

The Use of Community-Based Modified Directly Observed Therapy for the Treatment of HIV-Infected Persons

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Summary: Directly observed therapy, which has been successful in the treatment of tuberculosis, is being adapted for the treatment of HIV to decrease long-term morbidity and mortality. We describe the experiences of 69 HIV-infected individuals who were enrolled in a community-based modified directly observed therapy (MDOT) program. Participants were referred by their primary care physicians based on nonadherence to antiretroviral therapy, and/or active substance use. A near-peer outreach worker initially delivered medications to participants 5 to 7 days per week, with visits subsequently tapered to 1 to 3 days per week after 3 or more months. Questionnaires were completed and laboratory values were obtained at baseline, 1 month, and every 3 months after enrollment. At enrollment, 96% of participants had a history of substance use, 71% had a history of incarceration, and 93% were experienced with highly active antiretroviral therapy (HAART). At the time of their 6-month assessment visit, 31 of 69 participants were receiving observed therapy visits. The median baseline plasma viral load (PVL) was 4.8 log, and the median individual change in PVL from baseline to 6 months among participants receiving MDOT was a decrease of 2.7 log. Reasons why participants were not receiving visits included medication holidays, hospitalization or assisted living, incarceration, discontinuation of program involvement, and death. These results support that MDOT should be included in the spectrum of options available to enhance adherence to HAART among patients who are unsuccessful with self-administration of their medications.

Key Words: HIV, adherence, directly observed therapy, highly active antiretroviral therapy

(*J Acquir Immune Defic Syndr* 2005;39:545–550)

Received for publication August 31, 2004; accepted May 12, 2005.

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Supported by the National Institute of Drug Abuse (grants R01DA013767 and K23DA017622); Lifespan-Tufts-Brown Center for AIDS Research (National Institutes of Health [NIH] grant AI-42853); Tufts Nutrition Collaborative, a Center for Drug Abuse and AIDS Research (NIH grant DA-13868); National Institute of Allergy and Infectious Diseases (grants U01AI046381 and R01AI50505); Gilead Sciences; and Bristol-Myers Squibb.

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Many HIV-infected individuals have not realized the benefits of highly active antiretroviral therapy (HAART) because of difficulties in accessing care or an inability to adhere to medications; most of these individuals are active substance users, have mental health disorders, or deal with social instability such as homelessness.^{1–4} It is now recognized that innovative approaches are needed to increase access and adherence to HAART, especially among these hard-to-reach populations.^{5,6} Directly observed therapy (DOT), which has been so successful in the treatment of tuberculosis (TB), is currently being adapted for the treatment of HIV in multiple diverse settings in the United States, ranging from methadone clinics in urban cities to rural communities in the South.^{7–14} The goals of these interventions are to decrease the long-term morbidity and mortality from HIV/AIDS and to limit the development and transmission of resistant virus, particularly in high-risk communities. We present a description of the experience of 69 HIV-infected persons enrolled in a community-based modified directly observed therapy (MDOT) program in Providence, Rhode Island. In addition to describing the results of those who continue to receive the intervention, this report includes follow-up on a subset of individuals who were not receiving MDOT at assessment points, providing a comprehensive picture of participants' experiences.

METHODS

Primary care providers referred patients to the MDOT program if patients had persistent viremia despite multiple attempts at clinic-initiated adherence interventions, or if patients reported active substance use (including use of illicit drugs, misuse of prescription drugs, inpatient detoxification, and alcohol abuse) within the past 6 months. Participants were recruited from community- and hospital-based clinics in Rhode Island and southeastern Massachusetts. Appropriate informed consent was obtained from participants, and Lifespan guidelines for the protection of human subjects were followed in the conduct of this research.

