Developing a Directly Administered Antiretroviral Therapy Intervention for HIV–Infected Drug Users: Implications for Program Replication

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Directly administered antiretroviral therapy (DAART) is one approach to improving adherence to among human immunodeficiency virus (HIV)–infected drug users. We evaluated the essential features of a community-based DAART intervention in a randomized, controlled trial of DAART versus self-administered therapy. Of the initial 72 subjects, 78% were racial minorities, and 32% were women. Social and medical comorbidities among subjects included homelessness (35% of subjects), lack of interpersonal support (86%), major depression (57%), and alcoholism (36%). At baseline, the median CD4+ cell count was 403 cells/mL and the median HIV-1 RNA load was 146,333 copies/mL (log10 5.31 copies/mL). During the prior 6 months, 33% of subjects had missed a medical appointment, and 47% had visited an emergency department. Although most subjects (67%) preferred to take their own medications, 76% would accept DAART if it were made compulsory. A methadone clinic was the DAART venue acceptable to the fewest subjects (36%), and a mobile syringe-exchange program was acceptable to the most subjects (83%). Adherence was higher for supervised than for unsupervised medication administration (P < .0001), a finding that supports use of daily supervision of once-daily regimens. Moreover, DAART should incorporate enhanced elements such as convenience, flexibility, confidentiality, cues and reminders, responsive pharmacy and medical services, and specialized training for staff.

The use of potent antiretroviral therapy has resulted in impressive reductions in morbidity and mortality among people living with HIV/AIDS [1]. Unfortunately, HIV-infected drug users have derived less benefit from antiretroviral therapy than have those who do not use drugs [2–4]. Reduced antiretroviral therapy benefit for this population results from decreased access to and utilization of health care services [5–7], including treatment for HIV infection and antiretroviral therapy. Even for HIV-infected drug users offered antiretroviral medications, active substance abuse has been associated with decreased adherence to prescribed therapy [8–11]. Many health-care providers, therefore, either will not prescribe medication or will delay prescription until patients are abstinent from drug use [12, 13]. Unfortunately, antiretroviral therapy may not be delayed indefinitely, particularly for patients with advanced HIV disease. Once potent antiretroviral therapy combinations are prescribed, insufficient adherence will result in decreased therapeutic benefit and development of multidrug-resistant strains of HIV [14–18], which, in turn, may be transmitted to others [19–22]. To achieve full access and utilization of antiretroviral therapy, innovative interventions targeting HIV-infected drug users are urgently needed.

In recent years, communities have increasingly
adopted syringe-exchange programs to prevent the transmission of HIV and other bloodborne pathogens. Moreover, syringe-exchange programs have the opportunity to engage active drug users in other positive health behaviors, such as entry into drug treatment [23, 24], provision of methadone maintenance therapy [25, 26], direct delivery of health care services [24, 27–29], and provision of antiretroviral therapy [30]. Through its continuous contact with and nonjudgmental approach to drug users, health services located at sites of syringe exchange could incorporate treatment for HIV infection, particularly directly administered antiretroviral therapy (DAART). To date, a few pilot DAART pilot programs demonstrate clinical success and support recommendations for further evaluation. These have primarily been conducted in structured institutional settings, such as methadone maintenance treatment programs [31–34], skilled nursing facilities [35], and prisons [36–38]. Community outreach workers have also been successfully deployed in 2 pilot programs of DAART for HIV infection [39, 40]. To date, no description of DAART provided at syringe-exchange sites has been published.

Globally, directly observed therapy (DOT) has become the standard treatment for tuberculosis. Important differences between HIV infection and tuberculosis make wide-scale adoption of DOT for HIV infection unlikely; however, HIV infection and tuberculosis have some common attributes. Both are recognized as threats to international public health; result in premature morbidity and mortality if left untreated; and lead to the development of drug-resistant pathogens, if adherence to treatment is inadequate. In addition, available drugs used for treatment for both HIV infection and tuberculosis have considerable toxicities. The infections differ with respect to route of transmission, duration of treatment, complexity of treatment regimen, pill burden, and likelihood of cure, and the fact that quarantine laws for tuberculosis mandate DOT when adherence is a concern. Moreover, patients with tuberculosis do not universally accept the coercive nature of DOT [41]. This is particularly true for injection drug users (IDUs) who have had unpleasant interactions with the health care establishment [42]. Despite these differences, much can be learned about DOT programs for the treatment of tuberculosis with regard to the challenges of development and implementation of such interventions [43].

