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Richard Harding

► **To cite this version:**

Richard Harding. Adherence to antiretroviral treatment in patients with HIV in the UK: a study of complexity - AID IMPACT SPECIAL ISSUE. *AIDS Care*, 2008, 20 (04), pp.442-448. 10.1080/09540120701867032 . hal-00513446

HAL Id: hal-00513446

<https://hal.science/hal-00513446>

Submitted on 1 Sep 2010

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ISSUE**

Journal:	<i>AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies</i>
Manuscript ID:	AC-2007-07-0323.R1
Journal Selection:	AIDS Care
Keywords:	adherence, antiretroviral therapy, timing



Adherence to antiretroviral treatment in patients with HIV in the UK: a study of complexity.

Sherr, L; Lampe F; Norwood, S; Leake-Date, H; M Johnson, G Arthur, M Fisher, J Anderson, S Zetler, S Edwards, Harding, R

Lorraine Sherr (correspondence author)
Dept of Primary Care and Population Sciences
Royal Free University College Medical School
PCPS, Rowland Hill St, London NW3 2PF UK
Tel 44 207 794 0500
Fax 44 207 794 1224
Email : L.sherr@pcps.ucl.ac.uk

Fiona Lampe
Dept of Primary Care and Population Sciences
Royal Free University College Medical School

Sally Norwood
Dept of Primary Care and Population Sciences
Royal Free University College Medical School

Heather Leake Date
Brighton & Sussex University Hospitals NHS Trust

Richard Harding
Department of Palliative Care, Policy and Rehabilitation
King's College London School of Medicine

Margaret Johnson
Royal Free Hospital

Simon Edwards
Mortimer Market

Martin Fisher
Brighton and Hove

Gilly Arthur
Archway Sexual Health Clinic

Sarah Zetler
Homerton University Hospital NHS Trust

Jane Anderson
Homerton University Hospital NHS Foundation Trust

Adherence to antiretroviral treatment in patients with HIV in the UK: a study of complexity.

Abstract

Adherence to HIV treatment regimes is a core element to viral suppression. Yet measurement of adherence is complex. Although adherence levels are good predictors of outcome, they do not always provide full explanations of observed variations in responses. This study was set up to examine the complexity of adherence measurement and to examine rates of adherence in the presence of complex measurement. 502 consecutive attenders at HIV clinics in the UK (80.5% response rate), provided detailed measurement on adherence in the preceding 7 days, setting out dose adherence, as well as measures of timing and dietary conditions. In addition, a range of psychological, demographic and relationship data were gathered to understand predictors of full and partial adherence. Although 79.1% reported dose adherence in the previous 7 days, 42.8% had not taken the dose at the correct time, and 27.2% had not taken the dose under the correct circumstances. Using a more complex composite measure of full adherence, rates reduced from 79.1% to 41.5%. Comparisons of those deemed fully adherent, partially adherent and non adherent were carried out. Fully adherent significantly more likely to be older ($F=7.8$, $p<0.001$), UK born ($F=6.8$, $p=0.03$), code ethnicity as white ($F=5.3$, $p=0.07$), record higher quality of life ($X^2=8.7$, $p=0.01$), lower psychological symptoms ($X^2=15.2$, $p=0.001$) and lower global distress symptoms ($X^2=6.9$, $p=0.03$). There were no differences according to education, behavioural and attitudinal variables (disclosure, stable relationship, STI diagnosed, number of sexual partners, unprotected sex, optimism or treatment switching). Fully adherent groups were significantly more likely to be in agreement with their doctor on treatment initiation ($X^2=6.2$ $p=0.045$), satisfied with the amount of involvement in the decision making process ($X^2=7.3$ $p=0.026$), their wishes were considered ($X^2=12.5$ $p=0.002$) monitoring of their condition ($X^2=7.1$ $p=0.028$). Multivariate analysis showed that variables which contributed significantly at a 5% criterion level to complex adherence were physical symptoms (OR=0.56, $p = 0.05$), psychological symptoms (OR=2.37, $p < 0.001$).age (OR=0.96, $p = 0.02$), education (OR=0.54, $p = 0.03$), having more than one sexual partner (OR=0.46, $p = 0.03$), having risky sex (OR=4.30, $p = 0.002$), and being optimistic about treatments (OR=0.42, $p = 0.01$). The softer markers of adherence are not usually measured in follow up and may account for variations in treatment responses. The complexity of adherence needs to be understood and addressed to maximise treatment efficacy.

