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Directly Observed Antiretroviral Therapy in Substance Abusers Receiving Methadone Maintenance Therapy Does Not Cause Increased Drug Resistance

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Abstract

Direct observation of antiretroviral therapy (DOT) can increase adherence rates in HIV-infected substance users, but whether this affects the development of antiretroviral drug resistance has not been fully explored. We conducted a 24-week randomized controlled trial of methadone clinic-based antiretroviral DOT compared with treatment as usual (TAU) among antiretroviral-experienced substance users. To examine the development of new resistance mutations, we identified all participants with an amplifiable resistance test at both baseline and either week 8 or week 24. We compared the development of new drug resistance mutations between participants in the two arms of the trial. Among the 77 participants enrolled in the parent trial, antiretroviral DOT was efficacious for improving adherence and decreasing HIV viral load. Twenty-one participants had a detectable HIV viral load at both baseline and a second time point. Of these, nine developed new drug resistance mutations not seen at baseline (three in the DOT arm and six in the TAU arm; $p = 0.27$). Overall, five subjects in the TAU arm developed major mutations correlating with their current antiretroviral regimen, while no subjects in the DOT arm developed such mutations. Direct observation of antiretroviral therapy was associated with improved adherence and viral suppression among methadone maintained HIV-infected substance users, but was not associated with an increase in the development of antiretroviral drug resistance. DOT should be considered for substance users attending methadone maintenance clinics who are at high risk of nonadherence.

Introduction

Since the discovery of combination antiretroviral therapy (ART), patients infected with HIV have seen remarkable improvements in morbidity and mortality.[1–3] These benefits, however, are dependent on medication adherence, as poor adherence can lead to virologic failure, immune compromise, and the development of opportunistic infections. Poor adherence also allows the proliferation of viral mutations and the development of antiretroviral resistance, resulting in the loss of one or more classes of medications. Early studies of nonboosted protease inhibitor-based regimens found a nearly linear relationship between rates of adherence and virologic failure, with adherence rates less than 95% significantly associated with lower rates of viral suppression.[4–6] Follow-up studies, however, have demonstrated that the relationship between adherence and subsequent resistance is far more complex, and depends on several factors, including specific medication classes.[7] Given the different pharmacokinetics and toxicity profiles of various antiretrovirals, resistance to each class tends to occur at a different level of adherence.[8] Therefore, the linear relationship between adherence and viral suppression may be too simplistic. More recent research suggests that for some antiretroviral medications, better adherence can paradoxically increase the risk of developing viral resistance.[9]

Practitioners are often reluctant to initiate ART in HIV-infected substance users, believing that such patients are more prone to medication nonadherence and may therefore develop antiretroviral resistance.[10] Because substance users may engage in high-risk sexual and drug use behaviors, which can spread HIV, the development of drug resistance may have negative consequences for both patients and their communities.[11] When adherent, however, active substance users have outcomes similar to nondrug users,[12] and studies in clinical

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settings where substance users are aggressively treated with ART have not found increased resistance rates.[13]

Because of the known difficulty in maintaining high levels of adherence with medication for chronic diseases,[14,15] many studies have evaluated adherence-improving interventions for patients at high risk for antiretroviral nonadherence, such as substance users. Although adherence interventions are generally efficacious in improving adherence,[16] few data have been published about the impact of adherence interventions on the development of drug resistance.[17]

Support for Treatment Adherence Research through Directly Observed Therapy (STAR*DOT) was a randomized controlled trial designed to determine if DOT, delivered on-site in methadone clinics, is more efficacious than self-administered ART for improving adherence and reducing HIV viral load among methadone-maintained substance users. We previously reported that antiretroviral DOT was efficacious for improving adherence and decreasing HIV viral load,[18] but how such an increase in adherence affects drug resistance is unknown. The objective of the current analysis was to explore the impact of DOT on the development of new antiretroviral resistance mutations in subjects enrolled in the STAR*DOT trial.

