sician did not relate this event to the antiretroviral agents. Another patient experienced nausea and vomiting and discontinued lopinavir/ritonavir after 2 days of therapy.

None of the 18 evaluable patients experienced symptoms of opioid withdrawal, no patients requested a change in methadone dosing, and there was no indication for the prescribing physician to adjust methadone dosing based on daily clinical assessment during the 28-day evaluation period after starting lopinavir/ritonavir.

The results of this study corroborate anecdotal observations and a recent report by Clarke et al.[4] showing the absence of opioid withdrawal symptoms in patients receiving methadone (median dose, 80 mg; range, 40–100 mg) concurrent with steady-state lopinavir/ritonavir. In the latter investigation, a 36% reduction in methadone AUC_{0-24h} occurred after 14 days of lopinavir/ritonavir in 8 HIV-infected patients who were also receiving 2 nucleoside reverse transcriptase inhibitors.[4] These data are consistent with the 47% decrease in methadone AUC_{0-24h} observed in 11 healthy volunteer subjects receiving concomitant lopinavir/ritonavir.[1] Despite the significant pharmacokinetic interaction affecting methadone concentrations, there was no apparent diminution of methadone pharmacodynamic activity since none of the patients in the clinical study by Clarke et al.[4] or in this report experienced opioid withdrawal symptoms or needed supplemental methadone added to their maintenance dose.

The pharmacologic mechanism characterizing the discordance between the decrease in methadone concentrations and lack of opioid withdrawal symptoms has not been fully elucidated, but several mechanisms are plausible. Methadone metabolism appears to be mediated by hepatic cytochrome P-450 enzymes 2B6 and 2C19, and the drug may undergo *N*-glucuronidation.[5,6] These metabolic routes may be induced by lopinavir/ritonavir and would account for reduction in total methadone AUC_{0-24h}, as reported previously.[1,4] Lopinavir/ritonavir may produce stereoselective induction of methadone metabolism that would differentially decrease concentrations of the inactive S-isomer more than the active R-isomer as was noted with ritonavir/saquinavir.[5] Lastly, protein binding displacement of methadone by lopinavir/ritonavir, if it occurs, could result in lower total concentrations of methadone but less of an effect on free (active) methadone concentrations.[7]

In conclusion, concurrent use of lopinavir/ritonavir and methadone did not result in opioid withdrawal or the need for adjustment of methadone dose. Findings from this investigation and others[4] indicate there is no need for routine methadone dose adjustment when initiating lopinavir/ritonavir; however, as a precaution it is still recommended to monitor for opioid withdrawal.

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Pilot Study of Directly Observed Therapy in Highly Nonadherent HIV-Infected Patients in an Urban Community-Based Institution

To the Editor: The availability of highly active antiretroviral therapy (HAART) has drastically reduced AIDS mortality.[1] In spite of an almost universal availability of HAART in the United States, many challenges remain in the management of HIV. It has been shown that the most important predictor of sustained virologic suppression is adherence to HAART.[2] Also, virologic failure is directly associated with the degree of nonadherence.[3] HIV disease requires a potentially lifelong treatment. Since it is not feasible to provide directly observed therapy (DOT) indefinitely, there is a need to develop new DOT strategies. There have been studies to understand the feasibility of DOT as an adherence strategy. DOT for the management of HIV infection has been shown to be effective in pilot programs. So far, studies have evaluated DOT in special circumstances like clinical trials[4] and institutionalized patients such as substance abuse treatment programs[5–7] and prisons.[8,9] These results suggest that DOT is a viable option in such a controlled environment. However, these cohorts represent only a subset of the HIV patient population. Therefore there is a need to study DOT in other settings such as in a community-based clinic in a large urban area. Very few studies have so far evaluated DOT in outpatient settings.[10] The topic is addressed in this study.

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HIV-infected patients recognized by their provider to be nonadherent were referred to the DOT study. We have shown previously that adherence patterns have been improved through DOT with positive outcomes.[11] Based on this experience, we planned to have an outpatient DOT program for a 6-week period when drug compliance was monitored by an assigned case manager/volunteer after educational and adherence classes. After enrollment, patients were started on a regimen of saquinavir-soft gel (Fortovase, Hoffman La Roche), 1600 mg; boosted with ritonavir (Norvir, Abbott), 100 mg; and didanosine (Videx, Bristol Myers Squibb), 400 mg; combined with either efavirenz (Sustiva, Bristol Myers Squibb), 600 mg, or nevirapine (Viramune, Boerhinger Ingelheim), 400 mg once daily. Patients were visited daily for 5 days in a week (Monday to Friday) by an observer/volunteer to observe patients taking the medications. On weekends a MEMs-CAP reading was obtained. HIV viral load and $CD4^+$ cell counts were obtained at baseline and at 4, 8, 12, 16, 20, and 24 weeks. A 2-sided *t* test was used to determine the statistical significance of the changes observed in $CD4^+$ cell counts and viral load and a *P* value of <0.05 was considered to be statistically significant. Data were calculated using an intent-to-treat analysis (with all participants enrolled in the study, here n = 14) and an on-treatment analysis (with only those completely exposed to DOT intervention).

