Directly Observed Therapy for the Treatment of People with Human Immunodeficiency Virus Infection: A Work in Progress

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The principle of directly observed therapy (DOT) has its roots in the treatment of tuberculosis (TB), for which DOT programs have improved cure rates in hard-to-reach populations. Human immunodeficiency virus (HIV) and TB affect similar populations, and there are concerns about both regarding the development of drug resistance associated with poor adherence to therapy. Accordingly, DOT may benefit certain HIV-infected people who have difficulty adhering to highly active antiretroviral therapy. However, important differences exist in the treatment of these diseases that raise questions about how DOT can be adapted to HIV therapy. DOT for management of HIV infection has been effective among prisoners and in pilot programs in Haiti, Rhode Island, and Florida. Although DOT can successfully treat HIV infection in marginalized populations in the short term, a multitude of questions remain. This review provides an account of the preliminary development of DOT programs for the treatment of HIV-infected individuals.

Through experience with antiretroviral therapy during the past 5 years, the need for optimal adherence has been recognized [1]. What has also been recognized is the need for innovative approaches to increase access and adherence to highly active antiretroviral therapy (HAART), especially among hard-to-reach populations, such as people with substance abuse or mental health disorders and those with social instability, such as the homeless population. Programs that use directly observed therapy (DOT) for administration of antiretroviral medications have been proposed [2–4] to provide a framework in which the use of antiretroviral therapy would be feasible for patients thought to be inappropriate for self-administering HAART as a result of a perceived high risk for poor adherence or a known history of nonadherence to treatment regimens.

WHY DOES DOT WORK FOR TUBERCULOSIS?

The principle of observed therapy has its roots in the treatment of tuberculosis (TB), for which DOT programs have dramatically improved cure rates among marginalized populations [5]. Rates of completion of anti-TB therapy increased significantly in New York City after the initiation of DOT [6]. DOT has proven to be one of the most valuable tools for the prevention and control of multidrug-resistant Mycobacterium tuberculosis, and it has become the standard of care for the treatment of active cases of TB [7, 8]. In many cities where DOT has been implemented, all individuals referred for anti-TB therapy receive DOT.

There are several reasons why DOT works for the management of TB. For one, TB treatment is conducive to observed therapy, because therapy is short term, ranging from 6–12 months in duration, and doses can be administered 2–3 times per week. Second, there is a public health imperative to treat TB, so DOT programs can be coercive: if a patient does not adhere to the treatment schedule, legal means can be used to quarantine that patient. Finally, an important key to the success of DOT may be that it relies on outreach to the patient and not on an individual’s readiness to change a behavior, such as
a tendency toward nonadherence [9]. In programs that use additional outreach techniques, such as assistance with transportation, incentives, and food vouchers, very high levels of adherence were achieved in populations facing the most difficult barriers, such as homelessness, severe mental illness, and active substance abuse [10].

**SHOULD DOT BE APPLIED TO HIV INFECTION?**

In the treatment of both HIV and TB infection, there is concern about the development of drug resistance resulting from poor adherence. In addition, both diseases affect a disproportionate number of the urban poor population, including many people who are substance abusers, mentally ill, or homeless. Given these similarities and the success of DOT for TB, it makes sense that observed therapy be considered for the treatment of HIV infection. Observed therapy programs for HIV infection could help individuals in many ways. The primary goal would be to increase adherence to HIV therapy. This would lead to a decrease in HIV RNA level and an increase in CD4 cell counts, resulting in a reduction in morbidity and mortality caused by AIDS and a decrease in the development of viral resistance to HAART.

However, many additional benefits to observed therapy programs exist. Outreach workers can provide participants with a closer link to medical care. This connection can help with the early identification and treatment of adverse drug reactions and can encourage improved attendance at primary care visits. The outreach staff can also enhance patients’ outlook and attitudes toward HIV treatment; improve their ability to self-administer medication; and improve referrals, access, and use of mental health and substance abuse treatment.