Unlike DOT for tuberculosis, DAART programs are relatively new, require some additional consideration because of the added secrecy and stigma of HIV infection, and lack a rigorous discussion and evaluation of the necessary components. DOT programs for tuberculosis, however, are instrumental in the design of DAART programs. Similar to DOT programs for tuberculosis, DAART programs are likely to have the highest yield when provided in conjunction with enhanced services; these programs have been termed “enhanced” DOT. In a recent review of DOT programs for tuberculosis, enhanced DOT programs had higher efficacy than that seen with DOT alone, with modified DOT, and with self-administered therapy [44]. Here we describe the components of an enhanced DAART program (we refer to this as “DAART+”) that targets active drug users who are HIV-infected, and we present baseline information about the first 72 subjects enrolled. We also provide insights and lessons learned throughout the course of the development of the intervention, as well as considerations for communities who face similar issues in developing a comprehensive DAART program.

METHODS

The DAART+ intervention was developed in New Haven, Connecticut. This is the seventh-poorest city in the United States and has been profoundly affected by the HIV/AIDS epidemic. Before the availability of potent combination antiretroviral therapy, New Haven had become 1 of 15 US cities in which AIDS had become the leading cause of death for both men and women aged 25–44 years [45]. The AIDS epidemic in New Haven and Connecticut has been fueled by the parallel epidemics of injection drug use and poverty; >50% of all AIDS cases have been directly attributed to injection drug use, and the proportion approaches 70% when transmission of HIV to sex partners of IDUs is included [46]. Similar to other urban cities in the northeast, New Haven has been affected by substantial use of crack cocaine, which resulted in increased frequency of sexual behaviors that are a risk for HIV infection [47, 48], erratic use of health care [49, 50], and decreased rates of adherence to treatment for HIV infection (hereafter, “HIV treatment”) [51].

In creating the study protocol, characteristics of our pilot DAART program [52] and other successful DAART and enhanced tuberculosis DOT programs were identified from the medical literature. Each characteristic was considered and assessed in the development of the final DAART+ intervention. As part of this process evaluation, field notes from outreach workers, in-depth interviews with study participants, and field data were all reviewed. To ensure that details of the intervention as implemented remain well documented, outreach workers and clients are debriefed on a weekly basis, and precise field notes are maintained for each subject. For each component evaluated, selected data are provided, when possible, to address each component of the intervention. Finally, unresolved challenges and possible limitations that might influence development of similar interventions in other communities are discussed.

Selection of participants. Clinicians at the 2 community...
health centers and 2 hospital-based HIV/AIDS clinics in New Haven refer potential subjects to the DAART intervention. Community providers of HIV/AIDS treatment remain involved in the program to maintain levels of trust between the subject and his or her physician [53]. Inclusion criteria include being HIV-seropositive, age of ≥18 years, residence in the city of New Haven, current receipt of or eligibility for antiretroviral therapy, history of heroin or cocaine use within the previous 6 months, and having health insurance that pays for medications. Subjects meeting eligibility criteria, after providing written informed consent, are randomized to receive either the DAART intervention or self-administered therapy. The randomization process controls for antiretroviral experience, proximity to the DAART site, severity of alcohol abuse, and baseline HIV-1 RNA level and CD4+ lymphocyte count, by means of a stratified block randomization scheme [54, 55].

**Initiating DAART+.** Once randomized, DAART subjects are introduced to the DAART specialist, who introduces the subject to the staff on the Community Health Care Van (CHCV) staff. The DAART specialist is an outreach worker specifically trained to supervise DAART on the CHCV, a mobile health clinic that travels in tandem with the New Haven Syringe Exchange Program. Each DAART+ subject is provided an electronic paging device (pager) that is programmed to remind the subject to report for CHCV visits and to take all nonobserved medications, if dosing is more frequently than once daily; reminders for other scheduled activities, such as medical appointments, can also be programmed into the pager. Each DAART subject receives a medication bottle with a Medication Electronic Monitoring system (MEMS) 6 Smart Cap (Aardex) to monitor nonobserved doses. All medications, except schedule II narcotics, inhalers, and liquid medications, are provided as DAART. Although the DAART specialist can observe the subject taking his or her medications, the specialist cannot legally dispense these medications; therefore, the pharmacist indicates all doses on the medication labels, and the DAART specialist observes the subject taking the medications.

