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# Impact of an Adherence Clinic on Behavioral Outcomes and Virologic Response: Results from a Prospective, Randomized, Controlled Pilot Study

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## Abstract

**Background:** Adherence clinics have the potential to improve response to highly active antiretroviral therapy (HAART), but controlled trials are limited and do not account for regimen-related characteristics. A randomized, controlled pilot study was conducted to examine the effect of an adherence clinic on adherence and virologic outcomes over a 28-week period.

**Methods:** Consecutive eligible patients beginning new HAART in an indigent care clinic were randomized to an adherence clinic (AC) or to their primary care provider (PC) for education and monitoring. Group assignment was stratified prior to randomization according to antiretroviral regimen complexity (BID vs.  $\geq$  TID) and potential tolerability (ritonavir vs. non-ritonavir regimen). Patients in the AC group received active intervention in the adherence clinic for up to 12 weeks, consisting of education about appropriate HAART administration, food restrictions, side effect management strategies, and monitoring patient progress after therapy initiation. Adherence (electronic monitoring, patient self-report) and viral load (RT-PCR) end point assessments were performed at weeks 4, 16, and 28. All analyses were performed as intent-to-treat (ITT).

**Results:** Thirty-three randomized patients (AC, n = 16; PC, n = 17) comprised the ITT population. The majority of patients had received prior HAART (78%) and had an AIDS diagnosis (79%). Antiretroviral therapy included PI-based HAART (49%), NNRTI-based HAART (39%), and NNRTI/PI combinations (12%). The two groups were well-matched with respect to demographics and antiretroviral regimen. Mean adherence in the AC group at weeks 16 and 28 was 77% and 74% vs. 56% and 51% in the PC group (difference: 21.4% [90% CI: 1.1-41.7], 22.8% [90% CI: 1.2-44.4], respectively). The AC group had a greater proportion of patients who took their medication on schedule (69% vs. 42%; p = .025) and was more likely to exhibit  $>90\%$  adherence at week 4 (81% vs. 47%; p = .07). The proportion of patients with HIV-1 RNA  $<400$  copies/mL at week 16 was greater in the AC group (100% vs. 71% in the PC group; p = .04) and approached significance at weeks 4 and 28 (62% vs. 29% and 94% vs. 65%, respectively; p = .08).

**Conclusions:** Adherence and virologic response were consistently higher in patients followed in an adherence clinic over 28 weeks. This preliminary study suggests that an adherence clinic care model can improve adherence behavior and viral suppression with HAART.

## Background

Highly active antiretroviral therapy (HAART) has been demonstrated to decrease the morbidity and mortality associated with HIV infection [1]. Adherence to antiretroviral therapy is vital to achieve effective suppression of HIV replication and subsequent delay of disease progression. It is evident that high rates of adherence ( $>95\%$ ) for sustained periods of time are necessary for many patients to maintain virologic suppression [2,3]. However, significant barriers to adherence exist for patients with HIV infection. In addition to psychosocial aspects of the disease (e.g., denial, depression), drug toxicity, dosing frequency, food restrictions, and the necessity of taking medications on a strict schedule can all contribute directly or indirectly to non-adherence behaviors [4]. Therefore, effective education and management strategies that promote adherence are essential to produce desired virologic outcomes in many patients. An adherence clinic care model where patients receive structured, individualized education and follow-up monitoring has been implemented in some practice settings [5-10]; however, limited evidence has existed until recently regarding the incremental benefit of these services on adherence behavior and treatment outcomes [11-13].

## Objective

To evaluate the ability of an adherence clinic to improve treatment outcomes from antiretroviral therapy in indigent patients with HIV infection by promoting medication adherence.

## Methods

**Study Design:** Prospective, randomized, controlled trial.

**Stratification:** Prior to randomization, patients were stratified according to:

- Regimen complexity (BID vs.  $\geq$ TID dosing schedule)
- Regimen side effect profile (ritonavir vs. non-ritonavir regimen)

**Randomization:** Consecutive eligible patients were randomized in blocks of 4 to either the Adherence Clinic (AC) or their primary care provider (PC).

