1 year	18 (24)	8 (21)	10 (28)	0.83
1 – 5 years	34 (44)	18 (49)	16 (44)	
>5 years	21 (27)	11 (30)	10 (28)	
Number of pills in antiretroviral regimen, n (%) [¶]				
One	8 (10)	4 (10)	4 (10)	0.12
Two	39 (51)	25 (64)	14 (37)	
Three	24 (31)	8 (21)	16 (42)	
Four	5 (7)	2 (5)	3 (8)	
Five	1 (1)	0	1 (3)	
Frequency of antiretroviral dosing, n (%)				
Once per day	21 (27)	9 (23)	12 (32)	0.40
Two or more times per day	56 (73)	30 (77)	26 (68)	
Viral load (copies/ml), n (%)				
<75	36 (47)	20 (51)	16 (42)	0.11
75 – 400	5 (6)	4 (10)	1 (3)	
401 – 10,000	21 (27)	8 (21)	13 (34)	

	Total (n=77)	Directly observed therapy (DOT) study arm (n=39)	Treatment as usual (TAU) study arm (n=38)	P value [*]
10,001 - 100,000	12 (16)	4 (10)	8 (21)	
> 100,000	3 (4)	3 (8)	0	
HIV viral load < 75 copies/ml, n (%)	41 (53)	19 (49)	22 (58)	0.42
Mean viral load, log ₁₀ copies/ml	2.81	2.74	2.89	0.43
Median CD4+ T cell count, cells/mm ³ , (IQR) (n=74)	345 (151-494)	367 (189 - 509)	277 (110 - 453)	0.34
CD4+ T cell count ≥ 350, n (%)	37 (50)	21 (55)	16 (44)	0.35
Substance use characteristics				
Median duration methadone maintenance, years (IQR) (n=48)	10 (5-16)	9 (4-15)	10 (6-16)	0.93
Median methadone dose, mg (IQR) (n=74)	125 (90-180)	135 (90-170)	120 (90-185)	0.85
Reported use of illicit drug in 30 days prior to baseline, n (%)				
Heroin	20 (26)	9 (24)	11 (29)	0.60
Cocaine	22 (29)	9 (24)	13 (34)	0.31
Crack	27 (35)	14 (37)	13 (34)	0.81
Marijuana	11 (14)	7 (19)	4 (11)	0.30
Amphetamine	3 (4)	1 (3)	2 (5)	1.00
Hazardous alcohol use (AUDIT ≥8)	15 (20)	6 (16)	9 (24)	0.36
Positive baseline urine toxicology report, n (%)				
Opioid (non-methadone)	24 (31)	11 (30)	13 (35)	0.62
Cocaine (including crack)	42 (55)	19 (51)	23 (62)	0.35
Benzodiazepine	7 (9)	3 (8)	4 (11)	0.71
Marijuana	13 (17)	6 (16)	7 (19)	0.72
Amphetamine	0 (0)	0	0	1.00

^{*} p value for difference between DOT and TAU groups

[†] Categories not mutually exclusive

⁷Data missing for 1 participant

⁸Data missing for 4 participants

⁹Participants reporting <3 pills were prescribed combination antiretroviral medications co-formulated in one pill