

TABLE 1. Predictors of Atherogenic Lipid Profile According to NCEP Thresholds (Results From Separate Multivariate Logistic Regression Models)

Variable	Odds Ratio for Showing Atherogenic Lipid Levels (95% CI)		
	Total Cholesterol >6.2 mM	HDL Cholesterol <0.9 mM	Triglycerides >2.3 mM
Age (each 1 year more)	1.06 (1.01–1.11)		
Sex (female vs. male)		0.21 (0.09–0.50)	0.41 (0.22–0.80)
HCV antibody positive vs. negative status	0.19 (0.08–0.48)		
NNRTI-based vs. PI-based HAART		0.49 (0.24–1.03)	1.95 (0.28–1.00)

0.09–10.53), baseline total cholesterol (each 1 mg/dL higher, OR 1.03; 95% CI 1.01–11.05), while age, gender, HBV serostatus, baseline ALT, HIV RNA, and type of therapy were not associated. At multivariate analysis, independent predictors of total cholesterol >6.2 mM were older age and anti-HCV-positive status (Table 1). Univariate predictors of HDL <0.9 mM were NNRTI-based HAART (OR 0.44; 0.22–10.88) and female sex (OR 0.19; 0.09–10.40) but not hepatitis virus serostatus; both variables remained independent predictors of elevated HDL at multivariate analysis (Table 1). Variables associated with triglyceride levels >2.3 mM were older age (OR 1.03; 95% CI 1.00–1.07), female sex (OR 0.36; 95% CI 0.20–0.66), NNRTI-based HAART (OR 0.45; 0.25–0.84), and PI-based HAART (OR 1.95; 1.05–1.60), while hepatitis virus serostatus, baseline ALT and triglyceride levels, and viral load did not show significant associations. Virologic response showed a borderline association with triglycerides above NCEP cutoff (OR 1.88; 0.88–4.00). At multivariate analysis, factors showing an independent negative association with hypertriglyceridemia were female sex and the use of NNRTI-based HAART (Table 1).

This observational cohort study showed in HIV-infected individuals an independent association of HCV coinfection with a reduced risk of clinically relevant elevations of total cholesterol. Older age, male gender, and PI-based HAART as compared with NNRTI-based HAART were other significant predictors of an atherogenic lipid profile.

Our findings confirm and extend previous observations that coinfection with HCV is associated with a lower probability of total cholesterol elevations after HAART initiation. In particular, in HIV/HCV-coinfecting patients, 3 months after HAART initiation, we detected a mean 80% reduction in the adjusted risk of total cholesterol elevations judged clinically relevant by NCEP guidelines. Given that HCV did not show associations with HDL cholesterol levels in this study, it can be indirectly deduced that the lower risk of total cholesterol elevation is related to the non-HDL cholesterol component. While HCV had no influence on triglyceride elevations, NNRTI-based regimens as compared with PI-based as well as female sex showed a reduced probability of low HDL cholesterol and high triglyceride levels: these variables may therefore be associated with a lower cardiovascular risk. Although lipid levels represent only surrogate markers of the cardiovascular risk, factors associated with its elevations should be taken into account when choosing treatment regimens in the individual patient.

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Directly Observed Therapy for HIV Antiretroviral Therapy in an Urban US Setting

To the Editor:

In the United States, the use of antiretroviral therapy (ART) to treat HIV

has led to dramatic reductions in AIDS mortality.¹ However, not all those living with HIV in the United States have experienced the same reductions in mortality. Possible reasons for these differential death rates include tardy diagnosis, poor adherence, and differential access to health care and medications based on race, gender, class, mental illness, and substance abuse histories.²⁻⁵ Barriers to adherence with ART are complex and include a myriad of patient-, regimen-, and system-related factors.⁶ To improve HIV outcomes and reduce medical expenditures, there is a need for effective, sustainable, and replicable strategies to improve ART adherence. Directly observed therapy (DOT) has been used with success in the treatment of tuberculosis; this intervention has been suggested and piloted as a method to improve ART adherence.⁷⁻¹⁰ In Haiti, Partners In Health (PIH) successfully implemented a “DOT-ART” program in 600 patients.¹¹ For the first time, PIH’s Haiti experience has been translated to the urban United States. The Prevention and Access to Care and Treatment (PACT) Project, Boston’s first community-based integrated AIDS prevention and treatment project, initiated a program of “DOT-Plus”—home-based DOT of ART enhanced by case management and counseling. This DOT-Plus program was designed to improve HIV treatment outcomes among patients in whom self-administered ART had failed.

