Directly Observed Therapy (DOT) for Nonadherent HIV-Infected Youth: Lessons Learned, Challenges Ahead

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Abstract

Adherence to medications is critical to optimizing HIV care and is a major challenge in youth. The utility of directly observed therapy (DOT) to improve adherence in youth with HIV remains undefined and prompted this pilot study. Four U.S. sites were selected for this 24-week cooperative group study to assess feasibility and to identify the logistics of providing DOT to HIV-infected youth with demonstrated adherence problems. Once-a-day DOT was provided by DOT facilitators at the participant's choice of a community-based location and DOT tapered over 12 weeks to self-administered therapy based on ongoing adherence assessments. Twenty participants, median age 21 years and median CD4 227 cells/ μ l, were enrolled. Participants chose their homes for 82% of DOT visits. Compliance with recommended DOT visits was (median) 91%, 91%, and 83% at weeks 4, 8, and 12, respectively. Six participants completed >90% of the study-specified DOT visits and successfully progressed to self-administered therapy (DOT success); only half sustained >90% medication adherence 12 weeks after discontinuing DOT. Participants considered DOT successes were more likely to have higher baseline depression scores ($p = 0.046$). Via exit surveys participants reported that meeting with the facilitator was easy, DOT increased their motivation to take medications, they felt sad when DOT ended, and 100% would recommend DOT to a friend. In conclusion, this study shows that while community-based DOT is safe, feasible, and as per participant feedback, acceptable to youth, DOT is not for all and the benefits appear short-lived. Depressed youth appear to be one subgroup that would benefit from this intervention. Study findings should help inform the design of larger community-based DOT intervention studies in youth.

Introduction

Poor adherence to highly active antiretroviral therapy (HAART) has been associated with increased mortality¹ and remains one of the greatest challenges in the management of HIV-infected youth.^{2,3} Multiple barriers to adherence exist for this patient population^{4,5} and a number of interventions have been proposed.⁶ Building on the success of directly observed therapy (DOT) for the treatment of tuberculosis, DOT for adult HIV-infected patients has been tried in prisons,⁷ methadone clinics,⁸ and other community-based settings.^{9–11} Outcomes of DOT in adults with HIV have been mixed with at least some of the differences related to whether the intervention was tried in treatment-naïve¹² or

treatment-experienced and known or at-risk, nonadherent patients.^{9,10} Although the impact of DOT on HAART efficacy was no different than the standard of care in patients with limited prior HAART experience and adherence barriers,¹² DOT was clearly superior in HAART-experienced substance users.^{9,10} Published DOT experience in youth is limited but promising and is primarily from inpatient and clinic-based settings.^{13–15} DOT is resource intensive and before designing large-scale studies to assess DOT efficacy and associated behavior change among nonadherent youth, the feasibility and acceptability of this potentially intrusive intervention were assessed. Here, we describe the results of a pilot study to examine DOT feasibility in nonadherent youth with HIV.

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Materials and Methods

Study design and objectives

This 24-week pilot study [Pediatric AIDS Clinical Trials Group (PACTG) 1036B] incorporated information previously obtained from youth focus groups,¹⁶ and was based on combined theoretical aspects of the Health Beliefs Model¹⁷ and Self-Efficacy Theory.¹⁸ The primary objective was to examine the feasibility of implementing a community-based DOT model in nonadherent HIV-infected youth. Four sites (Detroit, Memphis, Los Angeles, and San Diego) were selected based on a review of site applications from all interested National Institute of Allergy and Infectious Diseases and National Institute of Child Health and Human Development PACTG sites. The protocol was approved by each participating site's Institutional Review Board and written consent to participate was provided by each study participant per respective institutional guidelines.

Study criteria

Eligible participants were youth, age 16 to <25 years, with HIV infection acquired via high-risk behaviors that were continuing, reinitiating, or changing HAART with demonstrated adherence problems (<85% of prescribed doses taken, as clinically documented on two consecutive occasions at least 1 month apart). Patients who were pregnant, breast feeding, had a comorbidity that required frequent monitoring and medical follow-up, or were receiving HAART that required more than twice daily (BID) dosing were excluded.