**CHCV.** The CHCV is a 36-foot-long mobile health clinic that was established in 1993 and was linked to the New Haven Needle Exchange Program. It has 2 examination rooms, 1 counseling room, a restroom, and a waiting area. The van operates 5 days per week from 8:00 A.M. to 8:00 P.M. at 4 distinct locations in the poorest neighborhoods of New Haven. Enhanced services available to DAART+ subjects include an on-site clinician who has experience with HIV infection, a drug treatment coordinator, a case manager, and dedicated bilingual/bicultural outreach workers. DAART+ subjects are not required to use these services but may be referred to them by the DAART specialist or through self-referral. For example, a DAART+ subject may experience adverse side effects from medications, which are assessed and treated by the CHCV clinician. Reports of all clinical encounters are faxed daily to the community HIV/AIDS treatment provider.

**Monitoring.** At baseline, each subject undergoes a 90-min, standardized, structured interview; phlebotomy (which includes measurement of the HIV RNA level and the CD4+ lymphocyte count and HIV-1 genotype determination), and hair

### Table 1. Baseline characteristics of 72 participants in a study of directly administered antiretroviral therapy for HIV-infected subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>42.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (68)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (32)</td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>43 (60)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (18)</td>
</tr>
<tr>
<td>White</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td></td>
</tr>
<tr>
<td>Heroin only</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Cocaine only</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Heroin and cocaine</td>
<td>47 (65)</td>
</tr>
<tr>
<td>Lives alone</td>
<td>62 (86)</td>
</tr>
<tr>
<td>Homeless</td>
<td>25 (35)</td>
</tr>
<tr>
<td>Has access to a car</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Has a telephone</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Incarcerated in past 6 months</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Missed at least 1 appointment with HIV/AIDS clinician in past 6 months when they needed it</td>
<td>24 (33)</td>
</tr>
<tr>
<td>Unable to see their HIV/AIDS clinician in past 6 months</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Used emergency department services in past 6 months</td>
<td>34 (47)</td>
</tr>
<tr>
<td>Has been in drug treatment in past 6 months</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Antiretroviral-naive</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Antiretroviral-experienced</td>
<td>61 (85)</td>
</tr>
<tr>
<td>Mean adherence score, %a</td>
<td>49</td>
</tr>
<tr>
<td>Adherence to &gt;75% of dosesa</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Depression statusb</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>41 (57)</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>13 (18)</td>
</tr>
<tr>
<td>None</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Treated for depression in past 6 months</td>
<td>34 (47)</td>
</tr>
<tr>
<td>Has severe alcoholismc</td>
<td>26 (36)</td>
</tr>
<tr>
<td>Median HIV-1 RNA load, copies/mL (log{10})</td>
<td>146,333 (5.31)</td>
</tr>
<tr>
<td>Median CD4+ lymphocyte count, cells/mL</td>
<td>403</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects, unless indicated otherwise. All comparisons between DAART+ and self-administered therapy arms were not significant.

a Self-reported adherence score by means of Adult AIDS Clinical Trials Group 3-day recall.

b Rated by means of the standardized Clinical Epidemiological Scale for Depression.

c According to the World Health Organization Alcohol Use Disorders Identification Test.
testing for heroin or cocaine use. Follow-up assessments are scheduled at weeks 4, 12, 24, 36, and 48. Before randomization, all subjects view a 30-min, standardized treatment-adherence video that was developed as part of the study. All laboratory information is faxed to the treatment provider, who either continues the current regimen or constructs a new one.

**RESULTS**

The baseline characteristics of the first 72 subjects are summarized in table 1. Of the 72 subjects initially interviewed, 68 were randomized to receive either DAART+ or self-administered therapy. Of the 4 not randomized, 1 was killed in a motor vehicle accident and 3 were lost to follow-up. The median CD4+ cell count for the 6 who refused intervention after learning they were randomized to the DAART+ group was 916 cells/mL, compared with 311 cells/mL for those who accepted DAART+ treatment. All of the subjects lived alone, and more than one-third were homeless. Not only did they not have the support of another person, but they were unlikely to have access to a car (85% of subjects) or a telephone (82%). Nearly one-sixth of subjects had been recently released from a correctional facility. Although only 17% were enrolled in a methadone maintenance program, 62% indicated that they were participating in self-help or other drug treatment programs for their drug addiction. Despite engagement in these programs, nearly all of them were actively using illicit drugs at the time of enrollment.