On enrollment, participants were placed on antiretroviral regimens recommended by the study team and patients' primary care providers after considering toxicity profiles, genotype results, and prior HIV medications. Most patients were started on a once-daily regimen; however, if they were unable to tolerate it, they were switched to a twice-daily regimen, with

the evening dose unobserved. Participants filled their own prescriptions and gave medications to the study nurse. Medications were delivered by a “near-peer” outreach worker (ORW) who received training specific to HIV, substance abuse, medication-specific side effects, safety in the field, and mental health. All participants kept at least a 1-week supply of medications with them so that they could self-administer their medications if an outreach visit was missed. Initially, the ORWs met with participants 5 to 7 days per week, with visits taking place at the time and location of the participant’s choice. The duration of this intensive MDOT phase varied by participant, but lasted for at least 3 months; after this intensive stage, ORW visits were gradually tapered to 1 to 3 days per week for a total study involvement of up to 12 months. Criteria for tapering included virologic suppression, greater than 80% adherence with ORW and physician visits, and demonstrated self-efficacy in refilling prescriptions.

The data presented describe the first 6 months of the participants’ involvement in the program. Adherence to ORW visits and self-reported adherence to unobserved doses were logged by ORWs on a daily basis. In addition, participants completed interviewer-administered questionnaires at 1, 3, and 6 months after entry into the study. At these assessment points, information about substance use, adherence to medications, and satisfaction with the program was obtained. Laboratory testing was conducted through routine clinical care, and plasma viral load (PVL) and CD4 cell count data were collected through medical chart review.

A patient was determined to be receiving MDOT if he or she received at least 2 visits per week (as recorded on the ORW daily log) for 2 of the 3 weeks surrounding the 1-, 3-, and 6-month assessment points. Some participants wanted to continue their involvement in the program but did not want to receive MDOT as dictated by the protocol. Participants in this category received “program support,” such as telephone calls and pill packing (but not MDOT) from the program. “No contact” was defined as ORWs not having any interaction with participants during the period surrounding the assessment point. Some of these individuals, however, were still completing interviewer-administered assessments and remained connected to the study. For participants not receiving MDOT at assessment points, information regarding reasons for discontinuation of MDOT was obtained from participant study charts.

We describe the experience of the 69 patients who engaged in an MDOT program, including study disposition, substance use, patient satisfaction, and viral load and CD4 cell count changes at the 1-, 3-, and 6-month assessment points. The first 24 participants in our sample were no longer followed after their 3- or 6-month assessment if they were not receiving MDOT at that time point.

Our data collection methods with regard to participation in MDOT changed over time, however. The next 45 participants remained in the study regardless of whether or not they were receiving MDOT. Among this subset of 45 patients, we evaluated changes in PVL and CD4 cell count over time, independent of MDOT status. We specifically analyzed the percentage of participants who demonstrated decreases in PVL of greater than or equal to 1 log and increases in CD4 count of greater than 50 cells/mm³, accounting

for missing data by assuming failure. In addition, we analyzed the median individual change in PVL and CD4 cell count among the subgroups receiving and not receiving MDOT at assessment points. Median individual change was determined by calculating the increase or decrease in PVL and CD4 cell count from baseline to the 1-, 3-, and 6-month follow-up points for each individual.

RESULTS

Experience of 69 Patients Who Initiated the Modified Directly Observed Therapy Program

Since 2000, 69 patients have participated in our MDOT program (Table 1). The median age of the participants was 43 years, with 61% being male and 41% being white, 27% black, and 22% Latino. Ninety-six percent had a lifetime history of substance use, with 80% reporting active substance use within 3 months of enrollment. Seventy-one percent had a history of incarceration, and only 9% were employed at baseline. Ninety-three percent were HAART experienced. All but 2 participants were started on a once-daily regimen. Once-daily regimens used long-acting nucleoside reverse transcriptase inhibitors (NRTIs) such as enteric-coated didanosine (ddI)-EC, lamivudine (3TC), and tenofovir, in combination with efavirenz- or ritonavir-boosted protease inhibitors. Of the 67 participants who started on once-daily regimens, 5 switched to a twice-daily regimen during the study because of their inability to tolerate their initial course of therapy.