DOT facilitators

One or two DOT facilitators were selected at each site, from existing or newly hired staff based on study-specified recommendations, to provide DOT. The protocol outlined desirable DOT facilitator characteristics based on youth feedback in PACTG 1036A.¹⁶ DOT facilitators were trained using a program developed by the PACTG 1036B team, which included (1) provision of DOT, (2) overview of HIV and its management, (3) safety training, (4) cultural competency, (5) basics of conducting research, (6) review of HIV-specific legal issues and confidentiality and boundaries of an outreach worker, (7) awareness of community resources for participants, and (8) practical training that included conference calls with experienced HIV DOT facilitators working with adults and field training with local TB DOT staff where feasible. In addition to maintaining a participant-specific log where details of each DOT visit were captured, DOT facilitators also kept a detailed log of the logistics of providing daily DOT including distances traveled and number of participants visited. Facilitators were provided cell phones to facilitate communication with participants and for personal safety.

Study details

Participants' HAART was not protocol specified but instead was left to the discretion of the participant's medical care provider. Study participants were introduced by the site to the DOT facilitators before initiation of DOT interactions. The location of the DOT interaction was determined by mutual agreement between the participant and the DOT facilitator. The study flow included an initial 2-week period of daily DOT that was tapered to 5 days a week for 6 weeks and

subsequently further reduced to self-administered therapy (SAT) based on participant's reported ongoing adherence to medications (Fig. 1). DOT was provided once a day, with participants who were on a twice a day regimen taking their second dose as SAT. While on DOT, participants were provided pagers for site staff to contact them and for automated medication reminders to assist them with non-DOT doses. For participants who were adherent to their HAART, the earliest they could completely transition from DOT to SAT was at their 12-week study visit.

Study measures included assessment of adherence to medications and DOT visits, HIV viral load (VL), CD4 count, barriers to adherence, and mental health measures. The DOT dose and unobserved doses of medications since the last DOT visit were recorded in a log at each visit by the DOT facilitator based on participant self-report. Thus, for participants who were receiving DOT 5 days a week, medication intake over the 2 days they chose to take their medications as SAT was recorded on the first DOT visit that followed. Information from these logs was used to calculate total percent adherence (PA) over 1 month while the participant was receiving DOT:

$$PA = \frac{(\text{Total expected doses} - \text{Total missed doses})}{(\text{Total expected doses})} \times 100\%$$

Additionally, to obtain a uniform adherence assessment throughout the study even after DOT ended, there was a 4-week participant medication recall at monthly clinic visits using the same formula of PA as shown above. An overview of the DOT process for each participant is provided in Fig. 2.

The study-specific exit survey instrument to obtain participant feedback on completion/early discontinuation of DOT was administered to each participant and included questions with categorical responses as well as open-ended questions. Responses were kept confidential, directly recorded on the survey form, and mailed to the central study data repository without site staff having access to participant responses or identity. Study accrual and site/facilitator feedback were monitored through monthly conference calls. Experiences providing DOT also were shared during these calls.

Analysis

To analyze DOT feasibility, DOT "success" (i.e., adherence to the prescribed course of DOT) was defined as an overall >90% adherence to DOT visits followed by successful weaning to SAT. Successful weaning implied the participant maintained adherence to SAT doses qualifying for the deescalation of DOT as shown in Fig. 1. Week 12 and 24 outcome measures were compared to baseline values using the Wilcoxon signed rank test. Comparisons between adherent and nonadherent subjects were made using the Fisher's exact test, and logistic regression also was used to relate adherence with outcome measures. Confidence intervals for proportions were obtained using exact methods.

Results

Study population

Twenty subjects enrolled in the study over 1 year (April 2006–2007). Participant characteristics are shown in Table 1. Participants first started antiretroviral medications a median

FIG. 1. Directly observed therapy (DOT) study overview.

of 2 years prior to study entry. Forty-five percent of participants were continuing HAART at entry. The remainder was off therapy following documented nonadherence to their previous HAART regimen. Eighty-four percent of participants at study entry were started/continued on a protease inhibitor (PI)-based regimen and 16% on an NNRTI-containing regimen. Eighty-four percent of the participants were on a once-a-day regimen at study entry. One participant was homeless.

