

Proactive Telephone Support from a Central Site to Improve ART Adherence: A Multi-site, Randomized Controlled Trial ACTG 731, an Adherence Substudy of ACTG 384

Nancy R. Reynolds^{1*}, Marcia A. Testa², Max Su³, Margaret A. Chesney⁴, Judith L. Neidig¹, Ian Frank⁵, Scott R. Smith⁶, Jeanette R. Ickovics⁷ and Gregory K. Robbins⁸ for the ACTG 731 and ACTG 384 Teams

¹Ohio State University, Columbus, OH; ²Harvard School of Public Health, Boston, MA; ³Phase V Technologies, Inc, Boston, MA; ⁴NCCAM, National Institutes of Health, Bethesda, MA; ⁵University of Pennsylvania, Philadelphia, PA; ⁶Agency for Healthcare Research and Quality, Rockville, MD; ⁷Yale University, Hartford, CT; ⁸Massachusetts General Hospital, Boston, MA.

Abstract

Background: Adherence to medication is critical to the success of antiretroviral therapy (ART). A number of adherence interventions have been employed, but to date there is little evidence supporting specific interventions to improve adherence to ART. This pilot study, ACTG 731, was conducted to determine whether an intervention delivered by telephone would improve adherence outcomes of persons starting ART.

Methods: The RCT was conducted with ART-naïve subjects (N=109) enrolling in ACTG 384 at 5 U.S. sites. Subjects (85% male, 51% white, mean HIV RNA of 442,406) consented to 731 were randomly assigned to receive standard care or standard care plus 12 structured telephone calls. The calls, delivered over the first 16 weeks of ART by a nurse at a central site (in accordance with HIPAA), were structured to proactively address common barriers to ART adherence and recommend self-management strategies. Outcome measures were collected over 64 weeks and included an ACTG adherence questionnaire, MEMS, and 384 study endpoints. Data were analyzed using descriptive, mixed model for repeated measures, Kaplan-Meier, and Cox PH regression techniques.

Results: The rate of self-reported adherence was high in both treatment groups [98%, mean wks 4-64] with over 64% reporting perfect adherence. Even with a sizeable ceiling effect, a significantly better overall treatment effect was observed in the telephone group (p=0.023). In a post-hoc analysis, the difference in overall treatment effect was strengthened (p<0.001) when the comparison was limited to subjects reporting <100% early adherence [mean wks 64 = 96% (telephone)/91% (SOC)]. Self-reported adherence was significantly associated with adherence as measured with MEMS. Comparing time to primary regimen failure, the KM survival curve for the telephone group remained above the SOC across weeks 20-64; a Cox PH model that controlled for baseline RNA stratification, baseline CD4, gender, age, race/ethnicity, and randomized ART Tx arm, showed telephone calls were associated with a lower relative hazard (HR = .68, 95% CI: .38-.1.23) for regimen failure, but the difference was NS (p=0.21).

Conclusions: Findings indicate that proactive telephone calls delivered from a central site unaffiliated with subjects' trial sites can improve adherence. The treatment effects appear durable, however, the intervention needs to be tested in a larger population with greater variance in rates of adherence to fully establish clinical benefits.

Introduction

- Poor adherence to medication is a major obstacle to successful treatment outcomes; interventions that improve adherence are needed.
- There is currently little evidence supporting specific approaches for improving adherence to antiretroviral regimens.
- We hypothesized that regular telephone calls delivered by a trained registered nurse and structured to proactively address common barriers to ART adherence and teach problem solving strategies would improve adherence and virologic outcomes.

Aim

- To determine whether structured, proactive telephone support improves adherence to antiretroviral therapy and clinical outcomes as compared to standard care.

Design

- Repeated measure, RCT design conducted with ART-naïve subjects (N=109) enrolling in ACTG 384[†] (parent study) at 5 U.S. sites.
- Participants randomly assigned to receive standard care or standard care plus 12 structured telephone calls.
- The calls, delivered over the first 16 weeks of ART by a nurse at a central site, were structured to proactively address common barriers to ART adherence and recommend problem-solving strategies.
- Outcome measures were collected over 64 weeks and included an ACTG adherence questionnaire[‡] and 384 study endpoints.

Methods

Sample:

- ACTG 731 was open to ACTG 384 participants at five U.S. ACTG sites: Ohio State University, University of North Carolina, University of Pennsylvania, Washington University and University of Nebraska.
- Subjects (N=109) were 85% male; 51% Caucasian, 43% Black; mean age 36.8 yrs; plasma HIV-1 RNA 442,406; CD4 236.

Comparison of treatment groups at entry (pretreatment)

Baseline Characteristics	Telephone & Standard Care (N=54)	Standard Care Only (N=55)	F	Df	P value
Age (mean)	36.4	37.2	.21	1	.64
Male (%)	83.3	87	1	1	.81
White, not Hispanic (%)	45.5	57.4	4	1	.38
Education (% <HS)	48.1	54.7	4	1	.49
CD4 cells/mm ³	243	228	.16	1	.69
HIV viral load	514,902	368,567	.57	1	.45
Prior (Non-ART) adherence [§]	98.9	98	1.2	1	.25
Depression [¶]	71.15	74.10	.69	1	.43
Self-Efficacy	69.97	72.90	.38	1	.55
Stress ^{¶¶}	62.37	61.90	.02	1	.88
Social Support ^{¶¶¶}	62.70	70.41	1.3	1	.25
Symptoms ^{¶¶¶¶}	78.44	82.61	.93	1	.33

Note: † 0-100 scale, higher better

No statistically significant difference was found between the groups pretreatment.