**Blinding:**

- Physician and the clinic nurse practitioner were unaware of group assignment.
- Clinical pharmacist was blinded to viral load results in the Primary Care group; physician and nurse practitioner were non-blinded to viral load results in both groups.
- All practitioners were blinded to adherence measurements.

## Methods (cont.)

**Patients:**

- Indigent/low income HIV-1 infected patients in the Ryan White Title IIIb HIV clinic located on the University of Oklahoma Health Sciences Center.

**Primary Inclusion Criteria:**

- Initiating a new combination regimen including either a PI or an NNRTI
- Patient responsible for self-administering medications.

**Primary Exclusion Criteria:**

- Treatment with a once-daily antiretroviral regimen or a triple NRTI regimen.
- Patients receiving a salvage regimen (suspected/documented resistance  $\geq 2$  agents).
- Patients currently participating in a pharmaceutical company-sponsored antiretroviral clinical trial or actively followed in the adherence clinic.

**Adherence Clinic Intervention:**

**Clinic visit at baseline prior to HAART initiation:**

- Discuss role of HAART
- Review common side effects and management strategies
- Design administration schedule
- Discuss consequences of non-adherence

**Follow-Up:**

- Phone follow-up at 1 week
- Clinic visit at week 2 to assess side effects and scheduling issues
- Clinic visit at week 4 concurrent with lab visit to assess adherence
- Additional visits scheduled up to week 12 depending on patient's needs

**Adherence Assessment:**

- Electronic monitoring cap (eDEM™ Monitoring System, AARDEX® Ltd.) was placed on one of the antiretroviral medications (typically PI or NNRTI) at the time therapy began. Electronic monitoring was performed for the duration of the 28-week study period, with scheduled scanning at weeks 4, 16, and 28.
- Validated, two-page questionnaire (Brief Medication Questionnaire [14]) used to assess self-reported adherence over the previous 7 days at weeks 4, 16, 28.

**Virologic Assessment:**

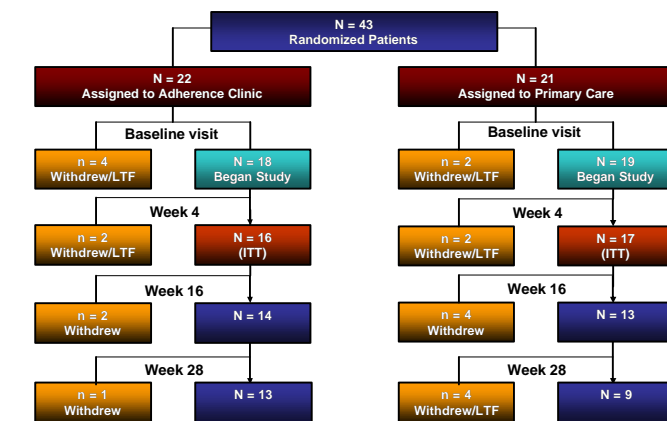
- Plasma HIV RNA (RT-PCR) measured at weeks 4, 16, and 28; existing values within 12 weeks of new HAART initiation were used as baseline.
- Specimens were archived on virology collection dates to allow quantitation to  $<50$  copies/mL if the standard assay yielded an undetectable level ( $<400$  copies/mL).

**Data Analysis:**

- Intention-to-treat (ITT) analysis includes all randomized patients who reached the first study endpoint visit at Week 4.
- Missing eDEM™ data were calculated as missed doses.
- Missing virology data were imputed for analysis (last observation carried forward)
- Fishers exact test (2 sided) was used for dichotomous variables.
- T test (2 sided) was used for continuous variables.

Adherence was calculated as: 1) the percentage of doses consumed divided by the number of prescribed doses within the monitoring period (**consumption**) and, 2) the percentage of doses taken within 1.5 hours of the scheduled administration time (**dose precision**).

