Impact of Enhanced Services on Virologic Outcomes in a Directly Administered Antiretroviral Therapy Trial for HIV-Infected Drug Users

Duncan Smith-Rohrberg, MPhil, Joanne Mezger, BA, Mary Walton, PA, R. Douglas Bruce, MPhil, and Frederick L. Altice, MD

Background: Directly administered antiretroviral therapy (DAART) is a promising intervention for improving HIV outcomes among active drug users, but the elements associated with successful DAART programs remain largely unknown. This study aimed to assess the impact of colocated medical, case management, and referral to substance abuse services (DAART-Plus) among the subjects receiving DAART as part of a larger randomized controlled trial comparing DAART with self-administered therapy.

Methods: The health services utilization of 72 subjects receiving DAART was analyzed for its impact on changes in HIV-1 RNA levels at 6 months. The primary outcome was virologic success, defined as achieving an HIV-1 RNA level $\leq$400 copies/mL or a $\geq$1.0 $\log_{10}$ reduction in HIV-1 RNA level. A second analysis consisted of linear regression assessing the effect of covariates on $\log_{10}$ HIV-1 RNA reduction from baseline to 6 months.

Results: In multivariate analyses, achieving virologic success at 6 months was associated with high medical services utilization [adjusted odds ratio [AOR] = 10.0 (1.4, 73.9); $P = 0.02$] and with the use of case management services [AOR = 5.8 (1.1, 30.5); $P = 0.04$]. Both services resulted in a larger reduction in $\log_{10}$ HIV-1 RNA from baseline (difference in slopes: -0.9 and -1.0, respectively; $P = 0.02$ for both). Referral to off-site substance abuse services treatment did not significantly predict either virologic outcome.

Conclusions: Among individuals who receive DAART, the utilization of on-site medical and case management services was independently associated with improved virologic outcomes. These results suggest the potential utility of integrating these services into DAART interventions (DAART-Plus) targeting HIV-infected drug users with problematic adherence.

Key Words: adherence, AIDS, HIV, directly administered antiretroviral therapy, injection drug use, substance abuse treatment, case management, medical care, health care utilization, randomized controlled trial, homolessness, vulnerable populations

(*J Acquir Immune Defic Syndr* 2006;43:S48–S53)

Interventions aimed at improving access and adherence to antiretroviral therapy (ART) for HIV-infected active drug users are crucial to improving health outcomes.[1] One such intervention, highly successful in tuberculosis control, is directly observed therapy (DOT). Although several reports have demonstrated the acceptability and feasibility of directly administered antiretroviral therapy (DAART; alternatively called directly observed therapy of highly active antiretroviral therapy [DOT HAART]) among active drug users and other marginalized populations,[2–9] no randomized controlled trials (RCTs) exist to evaluate this intervention rigorously among active drug users. One RCT of DAART among low-income predominantly non–drug-using patients in Los Angeles showed no effect of the intervention, but the relevance of these data to the injection drug user (IDU) population is uncertain.[10] If DAART is to ever become a strategy available to public health planners and clinicians treating HIV in the active drug-using population, outcomes research is greatly needed to determine the expected degree of effectiveness and the patient- and programmatic-specific determinants of its impact.

It already is clear that for DAART to emerge as an important component of public health practice for HIV-positive drug users, it requires more than merely witnessed dosing.[11] Fully functional DAART programs include important personal relationships between clients and DAART staff that can reinforce additional case management, substance abuse treatment, and medical and social services. As such, it is crucial to evaluate the role that these additional services might play in DAART outcomes and overall cost-effectiveness. Indeed, one might consider the utility of DAART versus "DAART-Plus," or DAART with enhanced colocated clinical and case management services, in achieving successful outcomes. The characteristics of DAART-Plus programs, however, remain undefined.

