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To cite this version:

Carmina R. Fumaz, Jose A. Muñoz-Moreno, Jose Molto, Maria Jose Ferrer, Raquel López-Blázquez, et al.. Sustained antiretroviral treatment adherence in survivors of the pre-HAART era: attitudes and beliefs. AIDS Care, Taylor & Francis (Routledge), 2008, 20 (07), pp.796-805. 10.1080/09540120701694022 . hal-00513436

HAL Id: hal-00513436

https://hal.archives-ouvertes.fr/hal-00513436

Submitted on 1 Sep 2010

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Sustained antiretroviral treatment adherence in survivors of the pre-HAART era: attitudes and beliefs

Journal:	*AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies*
Manuscript ID:	AC-2007-05-0201.R2
Journal Selection:	AIDS Care
Keywords:	adherence, antiretroviral treatment, highly experienced patients, health beliefs

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Original Paper

Main Title:

Sustained antiretroviral treatment adherence in survivors of the pre-HAART era: attitudes and beliefs

Running Head: Adherence in Pre-HAART Era Survivors

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Abstract

The objective of this study was to assess adherence of HIV-1–infected patients who started treatment in the pre-HAART era, and to determine variables associated with better adherence, including relevant attitudes and beliefs. This is a cross-sectional study enrolling patients who had received antiretroviral therapy for ≥10 years. Adherence was evaluated through self-reporting and plasma drug concentrations. Treatment variables, attitudes and beliefs were collected during structured interviews. The results show that for 87 patients the median (interquartile range) time on therapy was 13 (10-19) years; 80 were on therapy at the time of analysis. Adherence was ≥95% in 54 patients (67.5%), 90–94% in 22 (27.5%), and <90% in 4 (5%). Drug concentrations were below the lower limit of detection in 5 patients. Younger age ($P = 0.014$), female gender ($P = 0.005$), current substance abuse ($P = 0.004$) and hepatitis C virus coinfection ($P < 0.001$) were related to lower adherence. Adherence did not differ in relation to different drug families or once- or twice-daily regimens. Patients with adherence <95% were more likely to have interrupted treatment without doctor's recommendation ($P = 0.009$). Adherent patients exhibited a higher perception of risk of developing the illness and of benefits of therapy, higher self-efficacy and intention to adhere and were more influenced by events that motivate medication intake. To conclude, adherence was >90% in most patients on antiretroviral therapy for ≥10 years. Adherence was more related to beliefs about health and illness than to the characteristics of medication or level of knowledge about treatment. Care adherence interventions should include assessment of health beliefs.

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Introduction

Antiretroviral therapies available in the 1990s involved a high pill burden and complex schedule combinations. The efficacy of such treatments was limited by frequent adverse events and a significant interference of treatment in patients' lives [1]. In the present decade, strategies such as once-daily regimens have been developed to diminish the negative impact of treatment on quality of life and the appearance of less complex and toxic antiretroviral drugs has improved the management of HIV infection considerably [2,3]. The effects of the benefits of these regimens on adherence have been uneven, however [4], possibly because research has usually been carried out in already adherent patients with chronically suppressed viral loads [3,5].

In addition to treatment characteristics, patients' psychological status (e.g., depressive symptoms, use of avoidance coping skills) seems to be strongly related to lack of adherence and HIV infection progression [6]. Adherence is thus a multidimensional concept which includes contextual, intrapersonal and behavioural factors [7,8]. Furthermore, adherence to antiretroviral treatment seems to decrease with the time [9,10], in a pattern similar to that of other chronic diseases [11].

The objective of the present study was to assess the adherence levels of patients who survived the pre-HAART era, benefiting from the various therapeutic options that became available over time and then to determine the key variables associated with better adherence in this group, including patients' attitudes and health beliefs about HIV infection and antiretroviral treatment.