Acknowledgements

We wish to acknowledge the contribution of The Clinicians on the Switching team, research assistance from Amanda Jayakody, research nurses at participating clinics, and all survey respondents. This research was assisted with an unrestricted educational grant from GlaxoSmithKline, with input from the Adherence Strategy Group.

Adherence to antiretroviral treatment in patients with HIV in the UK: a study of complexity.

Introduction

Mortality and morbidity associated with HIV infection in the UK have declined exponentially since the introduction of highly active antiretroviral therapy (HAART) (Lundgren et al 2006). To achieve these gains patients and clinicians must engage with complex and demanding long term treatment regimens. These call for consistently high levels of adherence to perform to their maximum potential, maintaining viral suppression. Not only does poor adherence put the efficacy of treatment for the patient at risk, it also leads to the emergence of drug resistance. This in turn will compromise future treatment options for the individual and increases the risk of exposing others to drug resistant viral strains.

Non - adherence has been directly associated with treatment failures (Paterson et al 2000), viral rebound and a need for regimen switching. As treatment options are limited, this poses an urgent challenge. For maximum efficacy adherence levels of at least 95% are required – far higher than has been achieved for most medications that have previously been studied (Haynes et al 2002). Substantial rates of non – adherence have been widely described in the literature (Poppa et al 2004) despite a multitude of interventions that have been formulated to support and promote high levels of treatment adherence (Chesney et al 2000).

All interventions to promote or enhance adherence are reliant on accurate and adequate adherence measurement. Such measurement has proved to be problematic.. A number of studies have explored adherence measurement to generate a gold standard for audit and research purposes. Most adherence studies use a selection (or a single indicator) from five forms of measurement including patient self report, doctor report, repeat prescription filling, mechanical devices (such as Medical Event Monitoring System MEMS caps MEMS View 1998) and biological markers which were claimed would measure drug levels directly or indirectly. Some studies describe

electronic devices as the gold standard, while others use multiple measures to log adherence. Yet electronic caps can only tell if the container was opened and not whether the compound was ingested. It runs the risk of erroneously counting someone as adherent who opens the bottle but does not take the compound. It also runs the risk of counting someone as non-adherent who removes multiple doses at one time point, takes them all at the correct time, but is only recorded on the single occasion of opening the container.

Attempts to measure adherence, in themselves, do not interfere with levels of adherence (Sherr 2000). Efforts have been made to determine characteristics of patients (van Duleman et al 2007) who are particularly likely to be non-adherent (Simoni et al 2006). Factors that have been found to be associated with adherence levels include mental health problems (Mills et al 2006), preparation, disclosure, coping, attitude to treatment (Horne et al 2004), understanding (Poppa et al 2004) and the quality of the relationship between doctor and patient (Aronson 2007).

Although adherence levels are one predictor of clinical outcome, they do not always explain all the observed variations in response. Liu et al (2006) note that errors in dose timing may be crucial in understanding virological response and that percent of doses taken is insufficient to exclusively explain outcome effects that are monitored in their US samples (Liu et al 2006b). This would suggest that studies examining adherence which simply utilise a recall of dose are insufficient and a more complex measure of adherence, involving dose timing as well as adherence to circumstances of drug administration are important for a complete and accurate measure of adherence.

A closer scrutiny of existing studies reveal few, if any, that explore the detailed circumstances associated with adherence. This cross sectional study based in clinical settings in London and south east England examines the complex array of factors that impinge on adherence, both in terms of dose timing and contextualising this aspect in a broader analysis of patients lives and circumstances.