Here, we present data from the 72 patients enrolled in the DAART arm of an RCT comparing DAART with self-administered therapy (SAT) among IDUs in New Haven, CT. The main analysis of this RCT comparing DAART with SAT is presented elsewhere.[12] The focus of this analysis is on assessing the role of "enhanced services" (ancillary medical, case management, and substance abuse services) on virologic

From the Yale University AIDS Program, New Haven, CT.

Supported by the National Institutes on Drug Abuse (grants R01 DA13805 and K24 DA 170720 to R. Altice and K23 DA22143 to R. D. Bruce). D. Smith-Rohrberg receives funding from the National Institutes of Health Medical Science Training Program (GM07205).

Reprints: Frederick L. Altice, MD, Yale University AIDS Program, 135 College Street, Suite 323, New Haven, CT 06510–2283 (e-mail: raltice@aol.com and paula.dellamura@yale.edu).

outcomes among subjects receiving DAART. In addition, we investigate the impact of various psychosocial and demographic parameters, including age, gender, ethnicity, income, education, homelessness, depression, social support, self-efficacy, and drug abuse severity, in terms of the potentially confounding effect of enhanced services and as independent predictors of outcome.

METHODS

Patient Population and Study Design

Details of the DAART intervention have been published previously.[11] Briefly, the study was an RCT of DAART conducted in New Haven, CT and provided through a mobile community health care van (CHCV) compared with SAT. Subjects were recruited from all sites of care within New Haven. Inclusion criteria included being HIV-seropositive, age $\geq$18 years, residence in the city of New Haven, current receipt of or eligibility for ART, and a history of heroin or cocaine use within the previous 6 months. Subjects who met eligibility criteria and provided written informed consent were randomized to receive the DAART intervention or SAT.

Subjects randomized to the DAART intervention were introduced to the DAART specialist, a trained community outreach worker who observes the subject take his or her medication daily during weekdays on the CHCV and is also trained to provide social support and case management services. Weekend doses were provided on Fridays; subjects were also provided an emergency supply of 3 days of antiretroviral medications, and they carried a beeper to remind them when to take their evening dose (if applicable). Although subjects were encouraged to use DAART at a CHCV stop most convenient to them, the DAART specialist occasionally made trips to subjects' homes and work sites. The DAART intervention continued for a total of 6 months; at that point, subjects transferred directly to self-administration of their antiretroviral medications for the subsequent 6 months of observation.

HIV-1 RNA and CD4 T-lymphocytes levels were measured at baseline and at 1, 3, 6, 9, and 12 months for all subjects. Additional laboratory values from the sites of clinical care were added for time-dependent analyses.

This analysis is limited to the 72 patients who were randomized into the DAART arm of the study; 2 patients who died before 3 months on DAART were excluded from the analysis.

Community Health Care Van Health Services

The CHCV is a 36-ft mobile health clinic that was established in 1993 and is linked to the New Haven Needle Exchange Program. It has 2 examination rooms, 1 counseling room, a lavatory, and a waiting area. The CHCV operates 5 days per week from 8:00 AM to 7:30 PM at 4 distinct locations within the poorest neighborhoods of New Haven. Enhanced services available to DAART subjects on the CHCV include an on-site clinician who has experience with HIV infection, a substance abuse treatment coordinator, a case manager, and dedicated bilingual/bicultural outreach workers. DAART subjects are referred by the DAART specialist or through self-referral to the CHCV, but they are not required to use these services. Every client visit on the CHCV is recorded using standard reporting forms. For this study, the unique client identifier for CHCV services was used to extract utilization data for each of the DAART subjects. Administrative health care utilization data were categorized as general medical, referral to substance abuse, and direct provision of case management services. Individual counts were made for each of these types of service encounters for each subject only during the 6-month period that he or she received DAART. Medical services included any general outpatient primary care or specialist medical service provided to the subject on the CHCV; substance abuse services included evaluation of withdrawal symptoms by the medical team and referral services for inpatient or outpatient drug treatment and for individual or group substance abuse counseling. Case management services included assistance in obtaining entitlements, including insurance, medical, legal, food, education, and housing services. Each recorded encounter, coded for the type of service provided, was explored in multivariate analyses using the model-building approaches described elsewhere in this article.