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Methods

Study design and participants

This cross-sectional survey study investigated the adherence to antiretroviral therapy and the beliefs and attitudes in relation to the treatment and the infection in a group of HIV-infected participants recruited at the outpatient HIV clinic of a university hospital in Badalona, near Barcelona, Spain. Inclusion criteria were HIV infection, age ≥18 years, and a history of antiretroviral therapy for ≥10 years (starting with mono- or dual therapy). An exclusion criterion was physical or mental inability to participate and understand the study. Clinicians explained the study to all candidates during routine clinical visits and participation was voluntary. All patients approached agreed to participate and gave their informed consent.

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Demographic and treatment variables

After the patients left the recruitment visit they were interviewed by a clinical psychologist trained in HIV management. Demographic and clinical data were collected from patients' records. Information about job status, current substance abuse and current methadone use was collected from the questionnaires that participants had to fill in.

Adherence to antiretroviral treatment was evaluated based on patients' self-reporting and drug concentrations in plasma. Self-reported adherence was assessed with the use of one item. This measurement, used frequently by the study team both in clinical practice and in previous research, has shown strong correlation with other methods such as virological markers and drug levels in plasma [12]. Patients were asked about the number of doses missed within the previous two weeks. Appropriate adherence was defined as the consumption of at least 95% of the medication prescribed [13].

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Protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) trough concentrations in plasma were determined by high-performance liquid chromatography, according to a validated method [14]. Based on previously published data [15,16], drug concentrations were considered subtherapeutic if they were below 3.4 mg/L for nevirapine, 1.0 mg/L for efavirenz, 0.8 mg/L for nelfinavir, 0.1 mg/L for indinavir and for saquinavir, 0.15 mg/L for atazanavir, 4.0 mg/L for lopinavir, and 1.2 mg/L for amprenavir. In addition, patients whose drug concentrations were below the lower limit of quantification were considered non-adherent patients.

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The following variables were included in the interview: previous and current interruption of antiretroviral therapy upon a doctor's recommendation (the patient had followed in the past or was following at the study entry a structured treatment interruption decided upon by a doctor and with the patient's agreement), previous and current interruption of antiretroviral therapy without a doctor's recommendation (without the doctor's agreement, the patient had stopped the treatment in the past or was not taking treatment at the study entry)., and current presence of adverse events. All answers were recorded as *yes* or *no* and reported as percentages. Subjective perceptions of the interference of treatment in daily life and the degree of limitation due to adverse events were assessed with the use of 10 mm visual analogue scales (VAS) (0, absence; 1- 2, very low; 3-4, low; 5-6, moderate; 7-8, high, 9-10, very high).

Additionally, this study measured on patients' basic knowledge about their treatment schedule. For this purpose, participants were interviewed about the characteristics of their current antiretroviral therapy using three parameters: name of drugs taken, number of pills and schedule. Since some antiretroviral drugs can be taken as part of either a once- or twice-a-day regimen, investigators checked with the

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physicians to confirm agreement between the schedule described by the patients and the one that had been prescribed. This step also allowed evaluation of the patients' degree of knowledge about the characteristics of their antiretroviral treatment. Patients who responded correctly to the three parameters were considered "highly informed"; they were classified as "moderately informed" if two parameters were correct and "poorly informed" if only one parameter was correct.

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Attitudes and beliefs about HIV infection and antiretroviral treatment

First, a focus group with 15 long-term antiretroviral experienced patients (≥10 years on therapy) was convened to generate the items that would be included in the survey. Patients were recruited with poster displays in waiting rooms soliciting participation and focus-group patients were excluded from the later study. The focus group identified the themes that might be more representative of variables conforming the theoretical frames to be used (Health Belief Model and the Theory of Reasoned Action, as explained below). After identifying the themes, patients also participated in the writing of statements about them, using familiar, understandable phrases in Spanish. Participants responded to the statements on 5-point Likert-type scales with labels attached to each point on the scale (5, strongly agree; 4, somewhat agree; 3, neither agree nor disagree; 2, somewhat disagree; 1, strongly disagree). A score for each thematic set of items was generated and a theme score higher than the midpoint for a set (7.5 for 3-item sets and 5 for 2-item sets) was taken to indicate a positive score for that attitude or belief. The percentage of adherent and non-adherent patients scoring higher than the midpoint for each theme was analysed.

