Modified Directly Observed Therapy (MDOT) for Injection Drug Users with HIV Disease

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Injection drug use is an important factor in the spread of HIV infection, and strategies to enhance adherence to HIV therapeutics are critically important to controlling viral transmission and improving clinical outcomes. To this end, the authors sought (1) to enhance adherence to highly active antiretroviral therapy (HAART) among methadone-maintained injection drug users (IDUs) using modified directly observed therapy (MDOT), and (2) to define interactions between methadone and HAART and the potential contribution of drug interactions to adherence and HIV outcomes in this population. Adherence was explored here through a pilot, unblinded, 24-week study in a methadone maintenance program in which simplified HAART (efavirenz and didanosine [once daily] and a second nucleoside [twice daily]) was administered 6 days/week by clinic staff to HIV-infected IDUs ($n = 5$) with their methadone. Evening doses of riboflavin-tagged nucleoside and one full day of medication weekly were given as take home doses. As a result of HAART administration, four of five participants with mean viral load at baseline of $10^5$ copies/ml had undetectable viral load by 8 weeks of treatment ($p = .043$). Methadone area under the curve (AUC) decreased by 55% ($p = .007$) within 2 weeks of initiating this HAART regimen, and a mean methadone dose
The advent of highly active antiretroviral therapies (HAART) has produced a substantial reduction in morbidity and mortality from HIV. However, many medication regimens are complex, and a lack of rigorous adherence is the principal cause of treatment failure and the emergence of multi-drug resistant HIV. The chaotic lifestyles of some IDUs preclude adherence to complex HAART regimens. Methadone maintenance is a frequently utilized treatment for opiate-dependent IDUs with HIV disease. There have been several reports of drug interactions between methadone and antiretroviral agents that result in opiate withdrawal and could thus contribute to sporadic compliance or discontinuation of therapy.

Injection drug use remains a driving force in the spread of HIV infection. Strategies to enhance adherence, improve HIV outcomes, and decrease viral transmission are critically important. Directly observed therapy, in which health care personnel observe ingestion of medication, has been used successfully in the treatment of tuberculosis. This modality was extended successfully to the treatment of IDUs with tuberculosis in a methadone maintenance clinic setting. We report the results of a pilot study of modified directly observed therapy (MDOT), in which clinic nursing staff administered prescribed antiretroviral medications with methadone and gave participants unit doses of antiretroviral medicines that were to be self-administered outside of the clinic setting (hence use of the term “modified directly observed therapy,” because ingestion of every scheduled dose was not observed).

METHODS

Methadone-maintained IDUs with HIV who were deemed eligible by their HIV physicians for the study’s specific antiretroviral regimen (in accordance with treatment guidelines) were enrolled after providing informed consent. Study enrollment was based on referral by primary care physicians in the methadone maintenance program who had received information about the study from the investigators and a written description of the study. The physicians discussed the study with potential participants, and those interested were referred to the research staff to learn more about the study. Referring physicians continued to provide ongoing medical care to participants throughout the study. Baseline laboratory measures included HIV antibody (to verify infection), HIV viral load, CD4 count, complete blood count, liver function, amylase, lipase, hepatitis C antibody, and urine toxicology screen. Psychiatric diagnoses were obtained using the Mini-International Neuropsychiatric Interview (MINI). The Objective Opiate Withdrawal Scale was administered to determine the severity of opiate withdrawal symptoms (scores ≥ three indicate moderate withdrawal symptoms). After collection of timed plasma samples over 24 hours to determine baseline methadone pharmacokinetics, participants received...
efavirenz 600 mg, didanosine (600 mg of immediate release formulation or 400 mg of the enteric coated formulation [once available]) and a second nucleoside (lamivudine 150 mg [n = 3], stavudine 40 mg [n = 1], or abacavir 300 mg [n = 1]) at the time of methadone dosing six days per week. A second, riboflavin-tagged dose of nucleoside was given as a take-home dose six days per week. On Saturdays, an additional full day’s dose of the antiretroviral regimen was given as a take home dose for Sunday (clinics are closed on Sundays). Participants received calls to remind them to take their Sunday doses of medications. Research clinic visits occurred weekly, at which point adherence data were collected, urine analyzed for riboflavin-associated fluorescence, and toxicology, opiate withdrawal scales and adverse event data were obtained, and blood samples were collected for viral load, CD4 count, amylase, and lipase (every four weeks; to be described in the final study report). A second 24-hour study of methadone pharmacokinetics took place four weeks after HAART initiation (n = 1) or promptly upon onset of opiate withdrawal symptoms (n = 4) if they occurred sooner. When opiate withdrawal occurred, methadone dose was increased until the symptoms resolved. Participants were reimbursed for their time to participate in pharmacokinetic studies ($50 for 24 hours, including an overnight stay in the hospital) and research clinic visits that occurred once a week ($25 per visit). Research visits did not include administration of prescribed medications and took place at a site other than the participant’s usual methadone maintenance program.