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METHODS

DOT-Plus Eligibility Criteria

Within 3 months prior to referral, eligible patients had a CD4 count <350 cells/ μ L and HIV viral load greater than the lowest level of detection of the available assay despite at least 6 months of ART. Patients with new diagnoses of HIV who had not been on ART for at least 6 months were excluded from the pilot study. Eligible patients also met at least two of the following criteria: an AIDS-defining illness, as defined by World Health Organization (WHO) criteria¹² within the past 2 years, hepatitis C, mental illness, as defined by *Diagnostic and Statistical Manual of Mental Disorders IV* criteria¹³ or current prescription of psychiatric medications, active substance abuse within the 30 days prior to referral, or social instability, as defined by poverty (annual income <200% federal poverty guidelines), domestic violence within the 6 months prior to referral, present homelessness, or a lack of a social support network (as defined by lack of a family or friend on whom to call in the event of a medical emergency). In addition, entry into the DOT-Plus program required living within a 20-minute drive of PACT headquarters and a baseline HIV genotype demonstrating a viable once-daily ART regimen.

Selection of Once-Daily ART Regimen

Baseline HIV genotype was performed to ensure susceptibility to once-daily ART. Referring infectious disease specialists selected the ART regimens. Prepackaged pillboxes were delivered to patients on a monthly basis.

Training of DOT-Plus Workers

Two DOT workers were recruited from the community and received 30 hours of training and 10 hours of supervised fieldwork per an established PACT curriculum. (The PACT health promoter training manual will be published shortly.)

DOT-Plus Protocol

These 2 full-time DOT workers supervised once-daily ART doses (as well as other medications) in participants’ homes 7 days per week. Visits ranged from 15–90 minutes depending on the social, cognitive, and medical needs of each participant. The DOT workers collaborated with PACT health promoters who provided the “Plus” component of the DOT-Plus protocol. PACT health promoter activities including management of social crises such as domestic violence and substance abuse, accompaniment to medical and mental health appointments, education about medications and side effect management, and adherence counseling. Education and counseling were delivered weekly according to the PACT health promoter manual. PACT health promoters communicated with DOT-Plus participants at least 3 times per week and made 1 weekly home visit. PACT health promoters and DOT workers had daily phone communication and met weekly to discuss mutual patients.

Outcome Measurement

HIV viral loads and CD4 cell counts were obtained at baseline and 1, 3, 6, 9, and 12 months. Some viral loads were performed using the bDNA assay, and some using the Roche RNA assay. Adherence rates were calculated for observed doses, with the observed dose rate equal to the number of doses observed and kept down/total prescribed doses. Occasional failure to observe doses occurred if patients did not arrive at their scheduled DOT rendezvous. Therefore, “total adherence rates,” or adherence rates for [observed + unobserved but taken and kept down doses]/total prescribed doses, were calculated. An unobserved dose was only counted as having been taken if the pillbox was appropriately empty on the following day, and the patient reported having taken the dose at the appropriate time. If the patient vomited the medications, the dose was recorded as untaken. Patient satisfaction was reported through questionnaires ad-

ministered by research assistants. Regular communication with referring physicians and chart review enabled gathering of hospitalization and illness data. Health care utilization measures of interest included hospitalization data before and after the DOT-Plus intervention.

Study Timeline

The first cohort of 7 patients was enrolled in July and August 2002, and the second cohort of 8 patients was enrolled in January and February 2003, for a total of 15 patients. Patients enrolled in the DOT-Plus protocol received PACT services until they no longer wished to participate in the program. In this paper, 6-month data are presented for all 15 patients. Twelve-month data are presented for the first cohort only, as the second cohort has not yet reached the 12-month follow-up point.

Statistical Analysis

A 2-sided Wilcoxon sign-rank test was used to determine statistical significance of changes observed in CD4 cell counts and viral load. P value <0.05 was considered statistically significant. Intention-to-treat analysis was used. All patients had CD4 and viral load data collected and analyzed, even if they had dropped out of DOT-Plus.

Internal Review Board Approval

Approval was obtained from the Brigham and Women's Hospital Internal Review Board for conducting this study.

RESULTS

Participant Recruitment and Enrollment

In June 2002, we reviewed the PACT cohort and approached 7 patients who had been receiving PACT health promotion services but still met eligibility criteria for participation in the DOT-Plus study. All 7 patients agreed to enroll and began DOT-Plus in July 2002. In December 2002, we opened enrollment to non-PACT patients, who were subject to

the same eligibility criteria as the PACT-referred patients. Area infectious disease specialists referred 20 eligible patients to our project. We approached the 8 patients with the lowest CD4 counts; all 8 agreed to enroll in the protocol.

Participant Characteristics

The 15 DOT program participants had characteristics that have been associated in the literature with nonadherence and increased AIDS morbidity and mortality: nonwhite ($n = 15$), female ($n = 10$), active substance abuse ($n = 7$), clinical depression ($n = 11$), cognitive deficit ($n = 3$). Median viral load at baseline was 121,763 copies/mL (range: 69.0– $>500,000$ copies/mL), and median CD4 count at baseline was 83 cells/ μ L (range: 8–298 cells/ μ L).