The recruited subjects were poorly integrated into the existing health care system. Although 33% of subjects reported having missed at least 1 appointment with their HIV/AIDS clinician in the prior 6 months, nearly the same proportion (31%) also reported inability to be seen for acute medical problems when they tried to make an urgent appointment with their clinician. Emergency department use has also been a marker of fragmented medical care [56]. Of the 72 subjects evaluated, 34 (47%) had been to an emergency department within the previous 6 months, for a total of 75 visits (mean, 1.04 visits in 6 months, or 2.08 visits per person-year), and 24 subjects (33%) had been hospitalized overnight during the same time period.

Most of the subjects (85%) were antiretroviral-experienced. At study entry, subjects reported having taken a mean of almost one-half of prescribed antiretroviral doses. Twenty-five percent of subjects reported having taken >75% of prescribed doses. These subjects had multiple medical problems in addition to HIV infection, including comorbid mental illness, alcohol dependence, and chronic viral hepatitis. According to the standardized Clinical Epidemiological Scale for Depression, 57% of subjects had major depression and 18% had mild to moderate depression. Nearly one-half of subjects (47%) had been clinically evaluated for depression; evaluation for depression did not correlate with either the presence or severity of depression (P not significant). According to the World Health Organization Alcohol Use Disorders Identification Test, 26 (36%) had evidence suggesting problematic drinking.

Subjects were assessed before randomization regarding their beliefs about DAART (table 2). When asked about their preference for self-administered or supervised therapy, two-thirds of subjects (67%) indicated that they would prefer to take

<table>
<thead>
<tr>
<th>Belief about DAART</th>
<th>No. (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject would prefer to self-administer his or her own HIV treatment</td>
<td>48 (67)</td>
</tr>
<tr>
<td>Subject would accept DAART if it were made compulsory to receive antiretroviral therapy</td>
<td>55 (76)</td>
</tr>
<tr>
<td>Places in which subject would be willing to receive HIV medications on a daily basis, if DAART were made compulsory</td>
<td></td>
</tr>
<tr>
<td>At home</td>
<td>32 (44)</td>
</tr>
<tr>
<td>At a methadone maintenance program</td>
<td>26 (36)</td>
</tr>
<tr>
<td>At an HIV/AIDS clinic</td>
<td>59 (82)</td>
</tr>
<tr>
<td>At a pharmacy</td>
<td>58 (81)</td>
</tr>
<tr>
<td>At a mobile syringe-exchange program</td>
<td>60 (83)</td>
</tr>
</tbody>
</table>

Table 2. Beliefs about directly administered antiretroviral therapy (DAART) among 72 HIV-infected injection drug users.

<table>
<thead>
<tr>
<th>Type of dose</th>
<th>No. of doses recorded/expected on the Medication electronic monitoring system cap data</th>
<th>Percentage of doses taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised (Mon–Fri)</td>
<td>2334/3065</td>
<td>76.2(a)</td>
</tr>
<tr>
<td>Unsupervised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (Sun–Sat)</td>
<td>2134/4277</td>
<td>49.9</td>
</tr>
<tr>
<td>Weekday (Mon–Fri)</td>
<td>1439/3065</td>
<td>46.9(b)</td>
</tr>
<tr>
<td>Weekend (Sat–Sun)</td>
<td>695/1212</td>
<td>57.3</td>
</tr>
</tbody>
</table>

\(a\) P < .0001 for supervised doses vs. all other comparisons. 
\(b\) P < .0001 for unsupervised weekday doses vs. unsupervised weekend doses.

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medications on their own. More than three-quarters (76%), however, indicated that they would agree to DAART if it were made compulsory. When asked how they would prefer to receive DAART if it were made compulsory, subjects were more likely to accept DAART at the mobile syringe-exchange clinic (83%), their HIV/AIDS clinic (82%), and at their pharmacy (81%) and less likely to accept it within a methadone program (36%) or at their home (44%).

