Directly Administered Antiretroviral Therapy in an Urban Methadone Maintenance Clinic: A Nonrandomized Comparative Study

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Methadone-maintenance treatment clinics are strategically appealing sites for provision of directly administered antiretroviral therapy (DAART) to human immunodeficiency virus type 1 (HIV-1)–infected injection drug users (IDUs). We initiated an ongoing DAART protocol at a university-associated methadone clinic in April 2001, which continues to enroll participants. Participants ingested antiretroviral medications under direct supervision on days they attended the clinic; evening doses and doses on “methadone take-home days” were self-administered. Comparison IDUs receiving either standard care or treatment-adherence support were randomly selected from the population of the HIV-1 clinic where DAART participants received their primary care for HIV-1 infection, with frequency matching by sex, prior antiretroviral exposure, and receipt of methadone therapy. In an intention-to-treat analysis, 79% of DAART participants achieved HIV-1 RNA levels of <400 copies/mL by month 6 of therapy, compared with 54% in the standard care group (P = .035) and 48% in the adherence support group (P = .008). The preliminary results of this study both suggest that DAART can be feasible and acceptable to patients in a methadone clinic setting and provide impetus for further study of this treatment strategy in randomized controlled trials.

The use of directly observed therapy as part of a comprehensive tuberculosis control program has been shown to improve treatment outcomes [1], to decrease the incidence of disease in the community [2], and to reduce the burden of drug-resistant infection [3]. These same issues are highly relevant in the epidemic of HIV-1 infection. However, salient differences in the treatment of tuberculosis and HIV-1 infection pose challenges to the development of directly administered antiretroviral therapy (DAART) models [4]. Most notably, tuberculosis is generally cured with a 6-month course of therapy, whereas long-term suppressive treatment is necessary for HIV-1 infection. In addition, tuberculosis therapy may be administered as infrequently as twice weekly for the majority of the treatment interval, whereas once-daily or twice-daily dosing is required for antiretroviral therapy.

Because of these caveats, it seems likely that the scope of DAART will be restricted to targeted groups of patients or to selected treatment settings [4, 5]. Methadone-maintenance treatment clinics are strategically appealing settings for DAART programs. There is a high prevalence of HIV-1 infection among injection drug users (IDUs), and epidemiological data suggest that IDUs experience suboptimal treatment outcomes in the era of combination antiretroviral therapy [6, 7]. Moreover, frequent and ongoing contact between patients and health care staff in methadone clinics makes long-term provision of DAART feasible in this setting. We initiated a pilot study of DAART in a university-associated methadone maintenance clinic in 2001. We compared results for DAART participants with those for 2 nonrandomized cohort-matched control groups.
METHODS

Patients and protocol. In April 2001, we initiated a DAART program at a university-associated methadone clinic in Baltimore. HIV-1–infected patients were eligible to participate if they received HIV-infection care through a Johns Hopkins–affiliated clinic, had received methadone therapy for >30 days, and were initiating antiretroviral therapy for the first time or changing their antiretroviral regimen because of treatment failure. Exclusion criteria included clinically significant resistance to the 3 available antiretroviral classes or requirement that antiretroviral therapy be administered more frequently than twice daily. Participants provided written, informed consent and clinicians provided verbal consent. This study was approved by the institutional review boards of The Johns Hopkins University and the Centers for Disease Control and Prevention.

Participants’ antiretroviral regimens were selected by treating clinicians. Medications were prepackaged and labeled in single-dose units by a participating pharmacy. Medications for prophylaxis for opportunistic infections or other medical or psychiatric conditions were packaged with antiretroviral therapy if both the participant and his or her treating clinician were agreeable.

Participants ingested 1 dose of antiretroviral therapy on days when they attended the methadone clinic. A nurse or medical assistant observed ingestion of these doses at the methadone-administration window or in a nearby private office. Most patients preferred the latter setting because it permitted more time to ingest the medications and afforded greater privacy. DAART staff members also provided education about HIV infection to DAART participants, inquired about difficulties they might be having, facilitated communication with primary care providers, and helped participants gain access to needed medical and social services. Patients newly enrolling in the methadone program were required to come to the methadone clinic 7 days per week. According to protocol at the clinic, patients qualified to take home doses of methadone for self-administration as they met substance abuse treatment goals. Evening doses of antiretroviral therapy (when required) and doses to be taken on methadone take-home days were given to participants ahead of time in prepackaged units and taken on a self-administered basis. At study enrollment, participants were also given a 3-day emergency supply of medications, which could be used if participants were unexpectedly absent from the methadone clinic. This supply was replenished as needed during the study.

