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Managed Problem Solving for Antiretroviral Therapy Adherence: A Randomized Trial

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Abstract

Background—Adherence to antiretroviral therapy is critical to successful treatment of HIV. Few interventions have been demonstrated to improve both adherence and virological outcomes. We sought to determine whether an intervention derived from problem solving theory, Managed Problem Solving (MAPS), would improve antiretroviral outcomes.

Methods—We conducted a randomized investigator blind trial of MAPS compared with usual care in HIV-1 infected individuals at three HIV clinics in Philadelphia, PA. Eligible patients had plasma HIV-1 viral loads >1000 copies/ml and were initiating or changing therapy. MAPS consists of four in-person and 12 telephone-based meetings with a trained interventionist, then monthly follow-up calls for a year. Primary outcome was medication adherence measured using electronic monitors, summarized as fraction of doses taken quarterly over one year. Secondary outcome was undetectable HIV viral load over one year. We assessed 218 for eligibility, with 190 eligible and 180 enrolled, 91 randomized to MAPS and 89 to usual care. 56 participants were lost to follow-up: 33 in MAPS and 23 in usual care.

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The authors have declared that no competing interests exist.

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Results—In primary intention-to-treat analyses, the odds of being in a higher adherence category was 1.78 (95% CI:1.07–2.96) times greater for MAPS than usual care. In secondary analyses, the odds of an undetectable viral load was 1.48 (95% CI: 0.94–2.31) times greater for MAPS than usual care. In as-treated analyses, the effect of MAPS was stronger for both outcomes. There was neither a difference by prior treatment status nor change in effect over time.

Conclusions—MAPS is an effective antiretroviral adherence intervention over the first year with a new regimen. It was equally effective at improving adherence in treatment experienced and naïve patients and did not lose effect over time. Implementation of MAPS should be strongly considered where resources are available.

Trial Registration—ClinicalTrials.gov, NCT00130273

Introduction

Adherence to pharmacotherapy is key to preventing progression of treatable chronic diseases. Unfortunately, clinically significant non-adherence is common in diabetes [1], hypertension [2], hypercholesterolemia [3], and HIV [4], for example. Adherence barriers include depression [5], substance abuse [6], regimen complexity [7], poor social support [8], and low health literacy [9,10], among others. Adherence interventions have had limited effects, which often wane over subsequent months [11–13].

Patients may have multiple adherence barriers and so personalized strategies addressing multiple barriers hold the greatest promise for success. We developed Managed Problem Solving (MAPS) to address barriers to chronic pharmacotherapy adherence. It derives from Problem Solving Therapy (PST), an effective intervention for depression [14]. PST trains individuals in generalizable problem-solving skills including identification of difficulties, generation of solutions, and evaluation of outcomes [15]. It has been adapted to address coping with cancer and schizophrenia, family caregiving, and family relationships [16–18]. MAPS differs from PST; the participant is not trained to become a better generalized problem solver *per se*. Rather, the interventionist and participant work together to solve specific adherence barriers using the Problem Solving framework. An overlap with PST is starting with small, achievable goals to ensure success and establish credibility. Notably, MAPS does address some problems that patients believe are important, but are only indirectly related to medication adherence. This may reduce stressors that interfere with adherence and encourage continued participation.

We assessed whether MAPS resulted in better adherence to therapy for HIV than usual care. We chose antiretroviral therapy because the relationship between adherence and outcome was well described [19–22], as were the ensuing consequences of disease progression [23], further HIV transmission [24], and emergence of resistance [25].

Methods

Ethics Statement

The study was approved by the Committee on Human Subjects Research of the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center. All participants provided informed consent and were compensated $30 per data collection visit, but not intervention visits, for a total of $270 if all visits were completed. A Data and Safety Monitoring Committee reviewed severe intervention-related adverse events (e.g., suicidality). There were no early stopping rules. The ClinicalTrials.gov number is NCT00130273.

Study setting and participants

We conducted a randomized investigator-blind trial comparing MAPS to usual care in HIV-1 infected individuals. Recruitment was facilitated by flyers in the clinics and weekly querying of pharmacists and prescribers regarding potential patients at the two HIV clinics in the University of Pennsylvania Health System and the HIV clinic at the Philadelphia Veterans Administration Medical Center. Usual care included meeting with a pharmacist for regimen education and, if desired, provision of pill organizers.