MEMS cap data were available for DAART+ subjects, and openings were reflected for both the supervised and unsupervised dosing in this modified DAART program. Table 3 provides data on adherence levels for supervised weekday doses and for unsupervised evening and weekend doses. Adherence levels were significantly higher for supervised doses than for all other unsupervised doses (76.2% vs. 49.9%; \( P < .0001 \)). Among unsupervised doses, adherence levels were higher for weekend doses than for weekday doses (57.3% vs. 46.9%; \( P < .0001 \)).

Figure 1 demonstrates the proportion of DAART visits kept by subjects as the intervention started. During the first 10 months of the intervention, the proportion of the expected number of doses that were observed as DAART was 48%; this is no different than the proportion found among all subjects at the initiation of the study. This lower-than-expected outcome resulted in development of a 1-month training program to transform an outreach worker into a DAART specialist (see “Selection and training of staff,” below). During the subsequent 10 months, the proportion of DAART doses taken increased from 48% to 76% (\( P < .001 \)). Of note, the slope of the adherence curve was negative in the preintervention period and positive in the postintervention period.

Figure 2 is a map of New Haven showing the areas of highest density of HIV-infected drug users and the sites that were chosen for DAART locations; these sites are also associated with a high prevalence of drug use, drug arrests, and poverty. This map was generated as part of the planning process for the DAART intervention. New Haven’s largest HIV/AIDS clinic provided the city block–transformed addresses of all patients who had identified injection drug use as a risk factor for HIV infection. All address information was “geocoded” and mapped (i.e., address data was linked to locations on a map by means of a computer) with MapInfo Professional, version 7.5 (MapInfo).

**DISCUSSION**

Considerable information was learned during the initial phase of developing this DAART intervention. The baseline characteristics of the patient population argued strongly for providing enhanced services rather than services with strict DOT principles, as is done for DOT for tuberculosis. A DAART+ program has to rely on providing value-added services that will improve accessibility and acceptability, rather than supervised administration of medications alone, because DAART programs cannot rely on quarantine and incarceration to prevent against nonadherence. Information provided from this preliminary analysis can be used by other communities as they develop...
DAART interventions for HIV-infected drug users and others with antiretroviral adherence difficulties. The discussion will address several key issues for the DAART+ intervention that incorporate lessons from the tuberculosis literature, as well as those encountered in our clinical trial.

**Mobile versus stationary programs.** A variety of methods have been used successfully to provide DOT. Most programs have been adapted to the specific community and the availability of existing resources. In New Haven, there is a rich history of providing mobile health services, including prenatal care [57], training of medical residents [58], breast mammography [59], syringe exchange [60], and health care [24]. Given the presence of a mobile syringe-exchange program with linked health services for IDUs and ability of this program to interface with a large number of HIV-infected drug users, the CHCV was selected as the centerpiece of the DAART+ intervention. A previous pilot study on adherence with drug users who were not receiving treatment demonstrated promise with use of the mobile CHCV [52]. Information from the baseline interviews suggested that clients would prefer to receive DAART in a mobile community setting, rather than have staff visit their home. The mobile clinic allowed persons a choice of multiple sites for DAART and reflected the mobility of the targeted population, as well as their interest in separating their HIV treatment from their life at home (often to maintain confidentiality). In many cases, subjects live remotely from where they engage in other activities, such as using and trading illicit drugs, attending drug treatment, and receiving community outreach services from HIV/AIDS service organizations. Hence, the blanketing of the New Haven community is more easily done through a mobile health program but relies on subjects making a daily commitment to coming to the CHCV at predesignated times and locations.

**Convenience.** The mapping of the locations of HIV-infected drug users was instrumental in planning the DAART strategy within New Haven. Within the neighborhoods identified, the staff worked with the local police department, drug treatment programs, and community-based outreach efforts to select ideal sites convenient to the highest number of eligible candidates for the intervention. On the basis of our preliminary
data [30], it was anticipated that improved outcomes for HIV infection would result in a high frequency of subjects entering drug treatment and other services. Therefore, a site was situated adjacent to the largest methadone clinic and another was situated near 2 of the largest AIDS service organizations. One of these latter sites provides lunch daily and has a daytime respite center for people living with HIV infection. Hence, knowing the areas with the highest density of HIV infection, as well as sites that provide services to these patients on a routine basis, is critical for organizing DAART services.