Additional Covariates

In the multivariate longitudinal analyses described here, the following variables were used to adjust for any potential confounding with respect to health services utilization: age, gender, ethnicity, education, homelessness, income, injection drug use at baseline (cocaine, heroin, or both), depression as measured by the Center for Epidemiological Studies Depression (CESD) scale, substance abuse severity as measured by the Drug Abuse Screening Test (DAST),[13] social support,[14] and self-efficacy[15] using standardized measures. For the quantitative scales, the functional form of the scores was explored through visual inspection of histograms of the raw values and through the model-building process described elsewhere in this article. Linear and categoric functional forms were explored; only the optimal form of each variable is presented in the final tables.

Statistical Analysis

The primary outcome of the larger RCT was proportion achieving virologic success at 6 months, defined as achieving an HIV-1 RNA level $\leq$400 copies/mL or a decrease from baseline HIV-1 RNA level $\geq$1.0 $\log_{10}$ copies/mL. There was 1 subject without a measurement at 6 months; this subject was considered to represent a virologic failure.[16] All analyses were performed using logistic regression adjusting for baseline viral load. To confirm our results, a second analysis consisted of linear regression assessing the effect of covariates on $\log_{10}$ viral load reduction from baseline to 6 months, adjusted for censoring at the lower limits of detection (LLOD) using the SAS procedure LIFEREG with the dist = normal option.[17] For the linear regression of mean $\log_{10}$ HIV-1 RNA changes from baseline to 6 months, undetectable laboratory values were imputed as the LLOD and confirmed. The log viral load for the single missing value was imputed as the baseline value (ie, 0 change). Inferences were similar, although P values associated with main health services utilization tended to be smaller in the imputed case, suggesting that our method provides a more conservative, and certainly more realistic, assessment of changes in viral load. All analyses were performed using SAS (version 9.1, SAS Institute, Carey, NC).

For both models, all the covariates were initially fit to an "unadjusted" model consisting only of the covariate in question and adjusted only for baseline viral load. In these unadjusted analyses, several functional forms of each covariate, including linear and various polytomous and dichotomous forms, were explored; the Akaike information criterion (AIC) was used to choose the optimal form, and this form was then used in the multivariate analysis. Subsequently, a multivariate model was fit to the data, using backward and forward stepwise regression approaches, with P values of 0.20 to enter and leave the model. The AIC was again used to assess model fit, with attention given to the impact of each covariate on the effect of the main health services exposure variables; the optimal model was chosen at the convergence of the forward and backward models, with attention to parsimony so as to avoid overfitting the model. The 3 service utilization covariates and the baseline viral load were forced into all models.

All inferences were made based on a type I error rate equal to 0.05; "trends" were considered at 0.10. No correction was made for multiple statistical tests.

RESULTS

The characteristics of the study population are presented in Table 1. Most (69%) subjects were male and black (60%); 42% lacked a high school education, and 39% were homeless. The mean $\log_{10}$ HIV-1 RNA level was 3.8 copies/mL (SD = 1.6), although 31% of the subjects had a baseline HIV-1 RNA level at the LLOD. The mean CD4 count was 348 cells/μL (SD = 330).

The distribution of ancillary service utilization is shown in Table 2. Overall, 24% of the subjects used some form of substance abuse services, 80% used case management services, and 79% used general medical services (data not shown). Pairwise associations of the covariates revealed only a significant association between medical services and drug services utilization (Spearman rank correlation on continuous data = 0.43; P = 0.0001 and φ-coefficient on dichotomized values = 0.38; P = 0.001. The best-fit model for medical services used during the 6 months of DAART was stratified as "low medical services utilization" (defined as using 0–4 visits, n = 27) or "high use of CHCV medical services utilization" (defined as using 5 or more visits, n = 45). Case management utilization was stratified as having used 1 or more services (n = 58) or "no case management services" (n = 14). Referral for substance abuse treatment services was similarly dichotomized into "any use of substance abuse treatment referral services" (n = 17) and "no substance abuse treatment services" (n = 55). None of the polytomous scenarios provided a better fit to the model, according to the AIC, suggesting that there was no dose-response effect to be found in these data.