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Theoretical frames

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The Health Belief Model attempts to explain and predict health behaviours by focusing on the attitudes and beliefs of individuals [17,18]. This model has been adapted to explore a variety of long- and short-term health behaviours, including sexual risk behaviours and the transmission of HIV/AIDS [19]. The key variables of this model are Perceived Threat, which consists of two parts: Perceived Susceptibility (one's subjective perception of the risk of contracting a health condition) and Perceived Severity (feelings concerning the seriousness of contracting an illness or of leaving it untreated); Perceived Benefits, the believed effectiveness of strategies designed to reduce the threat of illness; Perceived Barriers, the potential negative consequences that may result from taking particular health actions (the only variable for which a positive score would be expected not to favour adherence); Cues to Action, events, either bodily or environmental, that motivate people to take action; and Self-Efficacy, the belief in being able to successfully execute the behaviour required to produce the desired outcomes.

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The Theory of Reasoned Action affirms that a person's behaviour is determined by attitude towards the outcome of that behaviour and by the opinions of the person's social environment [20,21]. The key variables are Attitudes, consisting of the beliefs that a person accumulates over a lifetime; Subjective Norms, beliefs about what others will think about the behaviour; Intention(s), probability, as rated by the person, that he will perform the behaviour; and Behaviour, transmission of intention into action. This theory has been applied to different health settings, including HIV infection [22].

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Data analysis

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The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous variables. Since variables other than current and nadir CD4 cell count did not follow a normal distribution, they were described by medians (interquartile range, IQR) and compared using a Mann–Whitney non-parametric test. The CD4 cell count and nadir CD4 cell count were described by means (standard deviation) and compared using a Student *t* test. For the discrete variables, number of patients and percentages were given and the χ^2 or Fisher exact test (as appropriate) were used. *P* values shown represent single-variable comparisons, to wit, the probability of statistical significance (0.05 confidence limit) when comparing 1 variable between 2 groups.

Cronbach's α was used to assess the reliability of the items that formed the constructs for evaluating patients' attitudes and beliefs about HIV infection and antiretroviral treatment. All analyses were performed with SPSS 12 (SPSS, Inc., Chicago, IL, USA).

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Results

The sociodemographic and clinical characteristics of the 87 patients enrolled are shown in Table 1. The median age was 44 (29-62) years, 63.2% were male, and 42.5% were men who had acquired HIV-1 infection through sexual intercourse with other men. Current substance abuse was reported by 34.4% of the patients, and 36.8% were co-infected with hepatitis C virus (HCV). The mean CD4 cell count was 558 (296) cells/mm^3 and 66.6% of the participants had a viral load below 50 copies/ml. Participants had been diagnosed with HIV infection and had first started antiretroviral therapy a median of 15 (8-23) and 13 (10-19) years before entering the study, respectively.

Eighty participants were taking antiretroviral medication upon entering the study. The most frequently used nucleoside reverse transcriptase inhibitors (NRTIs) were tenofovir (45%), lamivudine (57.5%) and didanosine (26.2%). The most frequently used protease inhibitor (PI) was lopinavir/ritonavir (36.2%) and the most commonly prescribed NNRTI was nevirapine (27.5%) (Table 2).

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Adherence to antiretroviral therapy

Among the 80 patients taking medication upon enrollment, 54 (67.5%) reported ≥95% of medication intake, 22 (27.5%) had adherence levels of 90-94% and 4 (5%) reported <90% adherence.

Concentrations of PIs and NNRTIs in plasma were determined in 69 patients. The remaining 11 patients were receiving only NRTI-containing regimens and were excluded from this analysis. Drug concentrations were subtherapeutic in 14/69 patients (20.3%), although 8 of them reported adherence >95%. There were no significant differences in the proportion of participants with subtherapeutic concentrations between

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the patients who reported adherence >95% and those with adherence < 95% (19.2% vs 22.1% respectively; p=0.752). On the other hand, 5 patients (6.2%), all of whom reported <95% adherence, showed drug concentrations below the lower limit of detection.