Materials and Methods

Design and setting

The STAR*DOT study design has been described in detail elsewhere.[19] Briefly, methadone-maintained patients were randomly assigned to one of two ART groups for 24 weeks: DOT intervention or treatment as usual (TAU) control. The trial was conducted on-site in a network of methadone clinics at the Albert Einstein College of Medicine and Montefiore Medical Center in the Bronx, New York.

Participants

Patients were eligible for inclusion if they (1) were HIV infected, (2) were prescribed ART, (3) received HIV medical care at their methadone clinic, (4) attended their methadone clinic 5 or 6 days per week to receive methadone, (5) were on a stable dose of methadone for 2 weeks prior to the baseline study visit, and (6) were genotypically sensitive to their prescribed antiretroviral regimen. Patients were excluded if they were unable or unwilling to provide informed consent, if they were already receiving antiretroviral DOT, or if their primary HIV care provider did not agree to their participation in the

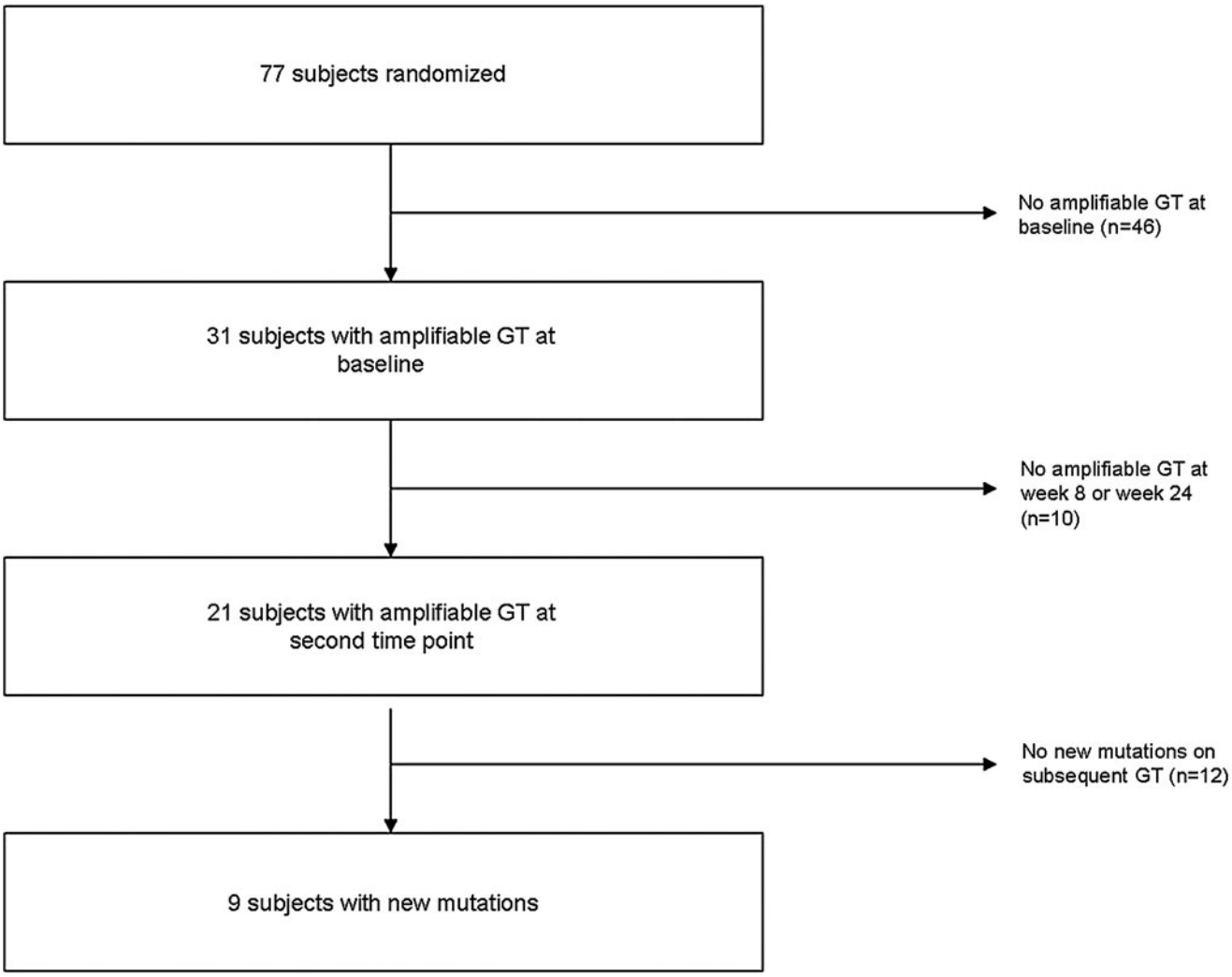

FIG. 1. Flowchart of subjects included in the study analysis. GT, genotypic resistance test.

study. For the current analysis, we included STAR*DOT participants with resistance testing at two time points (described below). Participants with an undetectable viral load at baseline were excluded because resistance testing was not possible in these participants; we would therefore be unable to determine if mutations detected at later time points were new or archived mutations.

Visit schedule

To determine eligibility for the STAR*DOT trial, all participants had a baseline visit at which blood was drawn for resistance testing. Subsequent study visits over the 24-week intervention occurred weekly for 8 weeks (weeks 1, 2, 3, 4, 5, 6, 7, and 8), and then monthly for 4 months (weeks, 12, 16, 20, and 24), for a total of 13 visits.

Viral load and resistance testing

HIV viral load testing was performed at baseline and weeks 8 and 24 using the VERSANT HIV-1 bDNA 3.0 assay (Bayer, Tarrytown, NY). Genotypic resistance testing was performed for those participants with a viral load >500 copies/ml. Resistance testing was performed using the TRUGENE HIV-1 Genotyping Kit (Siemens Healthcare Diagnostics, Deerfield, IL) by Bio-Reference Laboratories (Elmwood Park, NJ). We used the 2009 International AIDS Society–USA list of HIV drug resistance mutations[20] to define major and minor mutations. Resistance tests were not conducted in real time, but were batched and performed at study end.