Confidentiality. Confidentiality is considered critical in the development of a DAART intervention for people living with HIV infection. It was decided not to limit CHCV services solely to IDUs or persons with HIV infection, in order to avoid stigma [61]. The CHCV provides services to ~500 persons monthly for a variety of conditions [62], making DAART just one of many activities provided by the CHCV. A program that provides only DAART might reduce the likelihood that a wide array of subjects would agree to participate. Because DAART will likely remain voluntary, confidentiality issues may ultimately reduce the efficacy of such a program if persons refuse to participate because they believe their confidentiality was compromised.

Once inside the CHCV, irrespective of the reason for the visit, all CHCV clients (including those receiving DAART) are seen in private rooms to protect patient confidentiality. Therefore, both the wide array of CHCV clients seen and the private space provided protect the DAART subjects. Initially, a total of 7 subjects randomized to receive DAART stated concerns about confidentiality. After introduction to the CHCV staff and an explanation of how DAART would work, only 2 DAART subjects eventually refused to participate in the intervention because they perceived they would be identified as either HIV-infected or an IDU (neither was an IDU).

DAART versus modified DAART. Under ideal circumstances, DAART should include observation of the administration of every prescribed dose of medication. With regard to tuberculosis, this is more easily accomplished because of the availability of either once-daily or twice-weekly regimens. Most HIV treatment regimens prescribed by community HIV/AIDS physicians were twice-daily; therefore, we needed an approach that was feasible to reflect the practices of treating physicians. First, few once-daily antiretrovirals were approved by the US Food and Drug Administration at the time of study inception. It was therefore deemed unethical to coerce patients to take unapproved once-daily antiretrovirals with unproven efficacy unless the subject’s HIV/AIDS clinician prescribed such a regimen independent of the research intervention. Assigning patients to 2 experimental conditions, DAART and unapproved once-daily regimens, would have placed the subject in double jeopardy. Thus, we opted to provide modified DAART and allowed community HIV/AIDS clinicians to maintain important levels of trust [63–65] and to reflect the community standard of care. Second, most antiretroviral therapy regimens still have twice-daily dosing, despite the increasing number of available once-daily regimens [66, 67]. Once-daily regimens were also considered likely because many subjects would have received prior antiretroviral therapy and have fewer once-daily antiretroviral treatment regimens available to them. Third, most subjects had comorbid conditions requiring twice-daily therapy, including medications for conditions other than HIV infection. Fourth, our program was not able to supervise twice-daily dosing because of the logistical constraints of visiting several distinct areas of New Haven within a 12-h period. As more antiretrovirals become available, the use of once-daily regimens should be emphasized when administering a DAART+ program.

On the basis of MEMS cap information, our data confirm that treatment adherence is greatest for supervised doses. The adherence rate for unsupervised doses was no different (~50%) than the baseline adherence for all subjects entering the study. The implications for these findings are that future DAART programs should attempt to use approved once-daily regimens that are safe and effective and that DAART should be provided 7 days per week for all doses. The limitation of this approach, for our population, is that 85% of the subjects in this study were not antiretroviral-naive, thereby limiting once-daily antiretroviral treatment options.

Selection and training of staff. The outreach workers play a central role in DAART, and their activities can significantly alter retention in the program. The program modified the role of the outreach worker 10 months after starting the intervention. This resulted in a significantly higher level of adherence among DAART subjects. Initially, outreach workers from the CHCV were asked to add DAART responsibilities to their existing duties. Despite provision of basic training about the importance of adherence and the outreach workers’ previous experience with the targeted population, it was impossible to adeptly perform both duties. This was not recognized until the sample size increased and DAART attendance decreased. Because of the subjects’ complex lives and unmet needs, the outreach worker was presented by the subjects with challenges such as abrupt loss of insurance coverage, attainment of part-time jobs with schedules that conflicted with DAART, court hearings with expected incarceration, and difficulty developing trusting relationships with the outreach staff because of the outreach workers’ other required tasks in the CHCV.

In recognition of the many and complex evolving needs of the subjects, the role of the outreach worker was restructured. In fact, a dedicated DAART specialist was trained with skills specific for the DAART intervention. Though outreach workers were cross-trained to perform outreach and DAART respon-
sibilities, it was decided that for a given shift, one outreach worker would perform traditional outreach responsibilities and the other would focus on DAART; hence, a DAART specialist position was created. In the case of DOT for tuberculosis, provision of specialized training with tools necessary for DOT have resulted in improvement in adherence, when using lay workers [68].