The primary clinical outcome was change in viral load, and primary pharmacokinetic and pharmacodynamic outcomes were changes in methadone exposure and dose. Viral load change was analyzed using the Wilcoxon Signed Rank test, and analyses for pharmacokinetics parameters were completed using Student’s t-test for paired samples. Findings were considered statistically significant at $p \leq .05$ (2-tailed).

RESULTS

The study sample and treatment response is described in Table 1. Five methadone-maintained, HIV-infected IDUs (3 Hispanic men, 1 Hispanic woman, and 1 African-American woman) participated. Mean (SD) age was 36.6 (7.7) years. Years of opioid dependence were 15.6 (6.2), years since HIV diagnosis were 8.2 (5), and previous trials of antiretroviral therapy were 1.4 (0.9). Three met DSM-IV-TR criteria for current cocaine use disorders, two for alcohol abuse, and one for benzodiazepine abuse. Viral load range at baseline ranged from 6,722-658,030 copies/ml (Table 1), and methadone dose was 84 (29) mg daily (range 60-130 mg/d). The one patient with a viral load less than 10,000 at baseline was enrolled in the study despite his relatively low viral load because of having a history of precipitous decline in CD4 count, significant nonadherence, willingness to receive the DOT intervention, and the support of his physician for re-initiation of antiretroviral therapy.

Viral load decreased to less than 400 copies/ml within 8 weeks for 4 participants ($p = .043$). Missed doses of HAART were rare and ranged from 0-3 doses per participant (97-100% adherence) over the initial 8 weeks of treatment. Urine fluorescence was observed following initiation of HAART, with all samples collected at study visits that occurred on each of two days weekly and was variable for participants.

Four participants experienced opiate withdrawal symptoms within 2 weeks of initiation of HAART, as confirmed by decreased methadone AUC from 9504 (1961) to 4248 (901) ug-h/L ($p = .007$; see Figure 1). Mean peak and trough methadone concentration decreased from
### TABLE 1. Demographics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Substances Abused</th>
<th>Years of Opioid Dependence</th>
<th>Years of Methadone Maintenance</th>
<th>Years Since HIV Diagnosis</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>46</td>
<td>Male</td>
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<td>cocaine</td>
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<td>1</td>
<td>9</td>
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<tr>
<td>3</td>
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<td>African-American</td>
<td>cocaine, alcohol</td>
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<td>15</td>
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<tr>
<td>4</td>
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<td>opioids, benzodiazepines</td>
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<td>5</td>
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<tr>
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<td>31</td>
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<td>Hispanic</td>
<td>cocaine</td>
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<td>1</td>
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</tbody>
</table>

### MDOT Results for Study Participants

<table>
<thead>
<tr>
<th>Subject</th>
<th>Methadone Dose Baseline (mg/day)</th>
<th>Methadone Dose Post HAART (mg/day)</th>
<th>Viral Load at Baseline (copies/ml)</th>
<th>Viral Load at 8 Weeks (copies/ml)</th>
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</tr>
<tr>
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<tr>
<td>5</td>
<td>80</td>
<td>110</td>
<td>658,030</td>
<td>35,566</td>
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</tbody>
</table>
Methadone Plasma Concentrations Over a 24 Hour Dosing Interval: Pre and Post-HAART

![Graph showing methadone plasma concentrations over a 24-hour dosing interval pre- and post-HAART.]

FIGURE 1. Methadone plasma concentrations (ug/L) over a 24-hour dosing interval pre- and post-HAART.

547 (109) ug/L to 332 (23) ug/L ($p = .037$) and from 330 (78) ug/L to 130 (51) ug/L ($p = .002$), respectively. Increases in methadone dose in response to opiate withdrawal symptoms averaged 52% (from baseline 84 (29; range 60-130 mg/d) to 128 (15; range 110-150 mg/d) over an average restabilization period of 5 weeks (see Figure 2).