Methods

The study, carried out between 2005 and 2006 utilised a cross sectional, questionnaire based design. Consecutive attendees at four London and one South-eastern UK HIV treatment outpatient clinics who were currently on antiretroviral therapy were eligible for inclusion. Potential participants had to be over 18 years of age, deemed clinically well enough to participate by their doctor, able to speak sufficient English to complete the standardised inventory and give informed consent, and currently taking HIV medication. Participants were requested to complete the questionnaire, return it to a sealed receptacle or post it back directly to the research centre in a pre-paid envelope. A researcher was available to answer queries.

Comment [JA1]: ?? could they take home and post??

Comment [JA2]: Could they postb them??

Adherence was measured using patient self report recall over the preceding seven days. Participants were asked to provide detailed information on the number of missed doses over the past 7 days. For the medication taken, they were asked to record how many doses were taken on time (all, most or some) and how many under the correct circumstances such as food or an empty stomach (all, most or some). **Full adherence** was coded as no missed doses and all taken at correct time and under correct circumstances. Regimens and compounds that had no time or circumstance/diet requirements were automatically coded only on dose adherence. **Partial adherence** was coded as those who had taken all doses, but had not been fully adherent to dose timing and/or circumstances (when these were required). **Non adherence** included all other responses.

All participants then completed a standardised questionnaire to obtain information on:

- **Demographics** – information on race, ethnicity, residency, time in the UK, sexuality, education and employment was systematically gathered.
- **Sexual behaviour.** Partnership behaviour was monitored, together with sexual risk behaviour in the preceding 3 months, defined as unprotected sexual intercourse with someone of unknown or discordant HIV status.
- **Disclosure** of HIV status was recorded based on questionnaires validated in previous studies (Kalichman 2003).

- **Treatment** switching was monitored to note first treatment, single or multiple switch experience.
- **Symptom and pain levels** were monitored using the MSAS inventory (Chang et al 2004). This is a multiple symptom inventory that provides three total measures (Physical, Psychological and Global Pain Index), providing insight into pain and suffering symptoms within the preceding week.
- **Quality of life** was measured utilising the Euroquol (The Euroquol Group 1990) and study specific ratings on quality of life using a 5 point rating scale (not at all good to very good).
- **Satisfaction and attitudes** were measured in relation to medical care and treatment optimism using Lickert type rating scales of optimism and elements of doctor-patient care and communication (decision making, information, monitoring, agreement, involvement) rated on a 5 point scale.

Data was analysed using SPSS.pc statistical package. Data was entered into SPSS and analysed to explore consistent differences between those who were fully adherent, partially adherent and non adherent. A binary split was made between those who were fully adherent according to our stricter criteria versus the rest, in order to examine predictors of full adherence. Ethical approval for the study was obtained through the multiple site ethical approval process for each centre. The study received guidance from the Adherence Strategy group, which included multi-agency and multidisciplinary members and particularly patient representation.

RESULTS

Sample

During the study period, 1006 patients attended the 5 clinics, of whom 627 were eligible for inclusion, (276 not on treatment, remainder not fitting other inclusion criteria). 502 people with HIV on treatment provided complete data for analysis, representing an 80.06% response rate. They comprised 22.6% heterosexual females, 12.0% heterosexual males and 63.5% gay males. 67% reported their ethnicity as “white” and 33% as Asian, Black or mixed race.

Comment [JA3]: These are results not methods.

Prevalence of non-adherence

From the 502 patients, 397 (79.1%) missed no dose in the preceding week, 10.6% missed one dose, 4.4% missed two doses, and 6% missed three or more doses. Furthermore, 42.8% reported that they had not taken their dose according to the correct timing schedule and 27.2% reported that they had not taken their dose according to the correct food requirements. Figure 1 below sets out missed doses as well as dose timing and circumstance adherence.

Insert figure 1 here

According to a percent dose adherence model, 79.1% of the sample would be classified as adherent. However, according to the stricter measure where full adherence is measured including dose adherence and ensuring accurate dose timing and circumstance adherence, this figure falls to 41.5%

Insert figure 2 here

Full, partial and non adherence.