**CAN DOT BE ADAPTED TO HIV INFECTION?**

Although HIV and TB overlap in several areas, there are important differences in the treatment of these 2 diseases that raise the question regarding how DOT, so successful for TB, could be adapted to HIV infection. Unlike TB, the treatment for HIV infection is administered daily; treatment can also involve the administration of medications up to 3 times per day. In addition, the current treatment for HIV infection is lifelong, whereas the treatment of TB is limited in duration. Programs delivering observed therapy for HIV may want to help people develop the skills needed for independent medication administration. Traditional TB DOT programs do not promote the patient-level commitment needed to sustain adherence to therapy [9]. In addition, they often use financial incentives that may pose problems with the more prolonged therapy essential for the treatment of HIV infection.

Another difference between HIV and TB is the public health risk. Because *M. tuberculosis* is an airborne pathogen, there is a different public health priority to deliver DOT for TB [9]. HIV infection is not as easily spread as TB, and because the role of DOT in preventing HIV transmission has not been established, HIV-infected persons could not be forced to continue enrollment in observed therapy programs, as is the case with DOT for TB. This raises a question about the goals of DOT for HIV: is it to benefit the individual patient or public health? Ideally, patients receiving DOT would attain undetectable HIV RNA levels, which would benefit the individual. At the same time, one could also look at this success as a public health benefit, because lower HIV RNA levels are associated with decreased transmission [11]. This potential public health benefit, however, may be outweighed by concerns about potential consequences of a mandatory approach. If DOT for HIV becomes coercive, it may well drive HIV-infected persons “underground” to avoid contact with the medical system. This would ultimately defeat the purpose of this adherence interventions, which has the long-term goal of improving health and improving linkage to medical care.

Which populations of individuals with HIV infection will most likely benefit from DOT? There is currently no research to answer this question. Patients who are suspected of poor adherence to therapy would seem to be ideal candidates; however, doctors are poor predictors of adherence to therapy [12]. Given the experience with DOT for TB, individuals with substance abuse problems or mental illness may be the most likely to benefit. There may also be a role for DOT in less marginalized populations. DOT may be ideal for pregnant women, especially those with new diagnoses of HIV; observed therapy can be used for a defined period of time, with the goal of preventing neonatal transmission. Adolescents who confront many social and family pressures may also do well with the support of a consistent outreach worker. Finally, given the lifelong duration of HIV therapy, other individuals who have difficulties with long-term adherence may benefit from some modification of DOT.

When in the course of an individual’s treatment should DOT be started? Adherence interventions are often considered for individuals who have demonstrated poor adherence, but one could argue that DOT should be used for persons who are just starting therapy. Poor adherence with an individual’s first regimen may limit future treatment options [13]. Therefore, DOT may be most appropriate for individuals who are initiating therapy and who are at high risk of poor adherence [14].

Once a patient accepts DOT, how should it be implemented? Should DOT be administered through outreach visits to an individual’s home, or should DOT be administered at designated sites, such as medical clinics or methadone centers? Ideally, individuals should have the choice of where they want to receive their medications, with the option of changing the location as the individual’s needs change. In any case, DOT must
be structured so that it adequately maintains patient confidentiality and respects individual and cultural differences.

The next question that arises is, how many doses need to be administered, and how often? Should DOT be administered in regimens with once-daily dosing, or is a program of modified DOT, in which administration of only 1 dose is observed and the second dose is taken without supervision, adequate to maintain virus suppression? Although regimens with once-daily dosing may seem more appropriate for DOT, a regimen with twice-daily dosing that is well tolerated may be preferable to a new regimen with once-daily dosing. Furthermore, is DOT needed all 7 days per week, or can we do less? For persons with hectic family or work schedules, daily visits may not be possible. In addition, administration of 7 days of DOT per week may be more difficult for staff and, therefore, more difficult to implement. To maximize the benefit of DOT, it is important that these programs incorporate flexibility so that they are both practical and patient-centered.

In addition to administering medications, should DOT programs provide other social services? In a marginalized population, the social support provided by the consistent relationship with the DOT team may be a key to the program’s success. As such, there may be a role for combining DOT with case management to provide a more comprehensive care plan and increased social stability. This may ultimately affect long-term adherence.