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Sociodemographic and clinical variables were compared between patients with ≥95% adherence (adherent patients) and patients with <95% adherence (non-adherent patients). Younger age ($P = 0.014$), female gender ($P = 0.005$), current substance abuse ($P = 0.004$) and HCV coinfection ($P < 0.001$) were associated with lower levels of adherence (see Table 1).

The percentage of patients with an HIV-RNA load below 50 copies/ml was similar between patients with ≥95% adherence and those with adherence of 90–94% (72.2% versus 71.6%, respectively; $P = 0.964$). Five patients with ≥95% adherence had an HIV-RNA load higher than 10 000 copies/ml. Likewise, no differences were observed in CD4 cell count between different adherence levels (>95% adherence, 588 [313] cells/mm^3 versus 90–94%, 568 [275] cells/m^3; $P = 0.794$; >95% adherence versus adherence <90%: 405 [238] cells/mm3; $P = 0.258$).

No significant differences in antiretroviral drug use were observed between adherence groups (Table 2). Adherence did not differ between patients treated with NNRTI- or PI-containing regimens ($P = 0.139$) or between once- or twice-daily regimens ($P = 0.266$).

Variables related to antiretroviral treatment

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No relationship was found between years on treatment and level of adherence (*P* = 0.257).

Twenty-eight patients (32.2%) had had at least one treatment interruption ordered by a physician. Seven (8%) were in an off-therapy period when entering the study, all following medical advice. Twenty-one (24.1%) reported a previous treatment interruption not recommended by a doctor, the main reasons being adverse events (28.5%) and feeling tired of taking medication (23.8%).

Fifteen adherent (27.7%) versus 8 non-adherent (30%) patients had had a previous physician-recommended interruption (*P* = 0.797). Seven adherent (13%) versus 10 non-adherent (38.5%) patients had interrupted treatment in the past without medical advice (*P* = 0.009).

Thirty patients (34%) reported having adverse events related to their past or current antiretroviral therapy. The median degree of limitation due to these adverse events was moderate at a median VAS score of 6 (0-10). The median subjective perception of interference of treatment in daily life was very low at 2 (0-10).

Eighteen adherent (33.3%) versus 12 non-adherent (46.1%) patients reported adverse events (*P* = 0.465) and the degree of limitation in both groups was moderate at a median VAS score of 5 (0-10) versus 6 (0-7) (*P* = 0.774), respectively. Finally, the subjective perception of interference of treatment in daily life was very low and low at 1 (0-10) versus 3 (0-8) (*P* = 0.259), in adherent and non-adherent patients, respectively.

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When patients were interviewed about the characteristics of their current antiretroviral regimen, 72 patients (90%) were classified as highly informed, 6 (7.5%) as moderately informed and 2 (2.5%) as poorly informed. No relationship was found between level of information and level of adherence ($P = 0.472$).

Attitudes and beliefs about HIV infection and antiretroviral treatment

A total of 22 items were written with the focus group to assess the dimensions studied: 3 for Perceived Susceptibility (e.g. *After so many years living with the HIV, I believe that my health will be impaired in the future*), 3 for Perceived Severity (e.g. *I believe that I have an illness*), 3 for Perceived Benefits (e.g. *Taking my medication improves my quality of life*), 3 for Perceived Barriers (e.g. *The toxicity of the medication will affect my health in the long-term*), 2 for Cues to Action (e.g. *The support of my family and friends helps me to take my medication*), 2 for Self-efficacy (*e.g. I consider myself capable enough to take my medication properly*), 2 for Attitude (e.g. *I think that HIV infection can be controlled with antiretroviral medication*), 2 for Subjective Norms (e.g. *My family and friends encourage me to take my medication properly*), and 2 for Intention (e.g. *I have the intention to take my medication as prescribed*). The original statements were in Spanish, as shown in the appendix; translations are given here by way of example for informative purposes only.