The disposition of the 69 patients at each assessment point is summarized in Table 2. At 1 month, 56 patients were receiving MDOT; at 3 months, 44 were receiving MDOT; and at 6 months, 31 were receiving MDOT. Reasons why participants were not receiving MDOT at assessment points were varied and included medication holiday (patient- or

TABLE 1. Baseline Characteristics of 69 MDOT Participants

Median age (mean age), y	43 (38)
Sex	
Male	42 (61%)
Female	27 (39%)
Race/ethnicity	
White	28 (41%)
Black	19 (27%)
Latino	15 (22%)
Other	7 (10%)
Substance use	
Lifetime history of substance use	66 (96%)
History of substance use in past 3 mo*	55 (80%)
History of substance use in past 6 mo*	56 (81%)
Incarceration	
History of incarceration	49 (71%)
Employment	
Current employment	6 (9%)
HAART experience	
Previous antiretroviral treatment	64 (93%)

*Includes use of illicit drugs, misuse of prescription drugs, inpatient detoxification, and alcohol abuse.

TABLE 2. Disposition of 69 MDOT Participants At 1-, 3-, and 6-Month Assessment Points

Category of Disposition	1 Month (N = 69) % (n)	3 Months (N = 69) % (n)	6 Months (N = 69) % (n)
Participant receiving MDOT*	81.16% (56)	63.77% (44)	44.93% (31)
Participant incarcerated	2.90% (2)	4.35% (3)	4.35% (3)
Participant receiving program support†	1.45% (1)	1.45% (1)	1.45% (1)
Participant medication holiday	1.45% (1)	10.14% (7)	13.04% (9)
Participant hospitalized or in more supportive living situation	4.35% (3)	2.90% (2)	7.25% (5)
Participant had no contact with ORW (refused, lost to follow-up, withdrew or discharged from program, moved)‡	8.70% (6)	17.39% (12)	23.19% (16)
Death	0% (0)	0% (0)	5.80% (4)

*Receiving MDOT, defined as MDOT visits at least 2 times per week for at least 2 weeks during the 3-week span.

†Program support is defined as patient continues contact with MDOT team but receives less intensive adherence support than ≥2 MDOT visits per week.

‡No contact means that participants were not receiving ORW visits during the period surrounding the assessment point; however, some of these individuals were still completing interviewer-administered assessments and remained connected to the study.

provider-initiated), hospitalization or movement to an assisted living situation, incarceration, discontinuation of involvement in the program, and death.

The median baseline value of log₁₀ PVL was 4.8 log₁₀ (data available for 68 of 69 participants). Among those individuals receiving MDOT visits at assessment points, the median individual decrease in log₁₀ PVL was 1.56 at 1 month (data available for 46 of 56 participants), 2.34 at 3 months (34 of 44 participants), and 2.7 at 6 months (27 of 31 participants). The median baseline CD4 cell count was 139 cells/mm³, with a median individual increase in CD4 cell counts of 42 cells/mm³ at 1 month, 57 cells/mm³ at 3 months, and 64 cells/mm³ at 6 months.

Because 80% of the 69 patients in our sample reported recent substance use at baseline, we examined available data on recent substance use, engagement in MDOT, and virologic suppression at follow-up points (Table 3). At the time of the 1-month assessment, 33% of participants reported substance use within the past 3 months. At the 3-month assessment, 26% reported substance use, and at 6 months, 36% reported substance use. Among participants reporting substance use at their 1-, 3-, or 6-month assessment, 83% were receiving MDOT visits at the time they reported active use. Available data show

TABLE 3. Available Data on Number of Participants Reporting Recent Substance Abuse, Their Engagement in MDOT, and Virologic Suppression

	Baseline (n = 69)	1 Month (n = 51)*	3 Months (n = 43)*	6 Months (n = 42)*
Recent substance use	46	17	11	15
Receiving MDOT	NA	16	9	11
PVL ≤500 copies/mL†	0	6	7	7
PVL ≤75 copies/mL†	0	2	4	5

*n represents the number of participants with substance use and PVL data available.

†Participants with a PVL ≤75 copies/mL are included among those with PVL ≤500 copies/mL.