The unadjusted univariate associations are shown in Table 3 for the logistic regression of virologic success at 6 months and the linear regression of mean change in viral load. The high ambulatory medical services utilization group was more likely to achieve virologic success (89% vs. 64%, odds ratio [OR] = 4.4; P = 0.03) and had a greater censored-adjusted mean log viral load reduction from baseline (crude censored-adjusted means: −1.6 to −0.9, difference in slopes adjusted for baseline: −0.8; P = 0.04). The group that used case management services was also more likely to achieve virologic success (79%–50%, OR = 4.0; P = 0.06) and showed greater viral load reduction, (crude means: −1.3 to −0.5, −0.9 difference in slopes). Although use of case management services did not reach statistical significance at the 0.05 level, the trend approached this value and was included in the adjusted multivariate analysis. The substance abuse referral

TABLE 1. Baseline Characteristics of the DAART Study Arm (N = 72)

Variable	Value
Age (y), median (IQR)	42.5 (37.1–48.3)
Gender	
Female	22 (30.6%)
Male	50 (69.4%)
Ethnicity	
Black, not Hispanic	43 (59.7%)
Hispanic	17 (23.6%)
White	12 (16.7%)
Language	
English	57 (79.2%)
Spanish	15 (20.8%)
Education	
Not high school graduate	30 (41.7%)
High school/GED	26 (36.1%)
Beyond high school	16 (22.2%)
Homeless	28 (38.9%)
Monthly income	
<$500	38 (53.5%)
$500–$1000	27 (38.0%)
>$1000	6 (8.5%)
Drug use during study	
Heroin only	4 (5.6%)
Cocaine only	14 (19.4%)
Heroin and cocaine	41 (56.9%)
No reported drug use	13 (18.1%)
DAST raw score	
Low (0–2)	22 (30.6%)
Moderate (3–5)	16 (22.2%)
High (6+)	34 (47.2%)
CESD score	
None (≤14)	13 (18.6%)
Mild to moderate (15–21)	22 (31.4%)
Severe (≥22)	35 (50.0%)
Antiretroviral naive	14 (19.4%)
Social support	
Low (≤60 Huba Scale)	25 (34.7%)
High (>60 Huba Scale)	47 (65.3%)
HIV-1 viral load	
>400 copies/mL	50 (69.4%)
Mean $\log_{10}$ (SD)	3.8 (1.6)
Median $\log_{10}$ (IQR)	3.9 (2.2–5.2)
Mean CD4 count, cells/μL (SD)	348 (330)
Median CD4 count, cells/μL (IQR)	261 (103–529)

GED indicates general education development; IQR, interquartile range.

TABLE 2. Types of DAART-Based Services Utilization Over 6 Months (N = 72)

Variable	Number	(%)
Medical services		
No utilization	15	(20.8)
Single utilization	10	(13.9)
2–4 utilizations	20	(27.8)
≥5 utilizations	27	(37.5)
Case management services		
No utilization	14	(19.4)
Single utilization	31	(43.1)
2–3 utilizations	13	(18.1)
≥4 utilizations	14	(19.5)
Substance abuse referral services		
No utilization	55	(76.4)
Single utilization	11	(15.3)
≥2 utilizations	6	(8.3)

services groups did not differ with respect to the proportion achieving virologic success (75% to 71%, OR = 0.9) or in change from baseline viral load (crude means: −1.7 to −1.7, −0.1 difference in slopes). Possible associations among the other covariates are shown in Table 3.