Table 3 shows that all the items that formed each dimension were highly consistent. Comparing adherent and non-adherent patients, a higher percentage of adherent patients were in agreement (strongly agree/somewhat agree) with the items that evaluated Perceived Susceptibility (adherent, 81.4% versus non-adherent, 53.8%; $P = 0.009$), Perceived Benefits (adherent, 68.5% versus non-adherent, 46.1%; $P = 0.036$), Cues to Action (adherent, 77.7% versus non-adherent, 42.3%; $P = 0.001$), Self-efficacy

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(adherent, 76.6% versus non-adherent, 54.4%; $P = 0.045$ and Intention (adherent, 98.1% versus non-adherent, 73.07%; $P = 0.001$). Perceived Barriers was the only dimension where a higher percentage of non-adherent patients was in agreement, consistent with the fact that a higher perception of barriers would be expected not to favour adherence, although the differences observed between adherent and non-adherent patients did not reach statistical significance ($P = 0.1$).

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Discussion

In our study, we assessed the adherence to antiretroviral treatment of a group of very experienced patients who had started treatment for their HIV infection ≥10 years earlier. Almost 70% of the patients enrolled had practically perfect adherence to their treatment. Moreover, only four patients had a self-reported medication intake <90%. Our findings suggest that, despite the obstacles that arise during treatment of a chronic process, a considerable number of patients are able to develop habits and strategies to take medication over very long periods of time. In this study, adherence was more related to beliefs about health and illness than to the characteristics of medication or level of knowledge about treatment. Adherent patients exhibited a higher perception of risk of developing the illness and of the benefits of therapy, higher self-efficacy and intention to adhere and were more influenced by the events that motivate medication intake. Contrary, non-adherent patients perceived more barriers from taking antiretroviral medication.

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Older age appears to be a beneficial factor favouring adherence [23]. Conversely, female gender [24] and active substance use [25] were related to lower levels of adherence. HCV-coinfected patients had worse adherence in our study, consistent with previous reports that indicate the relevance to adherence of factors like symptoms and increased morbidity derived from HCV disease and antiretroviral-related hepatotoxicity [26]. It would be thought that HIV-coinfected patients would have better adherence, considering that they are in a more vulnerable situation. However, we observe frequently in clinical practice that this is not the case. When facing a life-threatening prognosis, some patients may use mechanism of denial and minimise the seriousness of the situation. Finally, it should be highlighted that HIV-coinfected

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patients did not have higher rates of substance abuse in our study. Thus, substance abuse should not be considered the unique factor that explains the lower levels of adherence to antiretroviral therapy in this group of patients.

An interesting finding was that patients with adherence of 90–94% and ≥95% adherence had similar rates of viral suppression of <50 copies/ml. These findings are consistent with a previous study showing that patients with <95% adherence were also able to achieve viral suppression on NNRTI therapy [27]. Our study was performed on highly antiretroviral-experienced patients, and it is possible that the existence of resistant mutations may have contributed to the lack of differences between adherence groups. It may also be that patients reporting a medication intake at a rate of 90-94% during our study may fluctuate between different levels of adherence over time. Additionally, it is possible that new antiretroviral drugs with superior pharmacokinetic properties might not require such strict levels of adherence to be effective [28]. However, this hypothesis should be confirmed in larger studies. Finally, over reporting adherence should be considered among the possible factors that explain the similar rates of undetectable viral load amongst participants with adherence 90-94% and those with adherence >95%.

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The characteristics of the medication prescribed have been highlighted as a determinant of treatment adherence. However, in our study no relationship was observed between this variable and the level of adherence, confirming other studies carried out by our team [3]. Our experience reducing the number of pills and doses has a clear benefit in terms of patients' satisfaction with treatment and facilitates medication management in daily life. However, in this sample of highly experienced patients, treated in the past with very complex regimens and with current access to simpler

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schedules, the current differences between the adherence groups were better explained by psychological variables related to beliefs about health and illness than by pharmacological features. Similarly, no differences were found regarding the presence and limitation of adverse events between adherent and non-adherent patients. Although adverse events are one of the main obstacles for treatment's adherence, the specific characteristics of this highly treated population (as well, patients very experienced in dealing with adverse events) might explain this lack of difference.