Although a proportion of the study population reported frequent (≥ 4 times a week) use of alcohol (10%) and marijuana (40%), there was no reported intravenous drug use. Participants identified potential structural barriers to adherence including problems with medical insurance (20%) and transportation to pick up medications (10%) or keeping clinic appointments (15%). Of the nine participants who were receiving ongoing HAART at the time of study entry, 44% each reported forgetting the medications, being worried people would find out about their HIV, falling asleep before they took their medications, and thinking they did not need their medications anymore and 55% reported feeling as if they needed a break from medications as a frequent (≥ 1 –2 times a week) reason for nonadherence.

Logistics of delivering DOT

Distances traveled and time required delivering DOT varied by site and proximity of a participant's residence in relation to the site. Participants chose their home for their scheduled DOT visit 82% of the time (898 visits), followed by the clinic (11%; 121 visits) and public places such as a restaurant, store, library, courthouse, or street/park (7%; 73 visits). Participants and facilitators mutually agreed to schedule their DOT interaction before noon for 77% of planned visits, noon to 6 P.M. for 16%, and after 6 P.M. for 7%. There were no facilitator or participant safety concerns or participant breaches of confidentiality reported throughout the study period. As anticipated, per participant cost of delivering DOT varied by site primarily due to DOT facilitator costs, which were influenced by how the DOT facilitator was

hired (part-time, full time, hourly basis) and site accrual and also by transportation costs for the facilitator to move around the community. The site that hired social work students who were trained as DOT facilitators and reimbursed on an hourly rate recorded the lowest per participant cost as opposed to the site that paid a set salary to their DOT facilitator.

DOT feasibility

The proportions of kept DOT facilitator–participant interactions at weeks 4, 8, and 12 were (median/range) 91% (64–100%), 91% (33–100%) and 83% (57–100%) for the $n = 17$, 14, and 14 participants assessed at these time points, respectively. The observed “no-show” rate for planned facilitator–participant interactions was significantly higher earlier in the day (before noon) compared to the later part of the day (22% vs. 13%; $p = 0.001$). The proportion of scheduled DOT visits for which the participant showed did not significantly differ based on where the visit was scheduled (i.e., home vs. clinic vs. public place). Four (20%) of 20 subjects prematurely discontinued study participation by week 8 (three were non-adherent to study requirements and one moved out of the area) while another 6 (30%; 95% CI 11.9–54.3) were designated a DOT “success” based on adherence to $> 90\%$ of their study-specified DOT frequency and successful progression to SAT. No differences for DOT success were noted based on site, gender, marijuana use, or time of the day when DOT was scheduled. Participants categorized as a DOT success were more likely to have a higher baseline depression score (Beck Depression Inventory, 2nd ed., BDI-II total score > 13) compared to those who were not ($p = 0.046$).

Overall DOT feedback from the 14 participants who completed the exit interview was very encouraging, with 79% reporting DOT changed their motivation to take medications and all saying they would recommend it to a friend who was having adherence problems. At the exit interview, all but one of the 14 respondents reported taking medications in front of the DOT facilitator was easy and felt the DOT facilitator helped in ways besides taking medications. Eighty-three

FIG. 2. Daily directly observed therapy (DOT) process.

percent felt it was helpful to gradually reduce the frequency of DOT from 5 to 3 days a week before stopping DOT. Half of the survey respondents reported feeling sad DOT was ending and 85% reported missing not seeing the DOT facilitator.