The adjusted multivariate analyses are shown in Table 4. In these models, high use of medical services (adjusted odds ratio [AOR] = 10.0; $P = 0.02$) and case management services (AOR = 5.8; $P = 0.04$) were associated with an increased likelihood of achieving virologic success. Similarly, both were associated with a greater $\log_{10}$ HIV-1 RNA reduction (both $P = 0.02$). Three other factors were associated with improved virologic outcomes: (1) age ≥45 years, (2) increased substance abuse severity (DAST score >6), and (3) cocaine use during the study period.

DISCUSSION

This analysis from the intervention arm of an RCT of DAART among active drug users demonstrates the importance of integrating medical care and case management services into DAART programs serving active IDUs. In multivariate adjusted analyses using 2 distinct statistical models, utilization of high ambulatory medical services and case management services was associated with improved virologic outcomes over 6 months among DAART recipients.

There are individual and programmatic reasons why some individuals might utilize more services and benefit from them. Although this study is not able to address this issue specifically, it is likely that factors such as proximity to and convenience of the services contributed to these outcomes. Moreover, the quality of the interaction between the DAART staff may also contribute greatly to these outcomes, because many of the referrals to on-site ancillary services are initiated by the DAART specialist. For instance, although social support, per se, did not influence virologic outcomes, the DAART specialist provided the on-site case management services and likely developed a strong interpersonal relationship that facilitated use of social and medical services. Similar social support has been associated with improved outcomes in DOT programs for treating tuberculosis.[18,19] Moreover, there are several examples of where colocation of multiple services, particularly for drug users, has resulted in improved health outcomes.[20–22] The high rate at which these services were utilized in this study is not surprising, because HIV-infected drug users are known to have high rates of emergency room use[23] as well as multiple medical[24] and psychiatric comorbidities[25] and many preventive health care needs.[26,27] This study is the first to demonstrate an improved HIV-specific therapeutic improvement associated with such on-site service use.

TABLE 3. Univariate Analyses (N = 72)

		Virologic Success at 6 Months		Mean Log_{10} Reduction at 6 Months	
Covariate	n (N-n)	Adjusted OR (95% CI)	*P*	Difference in Slopes (95% CI)	*P*
High medical services	27 (45)	4.5 (1.2 to 17.4)	0.03	−0.8 (−1.6 to −0.1)	0.04
Case management services	58 (14)	4 (1.2 to 13.8)	0.06	−0.9 (−1.8 to 0.1)	0.07
Substance abuse referral	17 (55)	0.9 (0.3 to 3.1)	0.85	0.1 (−0.9 to 1)	0.93
Black (white)	43 (12)	0.7 (0.2 to 2.9)	0.62	0.02 (−1.1 to 1.1)	0.98
Hispanic (white)	17 (12)	0.8 (0.2 to 3.9)	0.69	0.5 (−0.9 to 1.7)	0.51
High school education	42 (30)	1.1 (0.4 to 3)	0.98	−0.1 (−0.9 to 0.7)	0.85
Age ≥45 years	28 (44)	4.7 (1.2 to 18)	0.03	−1.1 (−1.9 to −0.4)	0.004
Male gender	50 (22)	0.5 (0.2 to 1.8)	0.26	0.3 (−0.6 to 1.1)	0.59
DAST score ≥6	34 (38)	2 (0.7 to 6)	0.23	−0.7 (−1.5 to 0.1)	0.07
CESD ≥10	55 (16)	0.4 (0.1 to 1.6)	0.15	−0.43 (−1.4 to 0.5)	0.35
CESD ≥22	35 (33)	1.1 (0.4 to 3.1)	0.94	−0.7 (−1.4 to 0.2)	0.11
Homelessness	28 (44)	2.9 (0.9 to 9.9)	0.10	−1.1 (−1.9 to −0.4)	0.18
Cocaine use during study	55 (17)	1.5 (5 to 0.5)	0.58	−0.77 (−1.7 to 0.2)	0.09
Heroin use during study	45 (27)	1.9 (5.7 to 0.7)	0.26	−0.8 (−1.6 to −0.1)	0.04
Trust in physician ≤60	42 (29)	1.6 (4.7 to 0.5)	0.46	0.3 (−0.6 to 1.1)	0.51
Self-efficacy ≥70	42 (30)	1 (0.4 to 2.7)	0.86	−0.3 (−1 to 0.6)	0.61
Low social support	25 (47)	1.1 (0.4 to 3.2)	0.95	0.01 (−0.8 to 0.8)	1.00

N indicates total number of subjects in the study with nonmissing values for the covariate; n, number of subjects showing the value of the covariate in question; N-n, number of subjects showing the opposite value of the covariate; CI, confidence interval.