Adherence

Adherence was measured in both study arms using pill counts. 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 the entire 24-week study period.

Analysis

To characterize baseline resistance, we included all subjects with a detectable viral load and an amplifiable resistance test at baseline, noting all major and minor resistance mutations.[20] To examine the development of new resistance mutations, we identified all participants with an amplifiable resistance test both at baseline and at a second time point (i.e., at either week 8 or week 24), and recorded major or minor resistance mutations that had not been detected at baseline. If a patient had an amplifiable resistance test at either week 8 or at week 24, all mutations not seen at baseline were classified as "new." To explore the impact of DOT on the development of resistance, we stratified participants by study arm (DOT vs. TAU), and compared acquisition of new mutations. We then compared subjects' resistance mutations with their current antiretroviral

Table 1. Baseline Characteristics ($n=77$)[a]

Characteristic	*Overall sample*	*DOT arm* (n = *39*)	*TAU arm* (n = *38*)	p *Value*
Age mean (SD)	47 (7)	45 (7)	49 (7)	0.051
Gender—male	41 (53%)	19 (49%)	22 (58%)	0.42
ART exposure				
<1 year	18 (24%)	8 (21%)	10 (26%)	0.83
1–5 years	34 (44%)	18 (46%)	16 (42%)	
>5 years	21 (27%)	11 (28%)	10 (26%)	
Baseline ART regimen				
PI based	54 (70%)	24 (62%)	30 (79%)	0.10
NNRTI based	13 (17%)	8 (21%)	5 (13%)	0.39
Triple nucleoside based	11 (14%)	7 (18%)	4 (11%)	0.35
HIV viral load				
<75	36 (47%)	20 (51%)	16 (42%)	0.42
≥75	41 (53%)	19 (49%)	22 (58%)	
CD4 ($n=74$, missing 3)				
≥350	37 (50%)	21 (55%)	16 (44%)	0.35
<350	37 (50%)	17 (45%)	20 (56%)	
Major and minor DRMs				
Amplifiable GT at baseline	31 (40%)	14 (36%)	17 (45%)	0.38
No DRMs	4 (13%)	1 (7%)	3 (18%)	0.13
1–2 DRMs	18 (58%)	11 (79%)	7 (41%)	
>2 DRMs	9 (29%)	2 (14%)	7 (41%)	
DRMs to 1 class	21 (78%)	10 (77%)	11 (79%)	1.0
DRMs to 2 classes	4 (15%)	2 (15%)	2 (14%)	
DRMs to 3 classes	2 (7%)	1 (8%)	1 (7%)	
Major IAS DRMs only				
No DRMs	23 (74%)	11 (79%)	12 (70%)	0.85
1–2 DRMs	4 (13%)	1 (7%)	3 (18%)	
>2 DRMs	4 (13%)	2 (14%)	2 (12%)	