Table 1 below sets out comparisons on a range of variables for those who were fully adherent (41.5%), those who were partially adherent (36.1%), and those who reported being non-adherent (22.4%).

Insert table 1 here

Quality of life score (Euroqol-VAS) was significantly higher for fully adherent respondents (Mean rank 296.79) compared to partially adherent (258.21) or not adherent respondents (254.52) (Kruskal-Wallis $X^2=8.7$, $p=0.01$). This was true on a range of quality of life measurements - Euroqol-5D (mean rank fully adherent 282.45, partially adherent 247.60 and not adherent 243.99, Kruskal-Wallis $X^2= 7.6$,

$p=0.02$) and quality of life at present (mean rank fully adherent 191.78, partially adherent 172.41 and not adherent 140.41, Kruskal-Wallis $X^2=15.2$, $p=0.001$). Psychological and Global symptom burden scores were both significantly higher for non-adherent respondents (Psychological symptoms mean rank fully adherent 255.29, partially adherent 297.06, not adherent 318.50, Kruskal-Wallis $X^2=15.2$, $p=0.001$; Global distress was significantly lower for fully adherent respondents (index mean rank for fully adherent 265.46, partially adherent 289.60 and not adherent 311.66, Kruskal-Wallis $X^2=6.9$, $p=0.03$). There were no significant differences between the groups according to gender, sexuality, education or employment. However respondents who were UK born were more likely to be fully adherent (47.5% vs 37.3%) and less likely to be non adherent (17.2% vs 24.9% $\chi^2=6.8$ $p=0.03$). Length of residency in the UK also differed significantly with those in the UK for 5+ years more likely to be fully adherent (44.8% vs 34.5%) and less likely to be non adherent (18.0% vs 31.0% $\chi^2=7.7$ $p=0.02$).

Insert table 2 here

There were no differences according to education, behavioural and attitudinal variables (disclosure, stable relationship, STI diagnosed, number of sexual partners in the preceding 3 months, unprotected sex, optimism or treatment switching). Fully adherent respondents were significantly more likely to feel they were in agreement with their doctor on treatment initiation ($\chi^2=6.2$ $p=0.045$), the amount of involvement they had in the decision making process ($\chi^2=7.3$ $p=0.026$), the extent to which their wishes were considered ($\chi^2=12.5$ $p=0.002$) and satisfaction with monitoring of their condition ($\chi^2=7.1$ $p=0.028$).

Insert table 3 here

Comparisons between adherent and non adherent respondents

Univarvariate and multivariate analyses were carried out on the data where the groups were divided into fully adherent and the remainder – categorised as “not fully

adherent". Variables that were found to be significantly (at a 10% level) associated with full adherence in univariate tests (chi-square and t-tests as appropriate) were age, psychological symptom burden (MSAS-Psych). Patients who were fully adherent to their treatment (mean age= 42.22, sd=8.3) were older than patients who were not fully adherent (40.48, 8.7) ($t(512)=2.3$, $p=0.02$). Patients who were fully adherent to their treatment reported a lower psychological symptom burden (1.16, sd=1.0) than patients who were not fully adherent (1.44, 1.0) ($t(522)=-3.3$, $p=0.001$).

For the multivariate analysis, a binary logistic regression with a backward conditional method of entry was carried out to determine the independent predictors for reporting full adherence. Variables in the model that were found to contribute significantly to the model at a 5% criterion level were **Age** (OR=0.96, $p = 0.02$), **Education** (OR=0.54, $p = 0.03$), **Having one sexual partner** (OR = 0.27, $p <0.001$), having **more than one sexual partner** (OR=0.46, $p = 0.03$), having **risky sex** (OR=4.30, $p = 0.002$), being **optimistic about treatments** (OR=0.42, $p = 0.01$), **Physical symptoms** (OR=0.56, $p = 0.05$) and **psychological symptoms** (OR=2.37, $p < 0.001$). The Hosmer-Lemeshow test results (Chi-square = 6.8, $p = 0.56$) indicate that the goodness of fit is satisfactory. The Nagelkerke R² was 0.22, suggesting that the model has some use in predicting whether people will be fully adherent or not.