**COMMENT**

Physicians’ concerns regarding potential non-adherence and IDUs’ concerns that multiple medications may precipitate opiate withdrawal may lead to suboptimal antiretroviral care for this population. Strategies to optimize adherence with antiretroviral therapies are urgently needed. For drug users engaged in treatment, we report that MDOT with simplified HAART in a methadone treatment program is an effective intervention.

Several effective HIV medications that can be dosed once daily may produce opiate withdrawal in IDUs. The regimen used in this study was associated with opiate withdrawal and methadone dose increases in 4 of 5 participants, most likely resulting from efavirenz-induced metabolism of methadone, as has been previously reported. Lamivudine, didanosine, stavudine, and abacavir have previously been shown not to significantly affect methadone metabolism. The simplified regimen used in the current study for modified directly observed therapy requires close monitoring for opiate withdrawal symptoms and prompt methadone dose increase to reduce the risk of non-adherence and relapse to illicit drug use. It is notable that participants in this study were all abusing other drugs (cocaine or benzodiazepines) or alcohol. No studies have examined whether the abuse of illicit drugs or alcohol directly alters antiretroviral efficacy as a result of effects on hepatic cytochrome P450 metabolic enzymes. Alcohol has been reported to induce cytochrome P450 enzymes 2E1 and
3A4 in vitro and possibly in vivo. An elevation in the activity of these enzymes could increase antiretroviral drug metabolism and decrease therapeutic drug concentrations. However, in the present study, intermittent use of illicit drugs or alcohol did not impact antiretroviral efficacy, as demonstrated by the rapid and significant reductions in viral load in all participants.

An antiretroviral medication that has increased methadone metabolism, resulting in an increased daily methadone dose, presents a clinical challenge when the antiretroviral drug is discontinued (for example, because of the emergence of viral resistance or adverse effects). We have previously described a method for rapid diminution of methadone dose without opiate toxicity or substantial withdrawal. While this process can be clinically challenging, such procedures enhance treatment outcomes for this population. It is important to emphasize that clinicians providing methadone maintenance must be familiar with medical histories of those with HIV as well as concomitant medications, including potential interactions with methadone that can affect the clinical course both of substance abuse and HIV treatment. MDOT offers the advantage of frequent assessment by clinic staff that can optimize clinical outcomes by early identification of adverse events and rapid clinical intervention.

It cannot be assumed that medications known to induce cytochrome P450 enzymes important to opioid metabolism will uniformly result in opiate withdrawal. In the present study, four of five participants required methadone increases, but one subject, whose methadone AUC decreased, exhibited no withdrawal symptoms and...
underwent no methadone dose alteration. This finding underscores the need to monitor each patient clinically, basing specific methadone dose adjustments on individual presentation.

CONCLUSION

MDOT for the treatment of HIV in IDUs is a promising intervention that can be incorporated into methadone maintenance treatment. Daily administration of HAART for HIV with methadone provides an opportunity for the frequent medical contact and close supervision necessary to optimize both substance abuse treatment and HIV care. The duration of MDOT can be titrated based on clinical considerations. This study also demonstrates a significant interaction between methadone and the antiretroviral medication, efavirenz, in which efavirenz treatment substantially and significantly reduced methadone serum concentrations, often producing opiate withdrawal symptoms and necessitating increases in individual methadone doses. Limitations include the pilot nature of the study, and the fact that no control group was included in this initial study undertaken to examine feasibility and potential benefit of an MDOT intervention. It is also possible that some selection bias occurred with those referred into the study by their physicians in the methadone maintenance program. However, given that medical documentation showed at least one previous HAART discontinued as a result of non-adherence (no participant was being treated with antiretroviral medications at the time of study enrollment), it would seem any bias would have been in the direction of obscuring a positive effect of MDOT, since it could be argued that such individuals might be less likely to be adherent with HAART than others infected with HIV. Finally, while MDOT in the setting of methadone maintenance with on site primary medical care appears to be a promising intervention for this population, it could be more difficult to implement MDOT in methadone maintenance programs that do not provide on site medical care or in which coordination of medical services is limited. In summary, MDOT for antiretroviral therapy should be assessed in larger, controlled trials to determine if it is superior to self-administered antiretroviral therapy for HIV-infected IDUs.

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REFERENCES