[a]ART, antiretroviral therapy; DOT, directly observed therapy; TAU, treatment as usual; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; DRM, drug-resistant mutation; GT, genotypic resistance test; IAS, International AIDS Society–USA; IQR, interquartile range.

regimen to identify clinically relevant relationships. Finally, we compared median adherence rates between subjects who developed new mutations and subjects who did not develop new mutations, using the Wilcoxon rank-sum test.

The study was approved by the Institutional Review Board at Albert Einstein College of Medicine, and a Certificate of Confidentiality was issued by the National Institute on Drug Abuse.

Results

We enrolled 77 antiretroviral-experienced participants into the STAR*DOT trial (Fig. 1), of whom 39 were randomized to DOT and 38 to TAU. Baseline characteristics are shown in Table 1. At baseline, 31 participants had a viral load >500 copies/ml. The resistance profile of these 31 participants is shown in Table 2. There were no significant differences in pre-enrollment resistance between study arms. Sixty-five participants completed the 24-week intervention; our overall retention rate was 84%.

Of the 65 subjects who completed the 24-week intervention, 30 (46%) had an undetectable viral load at baseline, and were excluded from this analysis. Of the 35 subjects who had detectable HIV viral loads at baseline, 14 were undetectable at the end of the intervention, and were also excluded from the current analysis, leaving 21 participants with resistance testing performed at baseline and either week 8 or week 24. Among these, four participants had resistance testing at baseline and week 8, and 17 participants had resistance testing at baseline and week 24.

Table 2. Prevalence of Drug Resistance Mutations Among Subjects with Amplifiable Resistance Test at Baseline ($N = 31$)

	Study group	
Resistance mutation[a]	*DOT (number of mutations)*	*TAU (number of mutations)*
NRTI		
M41L	1	1
D67N	1	0
T69D	0	1
K70R	1	0
M184V	2	0
T215C/D/Y	1	2
K219Q	1	0
PI		
L10I/V	2	1
I13V	0	2
K20M/R	2	2
D30N	0	2
L33V/F	1	2
M36I/L	2	3
I47V	0	0
I54V	1	0
D60E	0	1
L63P	11	12
A71I/T/V	2	3
V77I	1	1
V82A/T	2	0
I84V	1	0
N88D	0	2
L90M	1	2
I93L	0	1
NNRTI		
A98G	1	0
K101E	0	1
K103N	1	1
Y181C	0	0
G190S	0	1

[a]Bold denotes major mutations.