Discussion

We demonstrate the importance of measuring both dose timing and dietary conditions, in addition to measures of simple dose adherence, if a true estimate of overall adherence is to be obtained.

Our data show that on dose adherence, 79.1% of the group appear adherent, but when all levels of adherence are taken into consideration this figure falls dramatically, to only 41.5%. Non-adherence showed little relationship to demographic, behavioural or attitudinal variables. This concurs with previous studies that were unable to identify any particular at risk groups for non-adherence. Our data shows that HIV patient non-adherence is widespread and not easily predictable on a variety of measures.

Participants who were fully adherent were older, had lived in the UK for longer and were more likely to be UK born. This would suggest that increased input regarding adherence be directed at younger people and those who are newly arrived in the UK. Length of time in the UK may be a proxy marker for other variables such as familiarity with the health care system, residency, and access to stable accommodation, economic status (which includes access to funds to buy food and other basic necessities) or social isolation. All these factors may affect the ability to adhere to the demands of a difficult regimen. Those who were fully adherent had both lower psychological burden and global symptom index scores. This may either imply that those who are well adjusted and feeling less ill, are more likely to adhere or that enhanced adherence is a trigger for fewer physical symptoms and hence improved psychological functioning. Having one sexual partner may be an indicator of a stable relationship, providing a more supportive environment to enhance and enable adherence. Optimism about treatment, , has been shown in this study to be associated with full adherence. Not surprisingly those who were fully adherent had a significantly higher ranking of their satisfaction with their own ability to adhere. Those who were fully adherent were also significantly more likely to agree with their doctor about treatment commencement, feel involved in the decision making process, feel that their wishes had been considered and feel satisfied with the regular monitoring of their treatment. This data points to the crucial role of good dialogue and interaction between doctor-patient at the time of treatment commencement and throughout ongoing monitoring.

There are some limitations to our data. Our adherence measure relies on self report. Yet none of the other methods can give insight into the levels of adherence we believe are important to measure. The timed electronic caps are prone to potential error, as they may record a missed dose if someone removes a double dose – even if both were taken - and they give no readings of actual consumption of the compound, only if the pill was removed from the container. Doctor reports and estimates are shown to be unreliable. Recall over 7 days provides a partial snapshot and may not be a sensitive enough measure to pick up fluctuations over longer periods of time and changes of the period of treatment. The cross sectional nature of the study is also a limitation, offering no longitudinal information or data on causal pathways. However, it does clearly point out associations and thus can direct future studies. .

This study advances the debate on adherence and highlights the need for a much more rigorous approach to adherence monitoring. Not only should timing and circumstance of adherence be underscored, but also compounds which release patients from such additional adherence obstacles, may assist in reducing the burden of adherence for patients. Clearly the removal of timing and circumstances constraints would mean that dose adherence is the only challenge, which was met by over three quarters of this sample. Newer treatment regimens, with less rigorous adherence demands, may ameliorate the burden of such precise adherence demands. The importance of good relationships and interaction should be incorporated into all treatment management protocols. This requires time, continuity and willingness. A satisfied patient is more likely to adhere.

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Figure 1. Reported adherence for those patients currently on antiretroviral treatment (n=502)