## Results



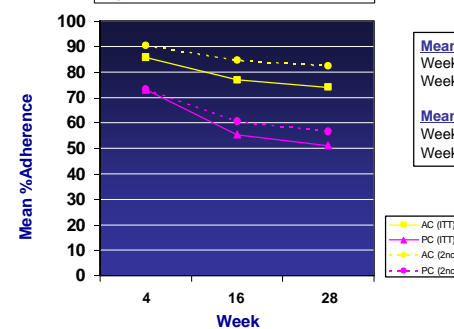
## Results

**Table 1: Baseline Characteristics (ITT Population)**

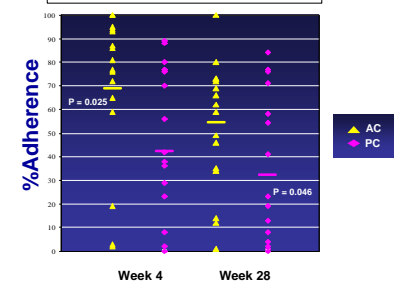
Variable	Adherence Clinic (n = 16)	Primary Care (n = 17)
<b>Demographics</b>		
Age, yrs (median)	38.0	38.0
Sex, male	12 (75%)	16 (94%)
Caucasian	12 (75%)	11 (65%)
African American	2 (12%)	5 (29%)
Hispanic	2 (12%)	1 (6%)
<b>Laboratory Values</b>		
Plasma HIV RNA (median)	22,025 copies/mL*	176,932 copies/mL
CD4 cell count (median)	296 cells/ $\mu$ L	104 cells/ $\mu$ L
<b>AIDS Diagnosis</b>		
CD4 $<200$	2 (12%)	5 (29%)
CDC Category C Condition	9 (56%)	10 (59%)
<b>HAART Experience</b>		
Treatment Naive	3 (19%)	5 (29%)
Treatment Experienced	13 (81%)	12 (71%)
<b>HAART Regimen</b>		
2 NRTIs + NNRTI	6 (38%)	7 (41%)
2 NRTIs + 2 PIs	7 (44%)	6 (35%)
3 NRTIs + 2 PIs	2 (12%)	0 (0%)
2 NRTIs + PI	0 (0%)	1 (6%)
1-2 NRTI(s) + NNRTI + 2 PIs	1 (6%)	3 (18%)

\*50% of patients in the AC group were on their previous HAART regimen at the time the baseline viral load was drawn vs. 18% in the PC group

**Figure 1: Adherence over 28 Weeks**



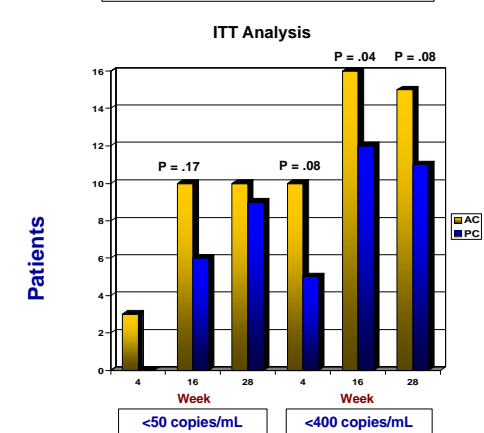
**Figure 2: Dose Precision ( $\pm 1.5$  Hr)**



Dose Precision at Weeks 4 and 28. Horizontal bars represent mean dose precision for the Adherence clinic group ( $\Delta$ ) and the Primary care group ( $\diamond$ ) at both respective time points.

## Results (cont.)

**Figure 3: Viral Suppression**



## Summary

- Patients who received education and monitoring in the adherence clinic demonstrated consistently higher adherence than patients receiving standard care (ITT analysis; Figure 1).
- When data were censored for four patients (AC = 2, PC = 2) who stopped or intermittently used their eDEM™ device (2<sup>o</sup> analysis), mean adherence in the AC group at weeks 16 and 28 was 85% and 82%, respectively, vs. 61% [P = .049] and 57% [P = .047] in the PC group, respectively (Figure 1).
- Patients in the Adherence Clinic group were significantly more precise in the administration timing of the monitored antiretroviral agent (Figure 2; 69% vs. 42% at Week 4; P = 0.025).
- Viral suppression to  $<400$  copies/mL and  $<50$  copies/mL was consistently greater in the Adherence Clinic group than the Primary Care group (Figure 3).

## Conclusions

Patients who receive education and monitoring in an adherence clinic demonstrated greater adherence and virologic suppression compared with patients educated only by their primary care provider.

## Acknowledgements

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