Table 3 summarizes the prescribed ART regimen, HIV viral loads, and resistance mutations for each subject who acquired mutations during the 24-week intervention period. After 24 weeks, 9 of the 21 subjects showed new drug resistance mutations: six in the TAU arm and three in the DOT arm ($p = 0.27$). Two of the subjects with new mutations developed the M184V mutation for lamivudine (both in the TAU arm), and both had been receiving either lamivudine or emtricitabine (004 and 006 in Table 3). One subject in the TAU arm (005), who had been receiving both stavudine and nevirapine, developed mutations associated with each medication (D67N, K70R, K219E/Q, and G190A). Two subjects developed the K103N mutation for nonnucleoside reverse transcriptase inhibitors (NNRTIs; one subject each from DOT and TAU arms), and one of these subjects (009) also had a Y181C mutation associated with NNRTI use. Of note, neither subject with new K103N mutations was receiving NNRTI-based regimens during the intervention period. Two subjects (004 and 007) had major protease mutations but these did not confer resistance to the antiretrovirals in their current regimen. Several additional minor protease mutations were seen, but the majority of these represented results of only two subjects (data not shown).

No participant changed his or her antiretroviral regimen during the 24 week intervention. The median pill count adherence rate for the seven subjects who developed new mutations was 0.76 (IQR: 0.72–0.92), compared with 0.74 (IQR: 0.63–0.79) for the 14 subjects who did not develop new mutations ($p = 0.51$).

Of the 21 subjects with resistance test results at two time points (baseline and either week 8 or week 24), only seven appeared to have no drug resistance mutations at baseline. This could represent infection with wild-type virus, or the presence of undetected, archived mutations. Four of these seven subjects (three TAU and one DOT) developed new mutations during the study, although one of these mutations did not correlate with the participant's ART regimen.

Overall, of these 21 subjects, five in the TAU arm developed major mutations correlating with their current ART regimen, while no subjects in the DOT arm developed any such mutations.

Discussion

Direct observation of ART is a treatment strategy that has been proposed for HIV-infected populations at high risk for medication nonadherence, such as substance users. DOT has been shown, in our trial and others, to improve adherence rates and decrease HIV viral load compared with self-administration of ART in HIV-infected substance users.[17,18] One concern about DOT, however, is that improving rates of adherence to intermediate levels could inadvertently increase the risk of drug resistance as each antiretroviral class is thought to have a different threshold of adherence necessary

Table 3. Profile of Subjects Who Developed New Drug Resistance Mutations During the Intervention Period ($N = 9$)[a]

Subject ID	Study arm	ART regimen	HIV viral load (copies/ml)			Drug resistance mutations				Adherence
			Baseline	Week 8	Week 24	No. baseline	Major baseline	No. new	Major new	
001	DOT	ATV(r)/ddI/TDF	10,897	82,300	1,460	14	I84V M184V M41L T215Y V82A/T	1	—	0.93
002	DOT	ABC/3TC/ZDV	1,034	<75	1,576	0	—	1	K103N[b]	0.95
003	DOT	LPV(r)/FTC/TDF	27,983	9,194	18,540	2	K103N	2	—	0.79
004	TAU	LPV(r)/3TC/d4T	782	697	96	5	K103N D30N	2	M184V	0.92
005	TAU	NVP/d4T/TDF	1,105	NA	554	0	—	6	D67N K70R G190A K219E/Q	0.72
006	TAU	FPV/3TC/ZDV/TDF	4,243	2,399	5,650	0	—	6	M184V D67N	0.73
007	TAU	ABC/3TC/ZDV	1,730	8,114	16,247	7	D30N	1	A62V	NA
008	TAU	ATV(r)/FTC/TDF	3,793	94,039	2,927	0	—	2	M184V	0.36
009	TAU	LPV(r)/ABC/3TC	692	184	25,855	2	—	4	K103N[b] Y181C[b]	0.89

[a]ART, antiretroviral therapy; LPV(r), lopinavir/ritonavir; ATV(r), atazanavir/ritonavir; FPV, fosamprenavir (unboosted); NVP, nevirapine; ABC, abacavir; 3TC, lamivudine; d4T, stavudine; FTC, emtricitabine; TDF, tenofovir; ddI, didanosine; ZDV, zidovudine. NA, not available.
[b]Mutation does not correlate with patient's ART regimen.

to prevent resistance. The resistance mutations associated with individual drug classes (and specific medications within a class) compromise viral fitness to varying degrees and this has been shown to play a major role in the likelihood of resistance when adherence to that medication or class is imperfect.[21]