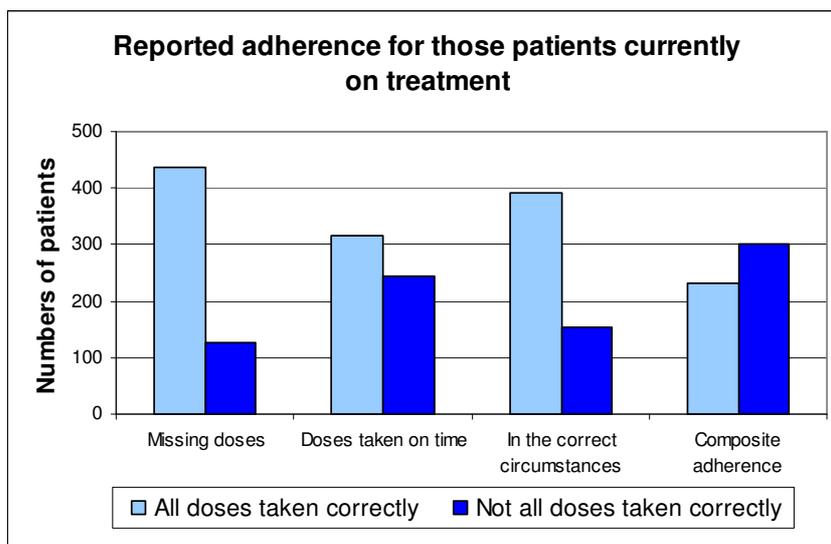


Figure 2 Difference between adherence rates when full or partially measured.

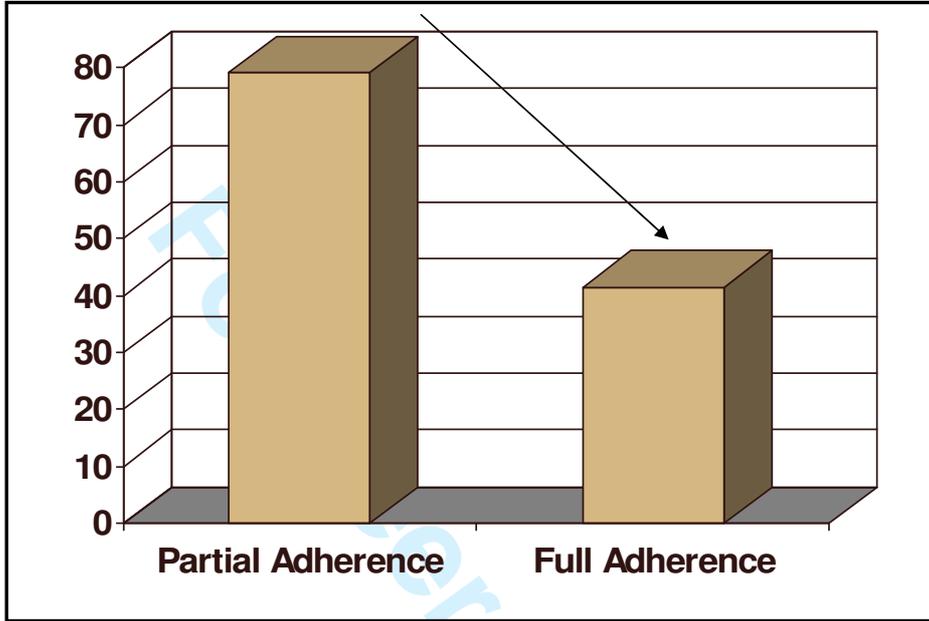


Table 1 – Comparisons between fully adherent, partially adherent and non-adherent respondents on Quality of Life and MSAS Symptoms variables.

	Full Adherent		Partial adherent		Not adherent		Statistic t-test		
	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	F	Df	Sig.
EuroQol	199	0.72 (0.3)	170	0.69 (0.3)	97	0.70 (0.2)	0.56	2	0.57
QOL general health	206	70.32 (20.7)	176	66.18 (19.5)	100	66.69 (20.8)	2.27	2	0.11
MSAS-Phys	214	0.80 (0.7)	183	0.76 (0.6)	105	0.91 (0.7)	1.78	2	0.17
MSAS-Psyc	214	1.14 (1.0)	183	1.38 (0.9)	105	1.53 (1.1)	6.39	2	0.002
MSAS-GDI	214	1.05 (0.8)	183	1.16 (0.8)	105	1.28 (0.8)	3.11	2	0.05
QOL before switch	132	3.00 (1.2)	103	2.65 (1.1)	60	3.07 (1.3)	3.24	2	0.04
QOL after switch	130	4.08 (0.9)	101	3.97 (0.9)	62	3.95 (0.93)	0.59	2	0.56
QOL today	135	4.17 (1.0)	102	4.02 (1.0)	60	3.80 (1.0)	3.14	2	0.05

Table 2 Comparisons between fully adherent, partially adherent and non-adherent respondents on demographic, behavioural and attitudinal variables.