Impact of DOT

At baseline, only one patient had an HIV viral load <400 copies/ml. Of the 14 patients who had virologic assessment at weeks 12 and 24, 9 (64.3%) and 6 (42.9%), respectively, showed virologic control (<400 copies/ml). Similarly, compared to baseline, the median increase in CD4 count at weeks 12 ($n=15$) and 24 ($n=11$) was 148 and 199 cells/mm³, respectively. Although the study was not designed/powerd to examine the efficacy of DOT, available data do not demonstrate a statistically significant difference in achieving an undetectable VL or increased CD4 count at weeks 12 and 24 between those who were considered a DOT success versus those who were not. However, overall at week 12 there was an observed median decline in VL of 2.19 and 1.46 log₁₀ copies/ml and an increase in CD4 count of 162 and 140 cells/mm³, respectively, in the six participants who were DOT successes versus the eight who were not. There was a median decline in VL of 1.64 log₁₀ copies/ml at week 8 and 2.12 log₁₀ copies/ml at 12 weeks even in the 12 participants who had been on the same antiretroviral regimen for at least 6 months prior to receiving DOT and whose regimen was not changed postinitiation of DOT. Of these 12 participants 64% and 40% achieved an undetectable (<400 copies/ml) VL at 12 and 24 weeks, respectively. Participant self-reported adherence (4-week recall at their monthly clinic visit) over the course of the study period was >93% in all six deemed a DOT success until week 16 but only three sustained adherence off DOT until week 24. In those deemed not to be a DOT success, self-reported adherence (>93%) rapidly fell from eight participants at week 4 to four at week 12 and two at week 24.

Discussion

Maintaining long-term adherence to HIV medications is difficult, especially for youth³ for whom barriers to adherence are multiple.⁵ We wanted to enroll such youth with demon-

strated adherence problems to study the feasibility and challenges of delivering a complex, resource-demanding, community-based DOT intervention as well as to refine the model to deliver it. Although excellent (>90%) adherence to the DOT visit requirements was seen in only about a third of participants, the acceptability of this intervention based on participant feedback was overwhelmingly positive.

Despite the choice to receive DOT anywhere in the community and at anytime in the day, most participants selected their home and the earlier part of the day to receive DOT. In light of these expressed preferences, the significantly higher DOT interaction "no-show" rate for visits scheduled earlier in the day is surprising and needs further exploration in future studies. For youth, the majority of whom were unemployed, not in school, and stably housed, we incorrectly anticipated the earlier part of the day as providing more predictable structure and likelihood for DOT success for what ended up being a predominantly home-based intervention.

DOT was clearly not for all, and even among the 14 participants who completed exit interviews and were overall very positive about the intervention, the ability to meet with the DOT facilitator at the prearranged time was quite variable. Perhaps the >90% adherence to DOT interactions to be deemed a DOT success was too high an expectation given the unpredictability of youth schedules and motivations. Substituting some of the DOT interaction requirements with cell phone-based support from DOT facilitators¹⁹ may be one strategy worth exploring to reduce the time commitment from the in-person meetings without compromising the frequency of participant contact.

Although this study was not designed/powerd to identify who is best suited for DOT, a higher baseline depressive symptom score was observed for participants who were adherent to DOT as prescribed, raising the possibility these participants found the interactions with the DOT facilitators supportive, and for that reason kept up with them. Similar findings were noted in a DOT versus standard of care randomized clinical trial for HIV-infected adults starting HAART therapy in Mombasa, Kenya.²⁰ Among participants who had moderate to severe depression at study entry, those who received DOT were seven times as likely to be adherent in the initial 24-week period and more likely to have viral suppress-

TABLE 1. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	Value
Study participants (total)	20
Detroit	3
Memphis	8
Los Angeles	8
San Diego	1
Age in years (median, range)	21 (18–24)
Female	13 (65%)
Race/ethnicity	
White (non-Hispanic)	1 (5%)
Black (non-Hispanic)	15 (75%)
Hispanic (regardless of race)	4 (20%)
Education and Employment	
Currently unemployed	15 (75%)
Grades 1–12 education completed	15 (75%)
Mental health (psychiatric related diagnosis)	
Major depressive disorder	10 (50%)
Other	1 (5%)
Substance use (>1–2 times a week)	
Alcohol	5 (25%)
Marijuana	9 (45%)
Viral load in log ₁₀ copies/ml (median, range)	4.61 (1.04–5.75)
Absolute CD4 count, cells/mm ³ (median, range)	227 (10–443)

sion at 48 weeks than similar controls. Decreased depression scores also were noted in these Kenyan participants after receiving DOT. This finding could be particularly relevant since depression is one of the commonly observed clinical barriers to medication adherence,²¹ suggesting DOT potentially would be suited to participants with this condition.