Analysis of antiretroviral drug resistance is complicated by methodological challenges. Different drug mutations have varying levels of clinical significance and cross-resistance, making absolute counts of mutations misleading.[17] In our treatment-experienced population, 87% of subjects with a detectable baseline viral load had at least one antiretroviral resistance mutation, although only 26% of subjects had major mutations. Among subjects with a detectable baseline viral load, very few in either arm developed new mutations at the end of the 24-week intervention period, and only seven developed major resistance mutations. For five of these seven subjects, the resistance mutations at week 24 were related to their prescribed ART regimen, but for two subjects (one from each study arm), new NNRTI mutations emerged even though the subjects had been prescribed a protease inhibitor-based regimen. We hypothesize that these NNRTI mutations were most likely present at baseline but were not detected because of testing artifact. Both subjects had relatively low baseline viral loads (1034 and 692 copies/ml, respectively), which has been shown to limit detection of archived viral subpopulations.[22] Alternatively, subjects could have been superinfected with a resistant strain during the intervention, or could have received antiretrovirals from another source, such as a separate physician, a leftover supply, or another person's medication.

Two other groups have examined rates of ART resistance in the context of DOT clinical trials.[17,23] Maru and colleagues, who also studied DOT among substance users,[17] found increased adherence among those receiving DOT, with no difference between study arms in the probability of developing new resistance mutations. Their trial compared 6 months of DOT to self-administered therapy, but targeted active substance users rather than methadone patients. Theoretically, this might have selected for a less adherent population than our study, but the proportion of subjects with detectable viral loads at baseline was similar to ours. In this trial, as in ours, randomization to the DOT arm was not associated with a greater number of drug resistance mutations. In another trial by Gross *et al.*,[23] DOT was evaluated in treatment-naive subjects receiving a lopinavir-based regimen. Prior or current substance abuse was not a prerequisite for study eligibility and was not reported. Of the 243 subjects enrolled in this study, 14 developed new NRTI mutations at the time of virologic failure, with no difference between treatment arms (DOT vs. self-administered).

Our analysis of drug resistance has limitations and results should be interpreted in this context. The trial was designed and powered to detect a difference in adherence between study arms, not drug resistance. Subjects were not treatment naive and were all receiving different ART regimens (with different levels of potency). Moreover, our analysis was limited to those who had amplifiable viral load at baseline. Several subjects who were undetectable at baseline experienced treatment failure with detectable drug resistance mutations at week 24, but without baseline resistance testing results; we are unable to say if these mutations were new or old. Lastly, we used conventional viral resistance testing, which is known to detect only major viral populations. Newer, ultradeep sequencing techniques may have provided more sensitive detection of archived mutations in smaller, viral

subpopulations.[24] Despite these limitations, and our small sample size, none of the subjects in the DOT arm developed any new major resistance mutations that were related to their antiretroviral regimen.

Two meta-analyses of trials examining directly observed ART have recently been published.[25,26] In their analysis of DOT randomized clinical trials, Ford *et al.* called into question the utility of DOT, finding no improvement in outcomes across broad U.S. and international study populations, except in certain high-risk populations.[25] In addition, Ford *et al.* included measures after DOT had ended, which may have diluted the impact of DOT. In contrast, Hart *et al.* included both randomized and nonrandomized studies in a second DOT meta-analysis, and found an immediate postintervention benefit to DOT.[26] We believe that the results of this trial lend further support to the provision of DOT to HIV-infected substance users enrolled in methadone maintenance programs.

Our results may also have implications for treatment programs in other countries, where HIV-infected substance users are often denied care and treatment. Our data support recent calls to integrate HIV and substance abuse therapy.[27] The increased medication adherence and decreased HIV viral load seen in this study were not accompanied by an increase in antiretroviral resistance mutations, and DOT may have protected against the development of resistance. Larger studies with greater power to detect differences in longitudinal acquisition of resistance will be needed to confirm our findings.

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Author Disclosure Statement

No competing financial interests exist.

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