Given the need for long-term therapy, can the frequency of visits be tapered? Once patients are successfully taking their medications, intensive DOT may no longer be necessary. What is not clear is how rapidly the frequency of visits should be tapered and how long some form of DOT should be maintained. The answer to this question depends on the answer to a bigger question: can a program of DOT provide individuals with the skills needed to maintain independent adherence to therapy? If DOT programs can lead to long-term adherence, we need to determine which components of the intervention provide participants with these skills.

Once initiated, what outcomes should be used for assessing the effectiveness of DOT for HIV infection? Suppression of HIV RNA level and increase in the CD4 cell count seem to be the obvious answer. For individuals with advanced AIDS and for those who are highly antiretroviral experienced, significant changes in these parameters may not be seen, and it is important to look at improvement in AIDS-related infections as well as quality-of-life measurements. DOT may also affect an individual’s contact with the health care system, and additional outcomes, such as follow-up with doctor’s appointments and substance abuse treatment, should be evaluated. Finally, the cost-effectiveness of these programs needs to be evaluated [14].

**USE OF THERAPY WITH ONCE-DAILY DOSING**

Although many question have been raised about the feasibility of DOT for HIV infection, the increased use of antiretroviral therapy with once-daily dosing may make observed therapy more amenable to the treatment of HIV infection. Currently, didanosine is licensed for administration in both once- or twice-daily dosing schedules [15–17]. Efavirenz, a nonnucleoside reverse-transcriptase inhibitor, is a potent antiretroviral agent developed and licensed for daily dosing [18, 19]. Tenofur, a nucleotide analogue that was approved fairly recently by the US Food and Drug Administration, is also dosed once per day [20]. In addition, several studies have been performed to evaluate the efficacy of once-daily HAART regimens in small groups of patients. These studies have involved regimens including didanosine, lamivudine (or emtricitabine) plus efavirenz or nevirapine; or regimens including the once-daily use of a protease inhibitor combination, such as ritonavir plus saquinavir, ritonavir plus indinavir, or ritonavir plus amprenavir [21–32]. In all of these studies, the regimens were well tolerated and resulted in sustained virus suppression in 47%–100% of participants. Other new drugs are under development, such as the protease inhibitor atazanavir, which will be dosed once per day, increasing the number of possible regimens in the future [33, 34].

Despite the potential benefits of once-daily therapy, there are concerns. Missed doses in regimens with once-daily dosing may lead to an increase in the number of 24-h periods without therapeutic coverage. This raises questions regarding the development of drug-resistant strains of virus that could occur in the setting of low levels of drug [35]. Alternatively, the potential improved adherence to once-daily dosing regimens may outweigh the risk. DOT would significantly decrease the risk of missing doses; however, there needs to be continued investigation on the use of regimens with once-daily dosing. There is currently a trial underway that plans to address some of these issues [36].

**OBSERVED THERAPY PROGRAMS**

Several programs that have been initiated involve some form of observed therapy for HIV infection. In a study by Fischl et al. [37] of treatment-naive AIDS Clinical Trials Group subjects, the outcomes for patients treated in the Miami AIDS Clinical Research Unit were compared with those for patients treated in the Department of Corrections. Participants in the prison received their medications by DOT, whereas those receiving care in the research unit did not. After 80 weeks of follow-up, 95% of the prisoners had HIV RNA levels of <400 copies/mL, compared with 75% of the participants in the self-administered therapy group. There have been several other reports discussing...
the use of observed therapy in the prison setting that have also noted successful results [38–40].

Observed therapy programs with HAART regimens have also been used in diverse community settings. One successful program was implemented in rural Haiti for individuals with HIV-associated morbidity [41]. In this community, observed therapy for TB has been highly successful. The DOT program for HIV infection is based on the TB program, in which a community health worker administers medications, observes ingestion of pills, responds to patient and family concerns, and offers moral support. CD4 cell counts and HIV RNA levels are not assessed during follow-up; however, the individuals receiving therapy through this program have experienced significant improvements in their health.

Although not all observed therapy programs have been highly successful [42], it is important to look at the existing programs and to evaluate their strengths and weakness, so that DOT for HIV infection can be appropriately modified to meet the needs of HIV-infected individuals. In this review, we will discuss, in detail, 2 clinic-based programs that have been developed, one in Providence, Rhode Island, and the other in Jacksonville, Florida.