Participant Retention

The retention rate for the protocol was 87%, with only 2 study participants dropping out of DOT-Plus, one because of domestic violence and the other due to extreme depression and alcoholism. Relevant outcome data continue to be collected for these 2 patients.

Adherence

For the 13 participants who continue to receive DOT-Plus, observed adherence rates have varied from 63–95%, with an average of 81%. Total adherence rates have ranged from 86–100% with an average of 97%. Reasons for missed doses have included vomiting of pills, patients not being home for DOT visits, or refusal of pills because of nausea, pill fatigue, or potential breach of confidentiality due to guests in the home. The 2 patients who dropped out of DOT-Plus stopped their ART medications completely for the remaining months of follow-up.

Clinical Outcomes

Of the 15 participants, all of them with long histories of ART therapy, most have had dramatic reductions in viral load and increased CD4 counts. Eleven participants have HIV viral loads less

than the lowest level of detection. Using an intention-to-treat analysis ($n = 15$), decrease in median viral load from baseline was $\log_{10}2.6$ copies/mL ($P = 0.001$) at 6 months. Median CD4 count among the 15 participants increased from 83 cells/ μ L (range: 8–298 cells/ μ L) at baseline to 106 cells/ μ L (range: 11–578 cells/ μ L) at 6 months ($P = 0.11$). During the 6 months prior to enrollment, there were 10 total hospitalizations with a total length of stay of 52 hospital days for the 15 enrolled patients. Seven hospitalizations were AIDS-related with a total length of stay of 48 days. During the 6 months after enrollment, there were 5 hospitalizations with a total length of stay of 16 days for the 15 enrolled patients. Three hospitalizations were AIDS related, with a total length of stay of 5 days. One hospitalization was related to toxicity of medications (nausea/vomiting) with a total length of stay of 2 days. Thus, we observed a dramatic decrease in the number of hospitalizations and number of hospitalization days within the 6 months following initiation of the DOT-Plus protocol. Further data will be necessary to determine the statistical significance of these findings.

As a secondary endpoint, 12-month data were analyzed for the 7 patients who had reached 1 year in the program at the time of analysis. Using an intention-to-treat analysis, decrease in median viral load from baseline at 12 months was $\log_{10} 2.96$ copies/mL ($P = 0.02$). Median CD4 count increased to 192 cells/ μ L (range: 16–262 cells/ μ L) ($P = 0.22$).

DISCUSSION

Preliminary results from this community-based DOT program suggest that daily DOT of a once-daily ART regimen among a challenging urban population is both acceptable to patients and feasible. Retention rates were high and many patients who are still receiving DOT-Plus at 15 months are requesting ongoing services. Although small sample size and short follow-up time limit our conclusions, preliminary results indicate that

>90% total adherence rates can be achieved in the majority of participants, and that clinically important improvements in CD4 and viral load can be observed within a relatively short period. In addition, there is a decrease in the number of total hospitalizations and length of stay comparing the 6 months prior to and after enrollment in the DOT-Plus protocol.

We applied the success of DOT of ART in rural Haiti to the urban United States, where HIV disease is increasingly associated with poverty and marginalization. DOT-Plus was offered to patients with advanced HIV disease in whom conventional self-administered therapy had already failed. Among these AIDS patients, most with some degree of ART resistance, 11 of 15 previously unsuppressed patients subsequently achieved undetectable viral loads. These rates of viral suppression exceed those observed in sociologically similar patient populations. In one study, Lucas et al.¹⁴ reported that only 37% of patients attending an inner city comprehensive HIV clinic had viral suppression 7–14 months after ART initiation.

CONCLUSION

This study evaluates the feasibility of DOT for a subset of difficult-to-reach patients in whom unsupervised therapy for advanced HIV disease has failed. We have shown that a DOT-Plus program is feasible and acceptable among a group of patients facing myriad social problems. Preliminary results suggest clinical improvement and reduced hospitalizations. A randomized controlled study with a greater number of patients is needed to demonstrate effectiveness, long-term participant retention, viral suppression and resistance repercussions, cost effectiveness, and sustainability of this complex adherence intervention. In addition, the relative contribution of the DOT vs. the case management components of the DOT-Plus intervention as well as the eventual transition to successful self-administration will need to be evaluated.

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HIV Protease Inhibitors Increase Adiponectin Levels in HIV-Negative Men

To the Editor:

Lower levels of adiponectin, a hormone secreted by adipose tissue, have been associated with insulin resistance and increased visceral adipose tissue.^{1,2} Adiponectin has been shown to directly and rapidly decrease endogenous glucose production and improve glucose metabolism and fatty acid utilization in the liver and skeletal muscles *in vivo*.^{3,4} The relation of adiponectin to insulin sensitivity is independent of changes in other known adipocytokines, including leptin.⁵ Adiponectin is inversely associ-

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