Twenty patients were referred to the study. Two patients (both women) did not meet inclusion criteria during screening. Of the remaining 18 (all men), 3 did not return for baseline visits after screening. One was discontinued 4 weeks into the DOT phase for administrative and disciplinary reasons. For the 14 patients in the study, average $CD4^+$ cell counts were 107 cells/μL (range: 8–367) and viral load was $\log_{10}$ 5.5 copies/mL [297,658 copies/mL (range: 2254–750,000)]. Six of 14 did not complete the study. Two of them did not tolerate medications, 2 developed resistance during the study and were switched to a different regimen, and 2 were lost to follow-up during the DOT phase. Eight completed the 6-week DOT phase. All 14 patients were followed with $CD4^+$ cell counts and viral load until completion of the study (24 weeks). Figures 1 and 2 summarize the changes in $CD4^+$ cell counts and viral load over time. Using intent-to-treat analysis (n = 14), the incremental mean $CD4^+$ cell count changes (increase) from baseline were, at 12 and 24 weeks respectively, 77 cells/μL ($P < 0.05$) and 37 cells/μL ($P > 0.05$). Using an on-treatment analysis (n = 8), changes at 12 and 24 weeks were increased by 71 cells/μL ($P < 0.05$) and 65 cells/μL ($P < 0.05$), respectively. Similarly, in the intent-to-treat analysis, decreases in viral load from baseline were, at 12 and 24 weeks respectively, $\log_{10}$ 0.5 copies/mL ($P < 0.05$) and $\log_{10}$ 0.1copies/mL ($P > 0.05$). In the on-treatment analysis, the decreases in viral load from baseline were, at 12 and 24 weeks respectively, $\log_{10}$ 1.2 copies/mL ($P < 0.05$) and $\log_{10}$ 0.7 copies/mL ($P < 0.05$).