The Rhode Island experience. A program of modified DOT (MDOT) was begun in 1998 at the Miriam Hospital in Providence for nonadherent patients being treated with a regimen with twice-daily dosing [43, 44]. A peer outreach worker delivered the morning dose of medication, observed the patient taking it, and left the evening dose for patients to take on their own. The outreach worker recorded self-reported adherence to the prior evening’s dose. Each participant was given an emergency pill pack with a week’s worth of drugs in case they were unable to meet the outreach worker.

Thirty-seven patients with a history of poor adherence to therapy were enrolled and observed for a mean duration of 10 months. The mean age of the patients was 38 years; 65% of the patients were women. Eighty-four percent were HAART patients who were enrolled and observed for a mean duration of 10 months. The mean age of the patients was 38 years; 65% of the patients were women; 63% of the participants, respectively, had a PVL of 50 copies/mL. The mean PVL decreased from 4.6 log_{10} copies/mL at baseline, at 3 months, and at 6 months of participation. The proportion of patients who felt comfortable with their knowledge about medications for HIV infection increased from 53% at baseline to 93% after 3 months. All participants believed that the outreach worker had helped them to adhere to therapy and learn more about their therapy. Given the success of the MDOT program, a pilot program of DOT that used a regimen with once-daily dosing was implemented for individuals who were active substance abusers and who had a history of nonadherence to prior antiretroviral therapy [45]. Participants began a regimen that was dosed once-daily and that included a “backbone” of didanosine (300–400 mg) and lamivudine (300 mg), which was combined with efavirenz (600 mg), nevirapine (400 mg), or ritonavir-saquinavir (100 mg/1600 mg). Medications were handled in the same manner as they were in MDOT, but, in this program, the outreach worker met with participants all 7 days per week to watch the participants take their medications. PVLs were recorded and project evaluations were made at baseline, at 3 months, and at 6 months.

From December 1999 through January 2001, 25 HIV-positive participants were enrolled. Twelve participants were women and 13 were men; 8 were African American, 7 were Latino, and 10 were white. The mean patient age was 41 years. A total of 21 (80%) of 25 participants continued participation in the program for 3 months, and 13 (52%) continued for 6 months. Two individuals withdrew from the program because they felt able to take their medications on their own, and 4 discontinued involvement because they moved to a facility that would provide delivery of medications. Of the remaining 6 individuals, 4 withdrew from the program because they missed or disliked the visits, 1 stopped taking HAART, and 1 died of AIDS-related complications.

All participants who stayed in the program for 3 and 6 months felt that the outreach worker had helped them adhere to their HIV therapy, and only 1 person felt that the visits were an invasion of privacy. Data regarding HIV RNA level for the 13 individuals who continued participation in the program for 6 months show that, at months 3 and 6 of participation, 50% and 63% of the participants, respectively, had a PVL of <50 copies/mL. The mean PVL decreased from 4.6 log_{10} copies/mL at baseline to 2.6 log_{10} copies/mL at 3 and 6 months of participation.

The Florida experience. A pilot DOT program was initiated at the adult HIV care clinic of the Duval County Health Department and the University of Florida, Jacksonville. The clinic currently serves >1400 patients (85% of whom are living below the poverty level), which represents ~70% of the identified HIV-infected patients in the county. There was a subset of patients
who, although willing, were unable to successfully self-administer medication through a clinic-based adherence program. A DOT program for HIV-infected patients was designed.

Entry into the DOT program was done either by clinic physician referral (80% of the patients), through the medication adherence program (15%), or by patient self-referral (5%). DOT was administered to patients whose illness failed to respond to the antiretroviral regimen. Salvage regimens were designed to be administered once or twice per day, according to the findings of genotyping. Most patients received a regimen with twice-daily dosing, so the DOT was modified so that the morning dosing was observed and the evening dosing was packaged for the patient to self-administer. DOT was performed 5 days per week; weekend doses were loaded into pillboxes and self-administered. Pill counts were performed on Mondays, and educational services were provided if the patient missed any doses. Medication stocks were maintained and distributed by the DOT worker for ~80% of the patients and at the patient’s home for the remainder. The worker maintained medications for patients with concurrent mental health diseases; patients who had difficulties with losing, misplacing, or storing medication; and patients who had, in the past, inappropriately taken a full day’s or week’s supply of medication in 1 large dose, despite good intentions.