TABLE 4. Multivariate Analyses (N = 72)

Covariate	Virologic Success at 6 Months		Mean Log_{10} Reduction at 6 Months	
	Adjusted OR (95% CI)	*P*	Difference in Slopes (95% CI)	*P*
High medical services	10.1 (1.3 to 79)	0.03	−0.9 (−1.7 to −0.2)	0.02
Case management services	6 (1.2 to 32.1)	0.04	−1 (−1.8 to −0.2)	0.02
Substance abuse referral	0.2 (0.1 to 1.8)	0.14	0.5 (−0.5 to 1.3)	0.33
DAST ≥6	2.7 (0.7 to 11.2)	0.17	−0.7 (−1.4 to −0.1)	0.04
Homelessness	3.4 (0.8 to 15.9)	0.13	—	—
Age ≥45 years	7.5 (1.4 to 41.7)	0.02	−1 (−1.7 to −0.4)	0.004
Male gender	0.4 (0.1 to 2.1)	0.25	0.5 (−0.3 to 1.3)	0.18
Cocaine use during study	—	—	−0.9 (−1.6 to −0.1)	0.04

Covariates that remained in the model-building process are described in text. For each of the parameters, 95% confidence intervals are in parentheses. See text for specification of description of each covariate.

These data suggest that the organization and array of services provided need to be taken into account in the design, implementation, and evaluation of DAART programs. In fact, the finding of a positive, negative, or null therapeutic effect in a DAART program may be more a function of the comprehensive (or lack thereof) nature of the program than of direct administration of medications. For example, in a recent case-control study by Lucas et al, DAART administered within a methadone maintenance program was found to be superior to a non-DAART historical control group. Methadone maintenance programs have a rich history of integrating medical and psychiatric services,[28–30] and these services may contribute greatly to the success of DAART interventions in that setting. In the main analysis of primary outcomes of our own study, DAART showed a strong effect on 6-month virologic outcomes compared with SAT.[12] In both studies, however, it is impossible to say what particular aspect of DAART contributed to the positive findings.

Oftentimes, the categorization of DAART as an adherence intervention separate from medical and case management services may be artificial. For example, the DAART specialist, by engaging the client proximate to the mobile medical services, would identify side effects and opportunistic infections and encourage the client to utilize clinical care (eg, antidiarrheals or antiemetics for acute adverse side effects) immediately on the CHCV. Similarly, our data showed a mild correlation between drug treatment and medical services utilization; this may be a reflection of the reality that for drug users, these kinds of services are intertwined. It is possible, then, that the effect of medical service utilization is more a measure of the effectiveness of the DAART specialist in engaging a particular client. Although these results cannot address these nuances and are far from definitive, they strongly suggest that these services should be incorporated into DAART programs, or what might be termed DAART-Plus, and that much attention needs to be paid to the nature and quantity of these enhanced services offered to DAART clients.

Although the presence of an effect of case management and medical services provides support for these services, the absence of an effect of drug treatment services should not necessarily argue against the provision of an on-site drug treatment program. The small sample size and possible inadequate adjustment for potential confounding variables are likely reasons for the lack of effect. Alternatively, it may be possible that there was a delayed response to drug treatment that was not evident by the end of the intervention but would only be detected if more follow-up were provided. During the course of their DAART intervention, only 17 of 72 subjects utilized drug treatment services. It is also possible that because many study participants were career drug users, they knew how to access and use drug treatment services elsewhere in the community without needing to use those available on-site.