Inclusion criteria were age ≥18 years, HIV-1 plasma viral load>1000 copies/ml, and being treatment naïve and initiating a standard regimen, or treatment experienced and either: 1)restarting their most recent suppressive regimen after >3 months off or 2)initiating a new regimen with three new antiretrovirals with resistance profiles different from their initial regimen or fully susceptible on an HIV resistance assay. After study initiation, we expanded criteria to include regimens with at least two fully active and one partially active drug based on a resistance assay. Treatment responses for this subpopulation were expected to be sufficiently similar to those for fully active regimens to allow for valid conclusions regarding the effect of the intervention on virologic outcome [26]. Exclusion criteria were inability to consent and residence in a setting with automatic medication delivery.

Permuted block randomization with 1:1 allocation was performed in random block sizes of 6–9 individuals. The biostatistician generated a randomization list by computer and placed assignments into sealed security envelopes numbered sequentially and maintained in a locked drawer by the study coordinator. At enrollment, the study coordinator selected the next envelope, which was opened only after consent. The investigators were blinded by prohibiting their access to the data and contact with participants.

Interventionists and Intervention

Interventionists were required to have a college degree and some prior experience working with a patient population. We trained three interventionists during the trial with 15 hours of training covering essentials of HIV management, behavioral science topics including depression and substance abuse, and the Managed Problem Solving treatment manual (available online — XXurlXX).

Managed problem solving consisted of a 5-step process of identifying participants' barriers to adherence, brainstorming for potential solutions, selecting the best option, monitoring its implementation, and whether the participant considered the implementation useful, and the participant's adherence. Unsuccessful plans were revised repeating the process. These activities were iterated over the first three months until an effective solution was chosen or no further options could be generated. Baseline screening aided in identifying common potential adherence barriers, using CES-D for depressive symptoms [27], the AUDIT [28] and ASI questionnaires [29] for substance abuse, and a questionnaire regarding HIV knowledge, health, and religious beliefs.

The first session began with education concerning the prescribed regimen, medication adherence expectations, common regimen side-effects, and medication misperceptions (e.g., if you drink alcohol, do not take medications that day). Problem solving addressed 1) daily routines and daily cues, 2) memory and cognitive aids for pill taking and prescription refills, and 3) identifying and utilizing social supports as encouragement. Depression, substance use/abuse, toxicity management, and competing demands were addressed when screening uncovered these potential barriers. In addition, the interventionist asked open-ended questions for participants to identify additional barriers.

MAPS participants met with the interventionist within two weeks of initiating therapy for approximately 60–90 minutes. Three monthly follow-up meetings lasted approximately 20–45 minutes. Follow-ups included displaying a calendar plot of the prior month's adherence generated by the electronic monitor. During the first three months, weekly telephone calls reinforced the in-person sessions and allowed for problem solving of new issues. Monthly telephone calls for the subsequent nine months reminded patients about obtaining refills and encouraged continuing the adherence strategies.

Prior to working with study patients, mock sessions were repeated until the interventionist was considered proficient by the investigators. Subsequently, trained staff assessed fidelity on 25 randomly selected intervention session audio tapes. Fidelity was scored using a 21-item tool developed for the protocol with scores ranging from 0–100; higher values indicated greater fidelity and >50 was considered adequate. More detail can be found in the MAPS manual at XXurlXX.

Outcomes

The primary outcome was antiretroviral adherence, measured using electronic monitors in all participants (Medication Event Monitoring System, MEMS, AARDEX, Zug, Switzerland), with each bottle opening considered a dose-taking event. Prospective participants planning to use a pill organizer were required to agree to maintain one medication in the MEMS monitored bottle (i.e., outside of the pill box). For patients on multiple antiretrovirals, an algorithm selected the monitored drug in the following order of preference: 1)non-nucleoside analog reverse transcriptase inhibitor, 2)protease inhibitor (ritonavir first), 3)integrase inhibitor, 4)entry inhibitor, or 5) nucleoside analog reverse transcriptase inhibitor.

We summarized adherence as fraction of prescribed number of doses taken over each quarter for a year, ranging from 0 to 1. The secondary outcome was undetectable plasma HIV viral load (UDVL), using a lower limit of 75 copies/ml and measured quarterly for a year (Versant, HIV-1 RNA 3.0, Bayer Corp. Berkeley, CA). These data were collected identically for each group during 9 follow-up visits with the study coordinator over the year.

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Analysis

The primary analysis used an "intention to treat" approach. To be most conservative, missing values were assigned a value of zero adherence. Fraction of doses taken was categorized as <0.7, >0.70–0.80, >0.8–0.9, >0.9–0.95, and >0.95. Generalized estimating equations (GEE) with ordinal regression were used to estimate the association between study group and adherence over all four quarters of the year. [30] In secondary analyses, we tested for potential confounding by measured variables by including covariates in the GEE models and inspecting for changes in the point estimate of the relation between study group and outcome.