Concurrent comparison groups and statistical analysis. To assess the effectiveness of DAART, 2 comparison groups of HIV-1–infected subjects were randomly selected from the Johns Hopkins HIV-1 cohort database. The cohort database contains comprehensive demographic, pharmacologic, laboratory, and clinical data on ~3000 HIV-1–infected persons currently receiving treatment in the HIV/AIDS clinic [8]. The first group of comparison patients (the standard care group) received standard medical and psychosocial services available in the HIV/AIDS clinic. The second group (the adherence support group) was selected from patients enrolled in a program that included case management, nursing education and medication tailoring, group education, and peer advocacy. Patients had been referred to this program in a nonrandom manner by their primary care providers for enhanced assistance with apparent poor adherence with therapy. All comparison patients had a history of injection drug use and initiated combination antiretroviral therapy or changed their regimen after 1 January 2000. When possible, comparison patients who were receiving methadone therapy were selected. Comparison patients were frequency-matched with the DAART participants by sex and prior antiretroviral experience (i.e., naive or experienced).

The proportions of patients who achieved suppression of HIV-1 RNA levels to <400 or <50 copies/mL by month 6 of therapy were compared in the 3 groups by means of an intention-to-treat, missing-equals-failure rule. Patients in the 3 groups for whom ≥90 days had elapsed since therapy was initiated were considered to have experienced treatment failure if an HIV-1 RNA level lower than the specified cutoff value had not been documented. For each patient, the lowest HIV-1 RNA level recorded between initiation of therapy and month 6 of therapy was used. In addition, we compared the HIV-1 RNA values obtained at month 6 (closest to but not after that time) in the 3 groups by means of a last-observation-carried-forward rule. Changes in CD4+ cell counts at 6 months compared with baseline were compared between groups by means of an intent-to-treat, last-observation-carried-forward rule. Categorical and continuous variables were compared with Fisher’s exact test and the Wilcoxon rank sum test, respectively. \( P < .05 \) was considered statistically significant, and analyses were done with Stata software, version 8.0 (Stata Corporation).

RESULTS

To date, 38 participants have been enrolled in the DAART intervention, and 50 standard care patients and 40 adherence support patients have been randomly selected. Demographic and clinical characteristics of DAART participants and patients in the matched comparison groups were similar (table 1). Most DAART participants were women, because the methadone clinic had a dedicated program for HIV-1–infected, uninsured women. All patients had injection drug use as a risk factor for HIV-1 infection. All patients in the DAART and standard care groups were receiving methadone therapy. However, because the overall pool of patients in the adherence support program was smaller, only 42% of selected comparison patients in this group were receiving methadone therapy.
Table 1. Baseline characteristics of HIV-1–infected patients enrolled in a study of directly administered antiretroviral therapy (DAART), standard care, or adherence support.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DAART (n = 38)</th>
<th>Concurrent comparison groups</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard care (n = 50)</td>
</tr>
<tr>
<td>Female sex*</td>
<td>74</td>
<td>76</td>
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<tr>
<td>Age, years</td>
<td>39 (37–45)</td>
<td>39 (37–44)</td>
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<tr>
<td>African American race</td>
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<td>90</td>
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<tr>
<td>Receiving methadone therapya</td>
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<td>100</td>
</tr>
<tr>
<td>Prior exposure to combination ARTa</td>
<td>63</td>
<td>76</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³</td>
<td>171 (43–282)</td>
<td>185 (39–361)</td>
</tr>
<tr>
<td>HIV-1 RNA level, copies/mL</td>
<td>78,221 (19,818–261,438)</td>
<td>38,117 (7576–111,336)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % of patients or median value (interquartile range). ART, antiretroviral therapy.

The disposition of patients enrolled in DAART is shown in figure 1. As of January 2003, the median follow-up time for participants who enrolled in DAART was 27 weeks (interquartile range [IQR], 10–48 weeks). Fifteen (39%) of 38 participants discontinued DAART during follow-up. Eleven (73%) of the 15 participants who discontinued DAART did so because they defaulted or were administratively discharged from the methadone program because of persistent drug or alcohol use or other infractions. Two patients discontinued antiretroviral therapy because of adverse effects and had not restarted antiretroviral therapy at last follow-up. One patient discontinued DAART at 27 weeks because of persistent nausea associated with ingesting antiretroviral therapy and methadone in close temporal proximity. This patient continued to take antiretroviral therapy on a self-administered basis. No patients discontinued DAART because of privacy or confidentiality concerns.