Measures:

- Clinical assessments and plasma HIV-1 RNA measurements were obtained at screening, entry, weeks 4, 8, 12, 16, 20, and 24, and every eight weeks thereafter per ACTG 384 protocol.
- Adherence was measured with the ACTG Adherence Questionnaire[‡] -- Percentage of doses reported missing for each antiretroviral 1, 2, 3 and 4 days ago, averaged over all antiretroviral medications.
- HIV-1 RNA levels were measured with HIV polymerase-chain-reaction assay (Roche ultrasensitive Amplicor assay, version 1.0) with a lower limit of detection of 50 copies per milliliter at a central laboratory.

Treatment:

- **Standard Patient Education (Control Condition).** All participants received standard ACTG patient education by a registered nurse or pharmacist at his/her participating site using ACTG Patient Care Committee education materials.
- **Telephone Support (Experimental Condition).** In addition to the standard ACTG patient education, the telephone group received regular telephone calls from a trained registered nurse. The telephone nurse specialist attempted to contact the participant at each of weeks 1-12, 14 and 16. Up to six attempts were made per scheduled contact point.

The telephone calls were delivered from a single, centralized site in order to prevent dispersion of the intervention to participants who served as the controls at the study sites; Participants did not have face-to-face contact with the telephone nurse specialist.

Tailored counseling regarding strategies to remember and integrate medication-taking into daily living and effectively solve problems that commonly threaten adherence over time (e.g., side effects, altered moods).

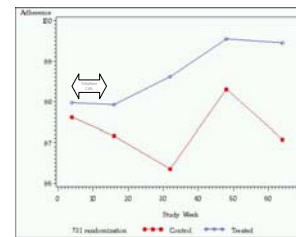
Analyses:

Data were analyzed using descriptive, mixed model for repeated measures, Kaplan-Meier, and Cox PH regression techniques.

Results

The rate of self-reported adherence was high in both treatment groups [98%, mean wks 4-64] with over 64% reporting perfect adherence.

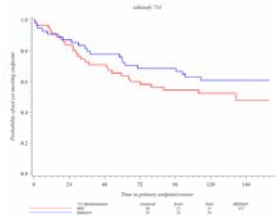
Comparison mean adherence over time



A better overall treatment effect (p = 0.023) was observed in the treated (telephone) group (N=54) in comparison with standard care (control) group (N=55).

In a post-hoc analysis, the difference in overall treatment effect was strengthened (p<0.001) when the comparison was limited to subjects reporting <100% early adherence (N= 39). Mean adherence at week 64 = 96% (telephone group) vs. 91% (SOC group).

Time to primary regimen failure



Comparing time to primary regimen failure, the KM survival curve for the telephone group remained above the SOC across weeks 20-64

A Cox PH model that controlled for baseline RNA stratification, baseline CD4, gender, age, race/ethnicity, and randomized ART Tx arm, suggested telephone calls may be associated with a lower relative hazard (HR = .68; 95% CI: .38-1.23) for regimen failure, but the difference was NS (p=0.21).

	Hazard ratio	95% lower confidence limit for HR	95% upper confidence limit for HR	PR > Chi square
ACTG 731 randomization	0.68	0.38	1.23	0.21

Notes:

- (1) There was no suggestion of benefit of structured calls with Cox PH models for other 384 main study endpoints: Primary endpoint (time to second regimen failure for 3-drug arms, and first regimen failure for 4-drug arms) and secondary endpoint (first virologic failure). The lack of a significant effect for the primary endpoint may have been in part due to the fact that "premature discontinuations" were included whereas they were censored for the first regimen failure analysis.
- (2) The effect of structured adherence calls in delaying first regimen failure appeared to be delayed, and became apparent after the calls had ceased (week 16).

Conclusions

- Findings are promising.
- Our ability to demonstrate the effects of the proactive telephone support was limited by the high rates of adherence observed in both the treatment and standard care groups.
- The treatment effects appear durable.
- The strength of study findings may be attributable to the centralized approach used for delivery of the telephone intervention and emphasis on patient-centered approach.
- The intervention needs to be tested in a larger population with greater variance in rates of adherence to fully establish clinical benefits.

Acknowledgements

Support:

U.S. NIH, NIAID, Adult AIDS Clinical Trials Group (A138858), The Ohio State University (A125924), Harvard University (A127659), and University of North Carolina (A125868) AIDS Clinical Trial Units. We wish to thank the participating ACTU personnel and study volunteers for their contributions to this project.

We would also like to acknowledge the contributions of the ACTG 384 team: Robert W. Shafer, Victor De Gruttola, Sc.D., M.D., Laura M. Smeaton, M.S., Sally W. Snyder, Carla Pettinelli, M.D., Ph.D., Ana I. Martinez, R.Ph., Michael P. Dube, M.D., Margaret A. Fischl, M.D., Gene D. Morse, Pharm.D., Richard B. Paulard, M.D., Robert Delapenha, M.D., Mostafa A. Nokes, M.D., Stephen Safran, PhD, Linda Gedeon, Tom Nevir, Mark I. Becker, Pharm.D., Mary Swingle, R.N., S. Debra McCarty, M.D. Richard T. D'Aquila, M.D., Stefano Vella, M.D., Thomas C. Merigan, M.D., Martin S. Hirsch, M.D.

References:

- Robbins, G.K. et al. (2003). Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *NEJM*, 349, 2293-2303.
- Chesney, M.A., Ickovics, J.R., Chambers, D.B., Gifford, A.L., Neidig, J., Zwicik, B. and Wu, A.W. (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG Adherence Instrument. *AIDS Care*, 12, 255-266.