The DAART training program involved daily hands-on training with a skilled case manager who trained by example. Elements of the Information, Motivation, and Behavioral Skills Model for behavioral change [69, 70] were taught, as well as motivational interviewing [71, 72]. Essential parts of the training included daily communication with subjects in an empathetic and nonjudgmental style, observing subjects taking their medications, and a nonpunitive style of inquiring daily about a number of possible issues. These sensitive issues include side effects, insurance and entitlement concerns, upcoming appointments and court cases, and problems the subject was encountering, such as continued substance misuse, expected changes in routine, and loss of housing. The DAART specialist was also provided training in how to address these issues or to refer the subject to a skilled case manager or other CHCV professional who could address the stated concerns. When problems with adherence were identified, the DAART specialist assessed the importance of adherence to the subject. If importance was low, information regarding adherence was provided and the subject was asked what it would take to increase the importance of adherence. If importance levels were high, then confidence in the subject’s ability to adhere to DAART was assessed, barriers were explored, and solutions were addressed. After the 1-month training, the DAART specialist has availability of the case manager to assist with any new issues that were not learned in the initial training. Intermittently, the case manager directly observes the interactions between the DAART specialist and subjects and provides feedback. Additionally, there is a weekly multidisciplinary case management meeting to discuss the relevant issues for each subject. This information further informs the DAART specialist on how to address continuing concerns. Hence, training is thorough and ongoing.

The DAART specialist also has a role in educating the subjects about their medications and training the subject in the use of the pager (see “Cues and reminders,” below). Over time, the subjects are taught to recognize their regimen so that they can become autonomous by the end of the 6-month DAART intervention. The DAART specialist is the initial contact to the health care system and also plays a central role in coordinating activities and establishing trust. When an unmet need is identified (e.g., acute side effects, interest in drug treatment, or impending homelessness), it is the DAART specialist’s responsibility to make sure that the subject is promptly put in contact with the necessary service. If a subject does not arrive at the CHCV despite multiple pager and phone contact attempts, the DAART specialist coordinates finding the subject by means of other CHCV outreach workers or traditional outreach efforts.

Cues and reminders. Cues and reminders have been integrated into adherence interventions that include adherence to medical appointments [73] and to medications [74–76]. Most subjects receive twice-daily regimens of medication for HIV infection and other conditions. Also, most subjects had a history of nonadherence with other appointments, and a reminder system was implemented to enhance DAART. Each subject randomized to receive DAART is provided with a pager with Internet access capability to generate standardized reminders. Subjects provide a list of scheduled events, including scheduled appointments, times the CHCV arrives in their neighborhood, and times to take unsupervised doses of medications. In addition to Web-based reminders to arrive at the CHCV for observed dosing, the DAART specialist can manually page subjects for additional and impromptu reminders by means of an alphanumerical pager (e.g., to provide secondary reminders when the subject does not show up). The pager was appreciated by subjects. The limitations on pager use, however, included occasional loss of pagers (by 12 subjects) and proactive need to change batteries. To reduce these problems, we recommend use of inexpensive pagers that can easily be replaced and changing the battery every 3 months.

Flexibility. The CHCV travels to the same 4 neighborhoods daily and has a well-advertised schedule. Although the CHCV schedule is not flexible, the DAART program is designed with flexibility in mind. For instance, if a subject cannot reach their designated stop, the DAART specialist arranges to meet the subject at a subsequent stop or will schedule a delivery to a neutral site. Although personal deliveries remain an option, subjects who attempt to over-utilize this service are counseled and reminded that such deliveries are for emergency needs. Another flexible feature of the DAART program is that subjects are provided a 3-day supply of backup medication so the subject will not feel stranded if she or he is temporarily unable to make it to the CHCV because of weather or other unanticipated conflicts. Also, if the subject identifies a need to be away from the city for a short period, the staff attempts to accommodate the subject.