Analyses of viral suppression were identical those of adherence except using logistic regression [30]. In secondary "as treated" analyses, missing adherence and viral load data were ignored. In further analyses, we assessed whether the effect of the intervention varied over time by including treatment group by time interactions in the models.

Finally, we assessed the relation between adherence (independent variable) and virologic suppression (dependent variable) again using GEE with logistic regression and including missing viral load as detectable.

Sample Size

The planned sample size was 200 individuals to achieve >80% power to detect a <10% difference in adherence between MAPS and usual care, ignoring the contribution of multiple outcome time points per individual. Recruitment was slower than expected and the target was decreased to 180 to achieve 80% power to detect a 10% difference in adherence.

Results

Enrollment and Baseline Characteristics

Between September 2005 and February 2010, 218 individuals were referred for participation, with 190 eligible and 180 (95%) randomized (Figure 1). Of those enrolled, 91 were randomized to MAPS and 89 to usual care. After the target of 180 was reached, enrollment was closed and follow-up extended until February 2011.

Participants' characteristics are displayed in Table 1. Of the 180 participants, 136 (76%) were on three drug regimens with two nucleoside reverse transcriptase inhibitors (NRTI) and a boosted protease inhibitor (PI) or a non-nucleoside analog reverse transcriptase inhibitor (NNRTI) (see Table 2). The remainder were on various combinations of up to 6 drugs with the most commonly used NRTI combination being tenofovir and emtricitabine in 88 (49%).

Dropouts occurred for 33 (36%) in the MAPS group and 23 (26%) in the usual care group (χ^2 (df=1) = 2.28, p=0.13). MAPS participants dropped out more commonly for "not wanting to follow the protocol" and moving too far away to follow-up at the site. Other reasons were similar between groups. Fidelity to MAPS was high with a mean score of 82 points (standard deviation=6 points), and ranged from 67 to 90 points.

Adherence Results by Study Group

The proportion of individuals in each adherence category in the MAPS and usual care groups during each quarter is displayed in Figure 2. In the primary analysis, the odds of being in a higher adherence category at any follow-up point was 1.78 (1.07–2.96) times greater for MAPS than usual care. Likewise, in the secondary analysis using an as-treated approach, the odds of being in a higher category of adherence at any follow-up point was 2.33 (1.35–4.05) times greater for MAPS than usual care. In further secondary analyses controlling for age, race, sex, treatment naïve status, use of efavirenz in regimen, baseline viral load and baseline CD4 count, there was no confounding of the relation between study group and adherence outcome. There was no evidence that MAPS' adherence effect differed over time–the study group by time interaction was neither statistically nor clinically significant (data not shown).

Virologic Results by Study Group

In the intention-to-treat analysis of virologic suppression, the odds of having an undetectable viral load at any follow-up point was 1.48 (95% CI: 0.94–2.31) times greater for MAPS than usual care. Likewise, in the as-treated analyses, the odds of having an undetectable viral load at any follow-up point was 1.98 (95% CI: 1.15–3.41) times greater for MAPS than usual care. At all time points, virologic suppression rates for MAPS exceeded those of usual care (see Table 3). Again there was no clear change in the relation between study group and undetectable viral load over time. In further formal analyses, there was no evidence that MAPS' effect on virologic suppression differed over time–the study group by time interaction was neither statistically nor clinically significant (data not shown).

Effect of Adherence on Virologic Suppression

As expected, there was a strong relation between adherence and treatment response. In the analyses where missing viral loads were imputed as "detectable", for every 25% increase in proportion of doses taken, the odds of having an undetectable viral load nearly doubled (odds ratio= 1.99 (95% CI: 1.64–2.41). In the analyses where missing viral load was left missing, the odds of undetectable viral load for every 25% increase in doses taken was more than double (odds ratio=2.41 (95% CI: 1.91–3.02).

Other Factors Associated with Adherence and Virologic Response

Treatment experienced individuals were 0.48 (95% CI: 0.29–0.81) times as likely to be in a higher adherence category and 0.48 (95% CI: 0.30–0.76) times as likely to have undetectable viral loads than treatment naïve individuals. Higher baseline viral load was associated with a lower likelihood of virologic suppression. For every 1 $\log_{10}$ higher baseline viral load, the odds of having an undetectable viral load was 0.80 (0.65–0.99). Neither of these relationships differed by study group.