NA indicates not applicable.

that 56% of participants who were receiving MDOT visits and reported substance use had a PVL ≤500 copies/mL.

Patient satisfaction questions were asked at 3- and 6-month assessment points. For patients who were receiving MDOT, these data were available from 38 (86%) of 44 participants at 3 months and from 31 (100%) of 31 participants at 6 months. At 3 and 6 months, 100% and 90%, respectively, of participants thought that the ORW helped them take their medications and most liked having ORW visits. Eighty-one percent of participants at 3 months and 94% at 6 months did not think that ORW visits were an invasion of privacy. At 3 months, only 58% thought that they were able to take medications on their own without the ORW; however, this increased to 81% at 6 months.

Subset Analysis of 45 Patients With Long-Term Follow-Up

After the first 24 patients were enrolled, we changed our follow-up methods and patients continued in the study regardless of their MDOT status. This allowed us to track participant involvement in the program over time. The MDOT status of individual participants (n = 45) at all assessment points is outlined in Table 4. Fifteen participants (33.3%) received MDOT at all their assessment points. Of the 30 participants who were not receiving MDOT at all assessment points, 11 were not receiving MDOT at 1 month, 22 at 3 months, and 26 at 6 months. Ten percent of participants who were not receiving visits at their 1- or 3-month assessment point re-engaged in the program and were receiving MDOT visits at a later assessment point. At each assessment point, the participants who had discontinued MDOT visits were not statistically different in terms of age, sex, race, and baseline CD4 cell count compared with those who were receiving MDOT visits at that point in time.

We conducted an analysis of changes in PVL and CD4 cell count from baseline among these 45 individuals independent of MDOT status, evaluating the number of patients with a ≥1-log drop in PVL and increase in CD4 cell count of

TABLE 4. MDOT Status of a Subset of 45 Individual Participants at All Assessment Points

Patient No.	1-Month Assessment	3-Month Assessment	6-Month Assessment
1–15	MDOT	MDOT	MDOT
16–17	MDOT	MDOT	No contact*
18	MDOT	MDOT	Incarcerated
19	MDOT	MDOT	Death
20	MDOT	MDOT	Hospitalization/assisted living
21	MDOT	Incarcerated	Incarcerated
22	MDOT	Medication holiday	No contact*
23	MDOT	No contact*	MDOT
24–26	MDOT	No contact*	No contact*
27	MDOT	No contact*	Hospitalization/assisted living
28	MDOT	No contact*	Medication holiday
29–33	MDOT	Medication holiday	Medication holiday
34	MDOT	Hospitalization/assisted living	Death
35	Hospitalization/assisted living	MDOT	MDOT
36	No contact*	MDOT	MDOT
37	Incarcerated	MDOT	MDOT
38	No contact*	Incarcerated	Program support
39	Medication holiday	Medication holiday	Medication holiday
40	Program support	Program support	Medication holiday
41	Hospitalization/assisted living	Hospitalization/assisted living	Death
42	Incarcerated	Incarcerated	Incarcerated
43–45	No contact*	No contact*	No contact*

*No contact includes participants who refused, were lost to follow-up, withdrew from program, and moved.

≥ 50 cells/mm³. Assuming that missing data represented failure to achieve these changes, 17 participants at 1 month, 21 participants at 3 months, and 15 participants at 6 months demonstrated a decrease in PVL of greater than or equal to 1 log. An increase in CD4 cell count of greater than 50 cells/mm³ was seen among 16 participants at 1 month, 18 participants at 3 months, and 17 participants at 6 months.

We then evaluated PVL and CD4 changes among these 45 participants based on treatment status (Fig. 1). We found that those who were receiving MDOT visits at the 3- and 6-month assessment points had a median individual decrease in PVL of ≥ 2 log as compared with little or no change demonstrated among those who were not receiving MDOT visits at these follow-up points. Available data show that at 3 months, 9 of 18 participants receiving MDOT had a PVL ≤ 500 copies/mL compared with 5 of 13 not receiving MDOT; at 6 months, 11 of 18 participants receiving MDOT had a PVL ≤ 500 copies/mL compared with 2 of 17 individuals not receiving MDOT.