Availability of other services. Subjects also receive all of their nonantiretroviral medications as part of the DAART program in recognition that there is a high prevalence of comorbid conditions among this population. If the subject identifies to the DAART specialist any unmet medical need when on the CHCV, he or she can see a medical clinician, an HIV/AIDS counselor (to discuss risk reduction interventions), or a drug treatment advocate, who serves as a case manager and facilitates entry into and continuity with drug treatment goals. If a subject
describes a medication side effect or has an acute medical problem during the DAART visit, the experienced HIV/AIDS clinician is available to examine the patient immediately. If a new medical treatment is deemed appropriate, the CHCV clinician contacts the subject’s primary HIV/AIDS treatment provider to highlight the details of the visit and discuss a mutually agreeable plan of care. This decreases the likelihood of fragmentation of HIV/AIDS care and retains the autonomy of the subject’s HIV/AIDS clinician. Some examples of CHCV clinician interventions include prescribing antiemetics for nausea or anti-diarrheals for diarrhea, contacting the methadone program if a subject experienced opiate withdrawal after starting a new regimen, and working with the primary HIV/AIDS treatment provider to modify the regimen if the subject is having difficulty adhering to a specific regimen.

Incentives. Subjects were not paid directly for participating in the DAART intervention. Other studies have demonstrated efficacy in using primary incentives for IDUs to return for tuberculosis screening and treatment programs [77]; however, tuberculosis identification and treatment have a finite duration. Also, because DAART is likely to be voluntary, incentives will not likely be incorporated into large-scale implementation, although this component will need independent evaluation. Though incentives were not provided for DAART, a $5 voucher was provided for each subject who retained their MEMS cap at the end of each week. This incentive was used to avoid the costly replacement of such devices and the possible loss of important adherence data. Other benefits conferred by participation and available to both DAART and control subjects included the routine provision of HIV-1 RNA test, CD4+ lymphocyte, and HIV-1 genotype results to their HIV/AIDS treatment providers.

CONCLUSIONS

This is the first randomized, controlled trial among HIV-infected drug users comparing DAART with the usual standard of care in a community. To date, most studies of DAART have small sample sizes, rely on highly motivated patients who specifically agree to participate in a DAART intervention, and do not use a randomized controlled design. In this study, we were able to develop a DAART intervention for a more broadly representative sample of HIV-infected IDUs and not solely for highly motivated persons willing to participate in the intervention at the onset. Several studies have demonstrated that the components of tuberculosis DOT can play an important role in adherence to therapy [41, 68, 78–80]. Many of these components were incorporated into the present DAART+ project and others were added so that lessons learned from this process will allow other communities confronted with similar issues of adherence to antiretroviral therapy by HIV-infected IDUs to develop appropriate programs.

As a note of caution, evaluation of adherence interventions must incorporate measurements of antiretroviral resistance. Our findings suggest that DAART improves adherence significantly and perhaps into a range that is likely to promote resistance if viral replication is not fully suppressed [81–83]. Unfortunately, these data are limited by the short-term measurements used and the lack of control for regimens containing agents with high and low genetic barriers to resistance.

It has been suggested that the medical establishment often mistreats IDUs, and this has resulted in the perception that DOT is coercive and punitive for IDUs [42]. In this study, very few persons were unwilling to participate in DAART once randomization was done. This suggests that if the infrastructure to provide DAART is acceptable to IDUs, they will participate willingly if they perceive personal benefit from the program. Problematic in this and other trials of DAART, referral bias may influence outcomes. It is likely that clinicians will refer only subjects who are deemed to be poorly adherent. The only way to overcome this bias is to enroll all antiretroviral-naïve subjects who do not already have experience with adherence or to enroll a population who would benefit from antiretroviral therapy and use a strict intention-to-treat analytic approach. It will be through the evaluation of randomized controlled trials that the efficacy and effectiveness of DAART interventions will be determined. Efficacy will be measured by the on-treatment analysis and effectiveness by the intention-to-treat analysis. Irrespective of the analytic strategy used, the unlikelihood that DAART will ever become mandatory necessitates the development of DAART programs that incorporate the important components that improve acceptability that are likely to result in successful outcomes [84–86]. The high prevalence of comorbid medical conditions and social disadvantages among this cohort suggest the need for ancillary services—including drug treatment, case-management, and medical services. This means that DAART will likely require enhanced services—that is, it will be what we term DAART+. This approach has been highly effective with DOT for tuberculosis treatment [87–89]. Because it is unlikely that DAART will become compulsory, as has been the case for the treatment of tuberculosis, it is critical that such programs targeting vulnerable populations be accessible and acceptable to the populations they aim to serve. Despite these limitations, DAART will likely be an effective approach to improve adherence to a population who has traditionally had problems with adherence and who has not derived the same benefit from antiretroviral therapy as have others with HIV infection.
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