Discussion

This randomized trial of MAPS demonstrated that it is effective at improving adherence over the first year of a new antiretroviral regimen in a population with relatively high rates of non-adherence. We found no evidence that MAPS was less effective in individuals with prior treatment experience despite those individuals being at higher risk of non-adherence. It did not lose effect over time. The impact of this increased adherence was borne out by the higher proportion of individuals with undetectable viral loads. This effect too persisted for the entire treatment period.

Numerous strategies to improve pharmacotherapy adherence have been tested, particularly for antiretroviral therapy [12]. Results have mostly been disappointing, with only a few strategies showing benefits for both adherence and virologic response [31,32]. Directly observed therapy (DOT) has been the most intensively studied, but in unselected populations, has not been associated with important [33] or sustained benefits [34]. However, some evidence suggests that DOT might be useful in select subpopulations, such as active substance abusers [35]. Technological interventions have had mixed results with text messages showing benefit in a developing world setting [32], but not in the developed world [36]. Behavioral strategies have also had mixed success. Simple financial incentives for adherence have had some effect while continued, but not consistently, and typically wane when the financial reward is stopped [37]. Feedback regarding adherence has been used successfully previously, but in a population excluding ethnic minorities, substance abusers, and the mentally ill [31]. Problem solving has been incorporated into larger intervention packages, but not studied on its own [38]. Use of multiple modalities to improve adherence has been suggested for years, but relatively little evidence to date has been generated). Notably, MAPS incorporates both a behavioral strategy and technology– the adherence feedback is generated via electronic monitors.

MAPS is relatively resource intensive, but such strategies can be presumed to be cost effective if they cost less than $1000 per year per participant for a 10% increase in adherence [39]. Although we did not perform a formal cost-effectiveness analysis, we estimate that approximately 20 participants were followed per year by an interventionist committing 15% effort at a salary of ~$50,000/year. Including approximately $150 per electronic monitor per participant, the cost for such an activity is substantially <$1000 per year.

There are several potential limitations to this study. First, although it was a randomized trial, participants could not be blinded to study arm. However, since the treatment was crucial to their health, it is unlikely that their awareness of study arm impacted their behavior outside of the interaction with the interventionist. In fact, it is possible that adherence in the control arm was better than would be expected in this population since this condition provided extra visits with the study coordinator, where more attention was paid to their medication taking. Second, participants were recruited from academic specialty HIV clinics where services for adherence may be greater than in general medical clinics. If so, the effect of MAPS may be even greater in less resourced settings. Third, it is unclear how the dropouts truly affected the results. Although both the intention-to-treat and as-treated analyses favored MAPS, the effect was stronger in the as-treated analyses. It is possible that imputing virologic failure for all missing data was an overly conservative assumption. Yet, in all secondary analyses, changing the assumptions regarding missing data did not change the direction of the effect-that is, MAPS was the favored strategy in all results. Of course, dropouts diminish the cost-effectiveness of the intervention; limiting dropouts from care should be a priority for future refinements of MAPS. Fourth, we used microelectronic monitors to generate the feedback over the initial 3 months. The current cost of these monitors may render them out of reach for most patients and programs. Other objective techniques have been established for monitoring adherence (e.g., pharmacy refill data [4,21,40]), yet it is unclear how they would perform if incorporated into MAPS instead of microelectronic monitors.

This study also has several particular strengths. The randomization, and the evident balance between the groups in most baseline characteristics, minimizes the likelihood that potential confounders biased the observed effect of MAPS. Second, fidelity to the manual of procedures always exceeded minimal standards. Third, the effect was present despite enrolling a population with many life challenges (i.e., poverty, unemployment). Fourth, the effect was apparent in the face of a rigorous and very conservative analytic approach of considering loss to follow-up non-adherence–this stands in contrast to studies analyzing only those who remained in care [31]. Fifth, the follow-up period extended for a full year and there was no attenuation of the effect. Finally, unlike prior multimodal interventions, we have developed an implementation manual and workbook, which were used by the staff in this study. Thus, MAPS has the potential to be implemented rapidly in settings where health behavior change expertise is unavailable.

In conclusion, MAPS improves pharmacotherapy adherence, although the benefit was somewhat diminished by dropouts. Since barriers to adherence and retention in care are similar, MAPS could be expanded to address retention in care as well; however, that remains to be evaluated. Since microelectronic monitors are not widely used in clinical practice, we believe MAPS should be refined to use other objective measures of adherence as the feedback tool. With the availability of the intervention manual, MAPS can be utilized immediately where the resources exist to implement it. MAPS should also be adapted and tested in other treatment settings where adherence to oral pharmacotherapy is critical to health outcomes.