DISCUSSION

The results of our study indicate that MDOT for HAART can be implemented among HIV-infected individuals who are unsuccessful with clinic-initiated adherence interventions. Participants who engaged in the intervention showed a decrease in log₁₀ PVL of ≥ 2 units by 6 months. Only a modest

increase in CD4 count was observed during the study; this may be attributable to the prior treatment experience of participants as well as to the small sample size and the short-term observation period. Nevertheless, these results are notable, because our population included a large percentage of patients with prior antiretroviral experience and active substance use at enrollment.

Most participants who completed assessments and continued to self-report misuse of illicit drugs, prescription drugs, and/or alcohol remained engaged in the MDOT intervention. Although information about substance use among those not completing assessments is not available, the data presented here do indicate that active substance abusers can successfully engage in an intensive adherence intervention. Furthermore, a significant proportion of these participants who were actively using drugs demonstrated a viral load less than 500 copies/mL at their 3- and 6-month assessments. These findings are particularly important given the fact that substance users in the "usual care" arm of other observed therapy trials have demonstrated dismal outcomes.¹⁵

Our ability to retain active substance users in a structured intervention may provide unique opportunities to integrate medication adherence with substance abuse treatment (eg, buprenorphine) as well as with secondary prevention of sexual and drug-using behaviors in this high-risk population. In addition, future studies should evaluate whether intensive community-based adherence interventions such as this can

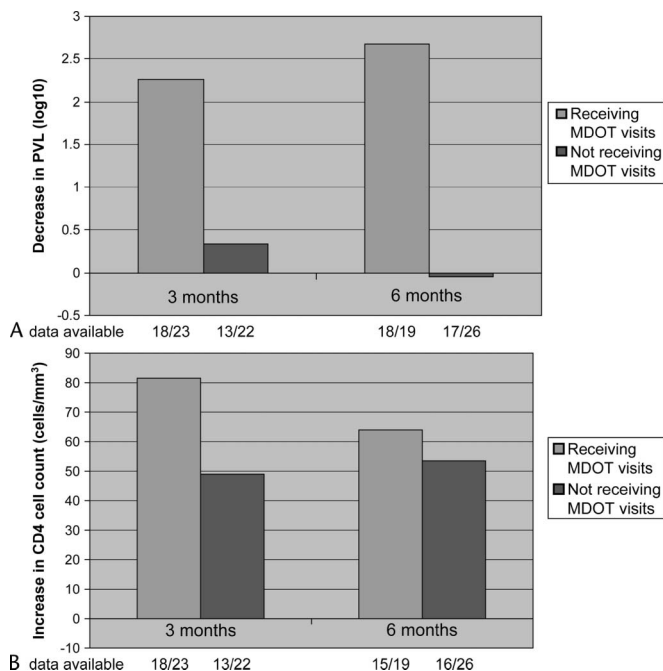


FIGURE 1. A, Median individual decrease in PVL (log₁₀) among 45 participants at 3 month and 6 month assessment points. B, Median individual change in CD4 among 45 participants at 3 month and 6 month assessment points.

influence access to antiretroviral medications in this population.

Although the results of our work are encouraging for participants who can engage in the MDOT intervention, the significant drop-out rate must be noted. Of the 69 patients who engaged in MDOT, only 31 remained in the program at the 6-month visit. We first realized that participant drop-out was an issue in our earlier work, when we found that the mean duration of participants' involvement in an MDOT project was 4 months¹⁶ rather than the intended 12 months. We thought that 12 months would be an appropriate duration for the intervention because it would allow time to engage participants and then transition them to self-administration. Patients received MDOT up to 7 of 7 days for up to 6 months. Unfortunately, this was not always compatible with chaotic living situations and the social instability of this population. Many patients worked sporadically and had varying family responsibilities. In addition, patients often rotated in and out of detoxification programs, assisted living facilities, and correctional facilities.