To date, 44 patients have been enrolled in the DOT program. The patients receiving DOT had a mean age of 41 years, and, compared with the general clinic population, they were more antiretroviral experienced, had lower mean CD4 counts, and were more likely to be African American heterosexual women or to have a had a history of injection drug use. Table 1 lists the 12–16 week virologic data for 23 of the original 44 patients, 19 (83%) of whom achieved a PVL of <1000 copies/mL. Of the remaining 21 patients, 8 were noncompliant with the program and were dropped from the study, 2 died of causes unrelated to HIV, and the remaining 11 began the program too recently to have 12–16-week data.

### Table 1. Virologic outcomes for 23 of 44 HIV-infected patients enrolled in a directly observed therapy program at the University of Florida, Jacksonville.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>HIV RNA level, mean copies/mL</td>
<td></td>
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<tr>
<td>At baseline</td>
<td>194,760</td>
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<tr>
<td>At 12–16 weeks of follow-up</td>
<td>2278</td>
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<tr>
<td>HIV RNA level at 12–16 weeks of follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>&lt;1000 copies/mL</td>
<td>19</td>
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<tr>
<td>401–1000 copies/mL</td>
<td>3</td>
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<tr>
<td>50–400 copies/mL</td>
<td>10</td>
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<tr>
<td>&lt;50 copies/mL</td>
<td>6</td>
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<sup>a</sup> Twenty-three patients completed 12–16 weeks of follow-up.

### SUMMARY

The results of the pilot programs described above indicate that observed therapy is successful for improving treatment of HIV and AIDS. These programs were acceptable to many participants, and individuals receiving DOT had a mean reduction in PVL. In addition, participants gained a better understanding of their HIV medications. The data also show that DOT may be feasible if 5 or 7 days per week of observed therapy with daily or twice-daily dosing schedules are used. These programs were patient centered and incorporated a significant degree of flexibility regarding the number of visits, the location of visits, and the location of medication storage. It is this flexibility of DOT for HIV that may be the key to success and may attract the patients who most need it.

Because these are pilot programs, however, there are limitations, especially in interpreting the HIV RNA level data. From these data, we are unable to assess the role of other factors that may have contributed to the HIV RNA level response, such as changes in an individual’s medication regimen or the effects of reinitiation of therapy after an individual has not received medication for some time. It will only be through randomized trials that these issues can be addressed.

Further research is also needed to clarify the best candidates for observed therapy because DOT may not be helpful for everyone. Some individuals may find DOT too intrusive, while others may prove to be too difficult for an outreach worker to reliably find to deliver medication. However, many patients may not benefit from existing adherence interventions, such as use of beepers or educational modules [46], but may benefit from DOT. This could allow clinicians to consider prescribing HAART to individuals who may otherwise be considered untreatable.

Although these programs can be successful for some individuals, we do not know whether they are cost-effective, and this needs to be rigorously assessed. We can infer from our experience that these programs may be cost-effective. For example, if an outreach worker, at a cost of approximately $25,000 per year, can support 10 participants, the average cost is $2500 per patient per year. Assuming the cost of antiretroviral therapy is $10,000 per year per patient, this is only one-quarter of the cost of medications for a program that has the potential to dramatically increase the efficacy of these medications.

There are still many questions that need to be answered about how to use observed therapy for the management of HIV infection. Because DOT for HIV infection cannot be the same as DOT for TB, creativity is needed in the approach to observed therapy. New medication regimens need to be used and protocols modified as they are applied to diverse populations, such
as pregnant women, adolescents, individuals leaving prison, and patients from different cultures. The pilot programs that have been performed thus far support the need to further develop and assess this intervention. Maybe, in the future, the term “directly observed therapy” should be abandoned and replaced with a more general term, such as “HIV observed therapy,” to indicate how the approach to observed therapy adherence interventions for HIV infection differ from those for tuberculosis.

The research in this study was performed in accordance with the ethical standards of the Institutional Review Board and with the Helsinki Declaration of 1975, as revised in 1983.

References