A lack of durable benefit post-DOT was clearly seen in this study, with only three of six participants who had >90% adherence at week 12 able to sustain this level after DOT was discontinued. A similar observation has been reported for other adherence improvement interventions^{19,22,23} suggesting the core barriers to nonadherence were not resolved during or as a result of the intervention. The optimal duration of initial DOT and the timing and duration of DOT “boosters” for waning adherence need to be further studied.

As seen from participant exit interview responses DOT is much more than merely the act of observing persons take their medications. A participant quote from one of the exit interviews with reference to missing the facilitator when DOT ended is particularly poignant and emphasizes the desire for support and investment in the lives of these youth. The participant states “[I] liked having the support and someone to see everyday—liked having someone to care about me and who I also care about.” One anticipates the facilitator–participant interactions create a relationship whereby the participant views the facilitator as a support person, a motivator, and a person who helps triage the participant’s needs. Although we incorporated many of these elements when defining the scope of the DOT facilitators’ role in this study and designing their training program, there is an opportunity to do more. For example, DOT facilitators could be trained in motivational interviewing to use these techniques in the field, thus taking

one additional adherence intervention of interest²⁴ to the patient’s doorstep. In addition, our study results and the youth participant feedback underscore the need to develop community-based support for HIV-positive youth that is innovative and may utilize “nontraditional” support systems such as the church,²⁵ peers,²⁶ and accompagnateurs.²⁷ Such community-based support rather than the mere act of being observed while taking medications, in the long run, may be the answer to sustaining the benefits from short-term DOT.

Finally, among the various interventions studied to improve adherence to medications, DOT has been particularly contentious given the resources it requires. While a recent systematic review and meta-analysis using virologic suppression as the primary outcome measure concluded no benefit from DOT over self-administered therapy in the general HIV patient population, it noted a marginal benefit of DOT in groups that were judged to be at high risk of non-adherence and in trials of short duration (<6 months).²⁸ Similarly, based on simulation models, in patients with lower baseline levels of adherence or advanced disease, even very expensive, moderately effective adherence interventions are likely to confer cost-effectiveness benefits that compare favorably with other interventions.²⁹ The cost of DOT is in large part driven by the salary of the DOT staff respective to case load with the cost distributed over the number of participants receiving this intervention. With limited patient accrual at each site, our pilot study cannot provide accurate cost estimates of this intervention. We anticipate when offered to a subpopulation of high-risk patients who are failing clinic-based interventions to improve adherence, and with creative approaches to improve program flexibility (start, stop, and reinitiation of DOT), cost-effective DOT is feasible.

In summary, although this study shows community-based DOT is safe, feasible, and as per participant feedback, acceptable to youth, it also highlights that this intervention is not for all and the benefits for those who improve their medication adherence are not sustained after DOT is discontinued. Depressed youth with poor social support appear to be one subgroup that would benefit from this intervention. As we recognize the limits of clinic-based interventions to improve adherence, DOT and other community-based interventions are the next frontier for adherence research. Given the cost and resources involved in delivering DOT and the need to get youth-specific feasibility and logistics information in this regards, we chose a small sample size and a pilot study design. The experience gained from this pilot study should help inform the design of future community-based intervention studies in youth. Clearly poor adherence is more than just “forgetfulness” and expectations from DOT for HIV-infected patients is more than just another reminder intervention. We see tremendous potential for and envision customizing community-based DOT “plus” interventions that address youth-specific barriers to adherence, by packaging elements such as case management, motivational interventions, and directly observed therapy and delivering them at the doorstep.

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Author Disclosure Statement

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