Notably, the counterintuitive result that individuals with higher baseline DAST scores and those who reported cocaine use during the study showed improved virologic outcomes should give pause to our ability to control adequately for key substance abuse parameters. One such explanation is that the group with the greatest need received the most attention from the DAART specialist. In other unpublished observations, we have seen that DAART tends to work best for the less healthy individuals with the most severe forms of substance abuse. These self-reported drug use data, however, need to be verified using objective criteria such as urine toxicology screens. Another potential reason for a lack of effect is that many subjects do not want to access drug treatment services because of a desire to continue substance misuse. These data suggest that regardless of willingness to participate in drug treatment, the substance user can benefit from (enhanced) DAART.

The primary weakness of this study is the small sample size, which may underpower the study. Although significant at the 0.05 level, the standard errors associated with the outcomes were large, and little can be said about the true effect size. Additionally, there was no evidence of a "dose-exposure" type relation, whereby the service utilization variables showed an ordinal or quantitative relation to virologic outcomes. Furthermore, there exists the possibility of a large selection bias, because individuals who utilized services may have been those who were most engaged in their own medical care and in the DAART intervention. Finally, it must be noted that the small sample size may lead to spurious positive results, and our conclusions must be validated by future prospective studies. Hence, from this observational substudy of an RCT, we can only say that there is a likely association of improved outcomes among those subjects who utilized these services and that this result should be examined through RCTs of DAART provided with and without the availability of on-site enhanced services.

In sum, these data provide compelling support for the provision of enhanced services for active drug users—notably, case management and medical services—colocated at the site of DAART intervention programs. Further study of the more specific functioning of these services as well as the patient characteristics of those most likely to benefit is crucial in informing the ongoing debate over the utility of DAART—and potentially DAART-Plus—for improving adherence and HIV outcomes among HIV-infected drug users.

ACKNOWLEDGMENTS

The authors thank the following individuals who contributed greatly to the outcomes found in this study: Rodolfo Lopez, Marian Hoy, and Natalie Lourenco. We would also like to thank Paula Dellamura for administrative Support in the preparation of this document.