Of the 38 patients enrolled in the DAART arm, 5 had been enrolled for <90 days at the time of this interim analysis and are not included in the efficacy aspects of this report. The percentages of patients achieving virus suppression by month 6 of therapy is shown in figure 2. By intention-to-treat, missing-equals-failure analysis, 79% of DAART participants (26 of 33 for whom ≥90 days had elapsed since therapy was initiated) achieved an HIV-1 RNA level of <400 copies/mL by month 6, compared with 54% in the standard care group (P = .035) and 48% in the adherence support group (P = .008). Fifty-eight percent of DAART participants (19 of 33 for whom ≥90 days had elapsed since therapy was initiated) achieved an HIV-1 RNA level of <50 copies/mL, compared with 22% in the standard care group (P = .002) and 23% in the adherence support group (P = .003). At month 6, HIV-1 RNA levels were significantly lower in the DAART group (median, 97 copies/mL; IQR, 50–2289 copies/mL) than in the standard care group (median, 554 copies/mL; IQR, 52–40,140 copies/mL; P = .04) and in the adherence support group (median, 729 copies/mL; IQR, 174–42,122 copies/mL; P = .009). The HIV-1 RNA levels at month 6 were not significantly different between the standard care and adherence support groups (P = .37). Compared with baseline, the median increase in CD4+ cell count at month 6 was 72 cells/mm³ in the DAART group, 52 cells/mm³ in the adherence support group, and 31 cells/mm³ in the standard care group (P > .1).

**DISCUSSION**

Adherence to combination antiretroviral therapy is a critical determinant of long-term clinical outcomes [9, 10]. HIV-1 infection is highly prevalent among persons receiving substance abuse treatment at urban methadone clinics, and HIV-1–infected IDUs experience suboptimal treatment outcomes compared with other risk groups [6, 7]. The preliminary results of this ongoing study suggest that DAART may be feasible for and acceptable to patients in a methadone clinic setting and that
this strategy may increase rates of virus suppression, compared with rates for patients receiving self-administered antiretroviral therapy. Nearly 80% of participants enrolled in our DAART initiative achieved suppression of HIV-1 RNA levels to <400 copies/mL, compared with ~50% in the comparison groups. Subjectively, we noted that DAART led to changes in the “HIV culture” at the methadone clinic, including greater dialogue among patients and staff about HIV infection and its treatment and greater collaboration between substance abuse providers and medical providers. Further research on integrated care models such as this one is indicated.

To date, the experience with DAART in methadone clinics has been limited [11, 12]. In an uncontrolled trial of DAART in a methadone clinic in British Columbia, Conway et al. [11] reported that 66% of patients achieved virus suppression, and Clarke et al. [12] reported that 65% of antiretroviral-naive and 51% of antiretroviral-experienced patients achieved virus suppression with DAART in an Irish methadone clinic.

An important limitation of our study was that it was non-randomized. Selection and other biases may affect comparisons with historical or concurrent control groups. Patients in the adherence support group were those considered by their providers to need increased assistance with adherence to treatment and thus may have been less likely to achieve an undetectable virus load. However, patients in the DAART arm and in the comparison groups received HIV-1 infection care through the same university-based clinic, and the primary providers of HIV-1 infection care determined the antiretroviral regimens for all patients. To minimize potential biases, we included only IDUs in the comparison groups and, when possible, only persons who were receiving methadone therapy. Frequency matching was done to ensure similar distributions according to other relevant covariates. The resultant comparison groups were similar to the DAART group with respect to demographic, behavioral, and clinical factors. An additional limitation was that our enrollment criteria for DAART included receipt of methadone for at least 30 days. Thus, our findings may not apply to persons who have recently enrolled in a methadone maintenance therapy program.

A final limitation of our DAART model was that nearly 40% of participants dropped out during the first 6–12 months, a figure that was driven almost entirely by participants who defaulted from methadone therapy. Default from methadone and other substance abuse treatment programs is common and creates a ceiling effect on HIV-therapy adherence programs that are linked to retention in substance abuse care programs. However, it is possible that an integrated-services program, such as DAART, may have salutary effects on substance abuse treatment. For example, a randomized clinical trial conducted by McLellan et al. [13] found that offering a greater breadth of services to methadone-program enrollees significantly improved retention in substance abuse treatment program and improved rates of negative urine drug screening results. The effect of DAART on substance abuse treatment outcomes for methadone recipients should be further evaluated in randomized controlled trials. In addition, linking tracking and outreach models to DAART may be helpful in fostering greater retention in substance abuse treatment programs.

Our study offers a strong impetus for the continued exploration of DAART in methadone clinics, and randomized controlled trials of this strategy are indicated. Important issues to be addressed include the virological, immunologic, and clinical efficacy of DAART, compared with those of self-administered therapy; the effect of DAART on acquired antiretroviral drug resistance; and cost-effectiveness.

Acknowledgments

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References

5. Bangsberg DR, Mundy LM, Tsilky JP. Expanding directly observed