VARIABLE	Category	N	Full Adherence	Partial Adherence	Non Adherent	X ²	Df	sig
Gender	Male	387	43.4%	35.7%	20.9%	0.18	2	0.91
	Female	109	41.3%	37.6%	21.1%			
Gender/sexuality	Female	109	41.3%	37.6%	21.1%	0.18	4	1.00
	Male (het)	57	43.9%	35.1%	21.1%			
	Male (gay)	326	43.3%	35.9%	20.9%			
Country of origin length of residency in UK	Non-UK	241	37.3%	37.8%	24.9%	6.76	2	0.03
	UK born	261	47.5%	35.2%	17.2%			
	UK 5+ yrs	362	44.8%	37.3%	18.0%	7.74	2	0.02
	UK <5 yrs	87	34.5%	34.5%	31.0%			
Ethnicity	White	335	46.0%	35.8%	18.2%	5.33	2	0.07
	Non-white	158	36.1%	38.6%	25.3%			
Education	No university	270	43.3%	35.2%	21.5%	0.27	2	0.87
	University	219	41.6%	37.4%	21.0%			
Employment	Employed	247	42.1%	36.8%	21.1%	0.32	2	0.85
	Not	217	44.7%	35.0%	20.3%			
Disclosure	No	30	40.0%	30.0%	30.0%	1.65	2	0.44
	1+	470	42.6%	37.0%	20.4%			
Stable relationship	No	195	43.1%	36.9%	20.0%	0.001	2	1.00
	Yes	269	43.1%	36.8%	20.1%			
STI (3/12 months)	No	351	43.0%	36.5%	20.5%	3.83	2	0.15
	Yes	23	56.5%	39.1%	4.3%			
Sexual partners 3/12	None	121	45.5%	36.4%	18.2%	3.29	4	0.51
	One	165	43.6%	37.6%	18.8%			
	> One	117	36.8%	37.6%	25.6%			
Risky sex	No	384	43.5%	37.5%	19.0%	0.70	2	0.70
	Yes	42	47.6%	31.0%	21.4%			
Infectiousness optimism	Not optimistic	373	43.2%	36.2%	20.6%	0.97	2	0.62
	Optimistic	97	41.2%	41.2%	17.5%			
Treatment Optimism	Not optimistic	349	43.6%	35.2%	21.2%	1.76	2	0.42
	Optimistic	110	40.9%	41.8%	17.3%			
Treatment switching	None	159	39.6%	40.3%	20.1%	3.44	4	0.49
	One	131	48.1%	33.6%	18.3%			
	Multiple	196	41.8%	34.7%	23.5%			

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Table 3. Comparison between Fully Partially and non adherent groups on communication and attitudinal variables.

Variable (5 point scale 1= not at all; 5= very much)	Fully <i>Mean Rank</i>	Partial <i>Mean Rank</i>	Non <i>Mean Rank</i>	Statistics Kruskal-Wallis χ^2 significance
New drug therapies make HIV people less infectious	265.57	271.13	265.10	0.19 ns
Less worried about HIV infection with improved treatment	251.94	272.06	255.51	2.1 ns
What extent did patient play part in decision to start treatment	280.30	254.04	258.87	3.8 ns
Think Doctor played a part in decision to start treatment	276.72	255.13	268.38	2.8 ns
Had adequate information about risks and benefits of starting treatment	273.32	254.05	253.85	2.4 ns
Felt they were in agreement with doctor to start treatment when it happened	276.71	249.65	249.77	6.2 p=0.045
Happy with amount of involvement that they had in the decision making process	281.74	251.52	251.16	7.3 p=0.026
Satisfied with monitoring of condition	165.81	155.17	135.83	7.1 p=.028
Satisfied with the extent to which their wishes were considered	171.60	145.78	136.28	12.5 p=.002
Satisfaction with the ability to adhere	170.53	146.06	131.10	12.2 p=.002

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