REFERENCES

1. Altice FL, Friedland GH. The era of adherence to HIV therapy. *Ann Intern Med.* 1998;129:503–505.
2. Lucas GM, Mullen BA, Weidle PJ, et al. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. *Clin Infect Dis*. 2006;42:1628–1635.
3. Lucas GM, Flexner CW, Moore RD. Directly administered antiretroviral therapy in the treatment of HIV infection: benefit or burden? *AIDS Patient Care STDs*. 2002;16:527–535.
4. Behforouz HL, Farmer PE, Mukherjee JS. From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston. *Clin Infect Dis*. 2004;38(Suppl 5):S429–S436.
5. Kagay CR, Porco TC, Liechty CA, et al. Modeling the impact of modified directly observed antiretroviral therapy on HIV suppression and resistance, disease progression, and death. *Clin Infect Dis*. 2004;38 (Suppl 5):S414–S420.
6. McCance-Katz EF, Gourevitch MN, Arnsten J, et al. Modified directly observed therapy (MDOT) for injection drug users with HIV disease. *Am J Addict*. 2002;11:271–278.
7. Conway B, Prasad J, Reynolds R, et al. Directly observed therapy for the management of HIV-infected patients in a methadone program. *Clin Infect Dis*. 2004;38(Suppl 5):S402–S408.
8. Mitty JA, Flanigan TP. Community-based interventions for marginalized populations. *Clin Infect Dis*. 2004;38(Suppl 5):S373–S375.
9. Mitty JA, Macalino GE, Bazerman LB, et al. The use of community-based modified directly observed therapy for the treatment of HIV-infected persons. *J Acquir Immune Defic Syndr*. 2005;39:545–550.
10. Wohl AR, Garland WH, Valencia R, et al. A randomized trial of directly administered antiretroviral therapy and adherence case management intervention. *Clin Infect Dis*. 2006;42:1619–1627.
11. Altice FL, Mezger JA, Hodges J, et al. Developing a directly administered antiretroviral therapy intervention for HIV-infected drug users: implications for program replication. *Clin Infect Dis*. 2004;38(Suppl 5):S376–S387.
12. Altice FL, Mezger J, Bruce RD, et al. Randomized, Controlled Trial Of Directly Administered Antiretroviral Therapy (DAART) Versus Self-Administered Therapy (SAT) Among HIV$^+$ Drug Users. World AIDS Conference, Bangkok, Thailand, July 11–16, 2004. Abstract ThP$_P$B2093.
13. Gavin DR, Ross HE, Skinner HA. Diagnostic validity of the drug abuse screening test in the assessment of DSM-III drug disorders. *Br J Addict*. 1989;84:301–307.
14. Huba GJ, Melchoir LA. *Module 64: Social Supports Form*. Culver City, CA: The Measurement Group; 1996.
15. Huba GJ, Melchoir LA. *Module 64: Self-Efficacy Form*. Culver City, CA: The Measurement Group; 1996.
16. Gilbert PB, DeGruttola V, Hammer SM, et al. Virologic and regimen termination surrogate end points in AIDS clinical trials. *JAMA*. 2001; 285:777–784.
17. Journot V, Chene G, Joly P, et al. Viral load as a primary outcome in human immunodeficiency virus trials: a review of statistical analysis methods. *Control Clin Trials*. 2001;22:639–658.
18. Davidson H, Smirnoff M, Klein SJ, et al. Patient satisfaction with care at directly observed therapy programs for tuberculosis in New York City. *Am J Public Health*. 1999;89:1567–1570.
19. Lertmaharit S, Kamol-Ratankul P, Sawert H, et al. Factors associated with compliance among tuberculosis patients in Thailand. *J Med Assoc Thai*. 2005;88(Suppl 4):S149–S156.
20. Gourevitch MN, Selwyn PA, Davenny K, et al. Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users. *Ann Intern Med*. 1993;118:350–355.
21. Scholten JN, Driver CR, Munsiff SS, et al. Effectiveness of isoniazid treatment for latent tuberculosis infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected injection drug users in methadone programs. *Clin Infect Dis*. 2003;37:1686–1692.
22. O'Connor PG, Molde S, Henry S, et al. Human immunodeficiency virus infection in intravenous drug users: a model for primary care. *Am J Med*. 1992;93:382–386.
23. Kerr T, Wood E, Grafstein E, et al. High rates of primary care and emergency department use among injection drug users in Vancouver. *J Public Health (Oxf)*. 2005;27:62–66.
24. Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Ann Intern Med*. 1993;119:1017–1028.
25. Rounsaville BJ, Anton SF, Carroll K, et al. Psychiatric diagnoses of treatment-seeking cocaine abusers. *Arch Gen Psychiatry.* 1991;48: 43–51.
26. Perdue T, Hagan H, Thiede H, et al. Depression and HIV risk behavior among Seattle-area injection drug users and young men who have sex with men. *AIDS Educ Prevent*. 2003;15:81–92.
27. Kuo I, Sherman SG, Thomas DL, et al. Hepatitis B virus infection and vaccination among young injection and non-injection drug users: missed opportunities to prevent infection. *Drug Alcohol Depend*. 2004; 73:69–78.
28. Rounsaville BJ, Weissman MM, Crits-Christoph K, et al. Diagnosis and symptoms of depression in opiate addicts. Course and relationship to treatment outcome. *Arch Gen Psychiatry.* 1982;39:151–156.
29. O'Brien CP, Woody GE, McLellan AT. Psychiatric disorders in opioid-dependent patients. *J Clin Psychiatry.* 1984;45:9–13.
30. Stein MD, Friedmann P. Need for medical and psychosocial services among injection drug users: a comparative study of needle exchange and methadone maintenance. *Am J Addict*. 2002;11:262–270.