Acknowledgments

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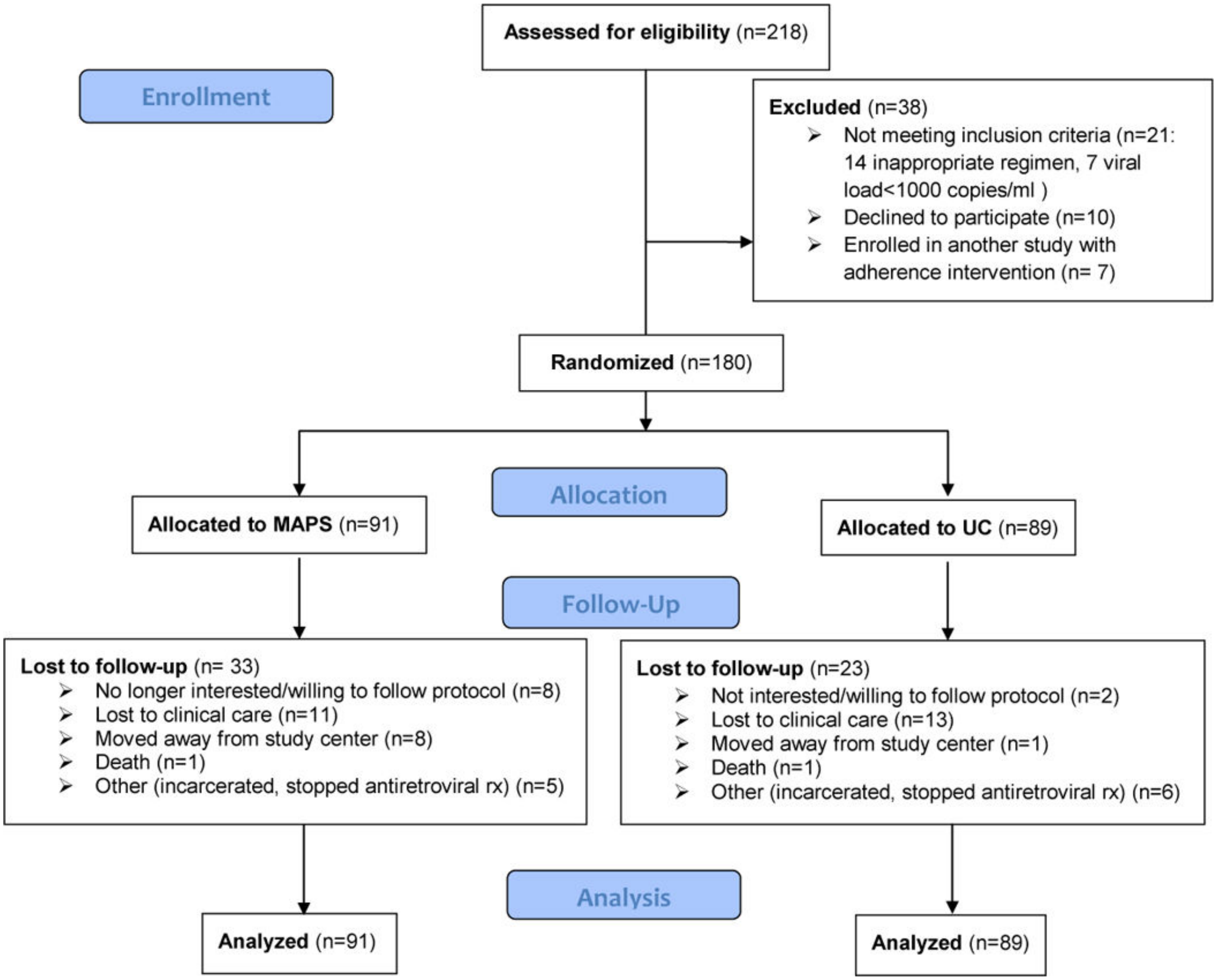