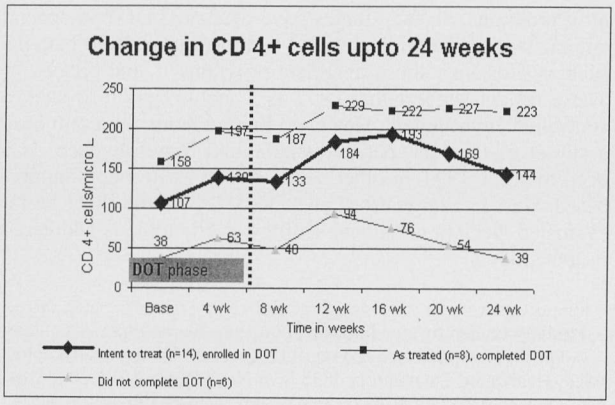

FIGURE 1. Changes in CD4+ cell counts

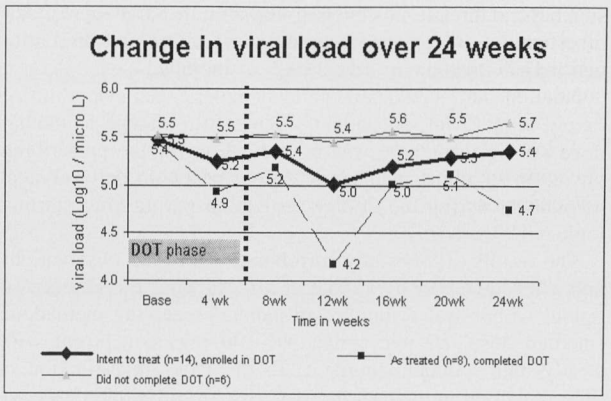

FIGURE 2. Changes in HIV-viral load

The results of our pilot program reveal that 6 weeks of DOT resulted in improvements in $CD4^+$ cell counts and viral loads at 6 months, especially in those who completed the 6 weeks of DOT intervention. Improvements in viral load followed a pattern similar to $CD4^+$ cell count changes, but the changes were maintained for longer duration. Intuitively, the more intensive and longer the DOT phase, the more impressive the outcomes and the longer they are sustained. It would be reasonable to assume that intensive adherence interventions have the greatest impact early in the process, with the effects waning over time. In our study, markers of HIV (average $CD4^+$ cell counts and viral load) improved during the 6 weeks of DOT intervention and after, but were not sustained (i.e., they plateaued or returned to baseline depending on whether the subject completed DOT or not). Even in those who had an increase in $CD4^+$ cell counts at the end of the study at 24 weeks, we cannot be sure that they will remain adherent and continue to maintain this benefit beyond this period. We have previously reported different patterns of adherence in HIV patients.[12] Extrapolating from this existing knowledge, it appears that a proportion of patients will relapse to nonadherence after completion of the DOT phase and they may continue to deteriorate. This group of patients may have to be reenrolled in a DOT program within 5 or 6 months when the effects of DOT tend to wear off. Perhaps they will benefit from a repeat DOT therapy—"re-DOT therapy" or "intermittent DOT therapy." Studies with longer follow-up periods are needed to assess this.

Our study has several limitations, such as sample size, other confounding factors, and the choice of therapy. With more drugs offering once-a-day dosing and with better tolerability, there will be wider choices available for DOT.

Our results suggest that a 6-week outpatient-based DOT aimed at improving adherence to HAART leads to a decline in viral load up to 24 weeks. However, we believe longer duration of intervention will yield more impressive and sustainable outcomes. Outpatient-based DOT seems feasible, if resources are available, and could be beneficial in maintaining viral suppres-

sion beyond the intervention period and up to 24 weeks. Further investigations that are larger and randomized are needed to refine DOT approaches and confirm the benefits in different populations and settings.

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Changes in Metabolic Profile Among Antiretroviral-Naive Patients Initiating Protease Inhibitor Versus Non–Protease Inhibitor Containing HAART Regimens

To the Editor: Lipodystrophic syndrome, insulin resistance, and frank diabetes are emerging as important metabolic consequences of protease inhibitor (PI) therapy in patients with HIV.[1–3] These metabolic abnormalities may be due to direct effects of PI on rates of whole body lipolysis, differentiation and apoptosis of adipocytes,[4] and inhibition of glucose transporter activity.[5] There are few prospective studies examining metabolic profiles in antiretroviral (ARV)-naive patients, in a clinical setting.

The study protocol was approved by the Baylor College of Medicine Institutional Review Board. Eligible patients were ARV naive, able to give informed consent, and initiated on a highly active antiretroviral therapy (HAART) regimen. Exclusion criteria included history of type 1 or 2 diabetes, endocrine disorders, acute illnesses, and use of drugs known to interfere with insulin secretion or action. Initially, 131 patients screened in for the study. Seventy-nine of these patients were subsequently initiated on HAART and therefore enrolled into the study. Of these, 41 were initiated on a PI-based regimen and 38 were on PI-sparing regimens. In the PI group, 4% of patients were on saquinavir/ritonavir, 16% were on indinavir/ritonavir, and 80% were on nelfinavir. In the PI-sparing group, 22% were on abacavir, 34% were on nevirapine, and 44% were on efavirenz.

Demographic and medical history data were collected by medical record review. Levels of low-density lipoprotein (LDL) cholesterol were calculated using the Friedewald formula.[6] Serum insulin levels were measured by radioimmunoassay and insulin resistance was assessed by the homeostasis model of assessment.[7] Anthropometry and laboratory measurements were repeated 6 months after initiation of HAART therapy. Baseline characteristics were compared between patients started on PI versus PI-sparing therapy using the Student t test, χ^2, or Fisher exact test as appropriate. A paired t test was used to test for differences within each group in values of variables from baseline to 6 months. Between-group differences in the change score for each variable in the PI versus PI-sparing groups were tested using Student t test.

Thirty-seven percent of the initial 131 patients had family history of premature coronary heart disease (CHD), 63% were current smokers, 8% had diabetes or existing CHD, almost half had high-density lipoprotein (HDL) cholesterol <40 mg/dL, a quarter had hypertension, 11% had Framingham risk score >10%, and 16% met the Adult Treatment Panel III definition for metabolic syndrome. Forty-six percent of the initial cohort had ≥2 risk factors and 27% had 1 risk factor for CHD.

At baseline, there was no difference between groups in age (median, 38 years), sex (35% female), race (67% African-American), viral load (median, 4.8 $\log_{10}$ HIV RNA copies/mL), and CD4 counts (median, 140 cells/mm^3). The 2 groups were similar in terms of metabolic variables such as

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