At the start of this study, we looked at ways to foster retention rather than decrease study duration. The intervention was modified so that it was increasingly tailored to the needs of individual participants. In the course of delivering the intervention, negotiation with participants occurred; there was agreement not to meet them on certain days, accommodation of work schedules, and an option of re-engagement in MDOT after a temporary discontinuation. Anecdotally, some participants did not want to be "observed" because they needed and/or wanted flexibility in the times they took their medications, and this required working with family and social net-

work members who usually live with the participant to have them complement the role of ORWs. In these situations, we chose to maintain program support so that patients could easily re-engage in MDOT should the need arise.

Even with modification of the program and increased flexibility, we still saw significant drop-out. Although a sizable percentage of the attrition continued to be attributable to structural changes, such as movement to a correctional facility, hospital, drug treatment facility, or assisted living facility, we also saw patients who went on medication holiday and who no longer wanted program support. Some of these individuals may not have been ready to take their medications no matter how individualized the program was, and MDOT may not have been the appropriate intervention for others.

To address this issue, screening tools that could evaluate readiness to take HAART as well as to participate in a program such as MDOT are needed. This would allow us to better define our efforts on those individuals who are most likely to benefit from this program. Given the ever-changing life situations, needs, and motivations of participants, we would also recommend that community-based MDOT interventions focus on relatively brief periods such as 3 months. Patients can be reassessed at that time; those who are engaged in the program would continue to receive visits, and those who no longer need or desire to be part of the program could be referred to more appropriate services.

By attempting to increase program retention, we can improve the cost-effectiveness of our intervention. Goldie et al¹⁷ presented a projected cost analysis showing that among patients with lower baseline levels of adherence or advanced disease, intensive adherence interventions are likely to be cost-effective. We are currently analyzing data from a randomized controlled trial of MDOT to answer these questions surrounding the cost-effectiveness and optimal duration of this intervention.

There are several limitations to this descriptive pilot study. Our determination of MDOT status was based on whether participants were receiving or not receiving MDOT at specific assessment points (ie, baseline, 1 month) as opposed to evaluating their participation continuously over time, thus limiting the ability to capture the full range of experiences for MDOT participants. In addition, the results presented here are only among patients who initiated MDOT, and there is not a control arm. The comparisons made in this analysis need to be interpreted with some caution because of the potential bias from unmeasured confounding; specifically, those who remain engaged in MDOT may also be taking other measures to improve their health and reduce the severity of their HIV disease.

Furthermore, the sample size is relatively small, particularly in the subset analysis, which is partially attributable to a change in methodology during the course of the study. There is a nontrivial proportion of missing data overall and substantially more missing data among those not receiving MDOT at the assessment points. The potential direction of the bias from missing data is not entirely clear, because some of the individuals not receiving MDOT may actually be doing better than those participating in the intervention, especially if they are in more supportive living situations or controlled

environments, such as residences for HIV-infected persons, where they are receiving medications. There are currently several randomized control trials under way that should be able to evaluate the effectiveness of DOT interventions over longer periods more completely.^{7,8,11}

The data presented here suggest that patients with active substance abuse disorders and those who were unsuccessful with self-administration of HAART and clinic-initiated adherence interventions had a considerable decrease in PVL when receiving MDOT. MDOT is not for everyone, however. The long duration of MDOT programs may be too intrusive for individuals who needed a “jump start,” and others simply may not be ready to take their medications no matter what the intervention may be.

Although the DOT model used in the treatment of TB has served as a foundation for the treatment of HIV, DOT for HAART must be modified. MDOT (also known as directly administered antiretroviral therapy [DAART]) may not be the only “solution” to managing nonadherence. Our results, however, support the finding that an observed therapy program that can accommodate ever-changing life situations should be included in the spectrum of options to enhance adherence to HAART.

ACKNOWLEDGMENTS

The authors thank the past and present staff of the MDOT program for their hard work. In addition, they thank the MDOT clients for their participation in the program.

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