Figure 1.
Participant Flow Diagram

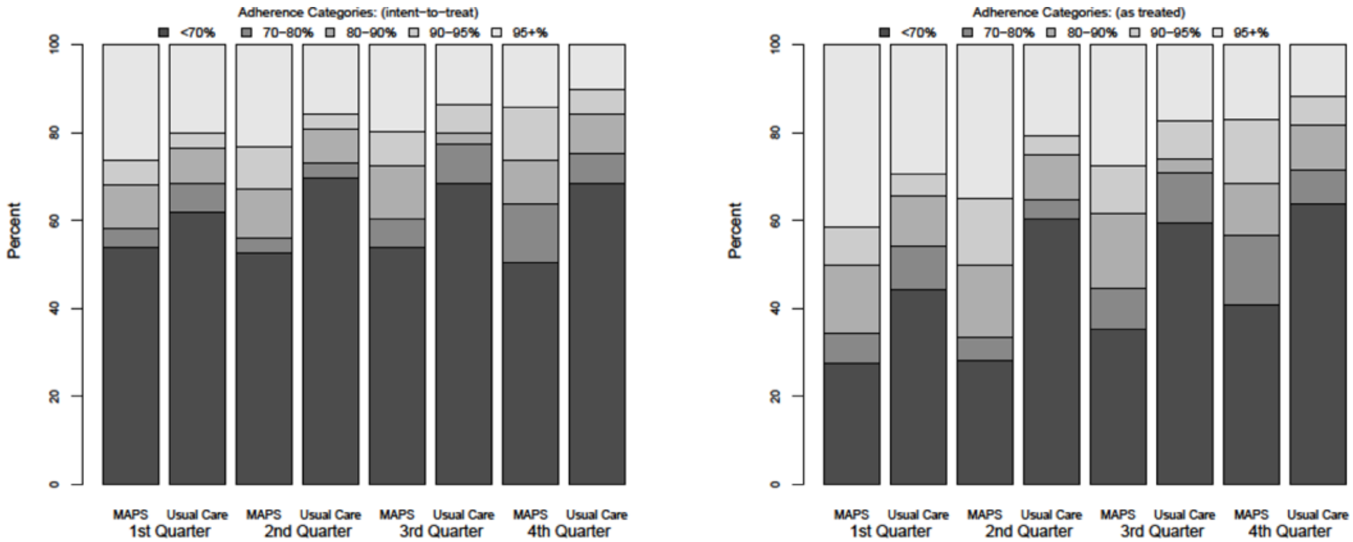

Figure 2.

Proportion of participants in each adherence category by arm, per quarter. The left panel displays the intention to treat results with missing values=0% adherence. The right panel displays the as treated results with missing values ignored.

Table 1

Baseline Characteristics by Study Group

	MAPS (n=91)	UC (n=89)
Median Age (Range) years	43 (20–65)	42 (19–60)
Male Sex	52 (57%)	56 (63%)
Race		
Race Black	80 (88%)	73 (82%)
White	9 (10%)	15 (17%)
Other	2 (2%)	1 (1%)
History of Injection Drug Use	16 (18%)	12 (14%)
Current Drug Use	21 (23%)	27 (30%)
Hazardous Alcohol Use	14 (15%)	18 (21%)
Unemployed	73 (85%)	69 (78%)
Yearly income<$5000	24 (28%)	33 (36%)
Treatment naïve	40 (44%)	32 (36%)
Once daily regimen	59 (65%)	58 (65%)
Median # pills per regimen (Q25,75)	3 (1–5)	3 (3–5)
Baseline viral load (log10 copies/ml)-Q25,75	3.24 (2.46–4.32)	3.47 (2.35–4.40)
Baseline CD4 count cells/mm3, Q25,75	287 (146–370)	244 (116–379)

Table 2

Index Antiretroviral at Randomization by Study Group

Index Drug	n	MAPS	Usual Care
Atazanavir/r	64	32	32
Efavirenz	48	30	18
Darunavir/r	31	15	16
Lopinavir/r	18	6	12
Fosamprenvir/r	7	4	3
Raltegravir	4	2	2
Nelfinavir	2	1	1
Nevirapine	2	0	2
Tipranavir/r	1	1	0

/r=ritonavir boosted

Table 3

Virologic Response Rates per Quarter by Study Group

A. Proportion with UDVL (missing=failure)	MAPS	UC
Q1	53/91 (58%)	42/89 (47%)
Q2	53/91 (58%)	47/89 (53%)
Q3	52/91 (57%)	39/89 (44%)
Q4	54/91 (59%)	45/89 (51%)
Proportion with UDVL (missing=missing)		
Q1	53/68 (78%)	42/67 (63%)
Q2	53/62 (86%)	47/70 (67%)
Q3	52/69 (75%)	39/59 (66%)
Q4	54/72 (75%)	45/76 (59%)