Regarding the evaluation of variables related to adherence, it was interesting that both adherent and non-adherent patients followed a similar rate of structured treatment interruptions (interruptions of antiretroviral therapy decided upon by a doctor and with the patient's agreement). One of the main concerns about this approach is that patients might have difficulties adhering to treatment when it must be reinitiated. In another study conducted by our team, interruptions upon a doctor's recommendation were not associated with lower levels of subsequent adherence [29]. However, our results confirm that patients with lower levels of adherence are more likely to interrupt their treatment without a doctor's recommendation. Thus, the use of this treatment strategy should be carefully monitored if patients have had adherence problems in the past.

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In this study, we measured on patients' basic knowledge about the treatment schedule but not the level of knowledge about antiretroviral treatment in general. Our results indicate that the level of knowledge that patients had about the specific characteristics of their antiretroviral treatment (number of pills, name of drugs...) was not related to reported adherence. Thus, checking and verifying this information with the patients does not ensure their adherence to treatment and taken in isolation should not be considered an appropriate method to verify adherence.

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Patients with better adherence showed a higher perception of risk of developing the illness as well as higher perception of the benefits of medication intake. Moreover, they were more influenced by the events that motivate medication intake and they had higher self-efficacy and intention to follow the treatment. In order to reinforce adherence, these findings strongly support efforts to understand patients' perspective regarding their own health [30] in addition to just gathering objective information about the patients' health condition.

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Adherence was evaluated in this study on the basis of patients' self-reporting and assessment of drug concentrations. Both methods have advantages and drawbacks. Self-reported adherence is accessible and cheap, and appears to be a good indicator of patients' behaviour in clinical practice [31]. However, its reliability depends on the quality of communication between clinicians and patients [32] and it also tends to overestimate adherence. On the other hand, although drug concentration assessment is an objective instrument, it is not feasible in some settings and can be difficult to interpret. Low drug concentrations may be due to high inter- and intra-individual variability, not only to treatment adherence [33]. In addition, this approach only reflects adherence within the days immediately before the clinical visit, when higher than usual adherence is possible. Our findings reflect these two limitations of drug monitoring to assess adherence. More than half of the patients with subtherapeutic drug concentrations assured adherence >95%. Moreover, drug concentrations were within the therapeutic range in 80% of the participants who admitted adherence <95%. Thus, the combination of the two methods improved the evaluation of adherence in this study.

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One inherent limitation of this study is that participation was voluntary. We might think that only highly motivated patients with good levels of adherence agreed to participate. However, all participants who were approached by their physicians in fact consented. On the other hand, it is possible that physicians might have biased the population, explaining the study only to those patients who might seem more interested (with higher levels of collaboration, more involved in their own care, etc.). However, we emphasized to physicians that the only exclusion criterion was physical or mental inability to participate. Finally, our results should be interpreted with caution due to the small sample size.

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In summary, a large number of patients are able to maintain a good adherence to their treatment after more than ten years. Better adherence in highly antiretroviral-experienced patients is more related to beliefs about health and illness than to the characteristics of medication taken or level of knowledge. Thus, it is essential to include health beliefs assessment in the routine care of these patients to ensure their adherence to antiretroviral therapy.

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References

1. Moyle, G.J., & Gazzard, B.G. (1999). A risk-benefit assessment of HIV protease inhibitors. *Drug Safety,* 20(4), 299-321.

2. Swindells, S., DiRienzo, A.G., Wilkin, T., Fletcher, C.V., Margolis, D.M., Thal, G.D., et al. (2006). Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *Journal of the American medical association,* 296(7), 806-814.
3. Negredo, E., Molto, J., Munoz-Moreno, J.A., Pedrol, E., Ribera, E., Viciana, P., et al. (2004). Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. *Antiviral therapy*, 9(3), 335-342.
4. Hammer, S.M., Saag, M.S., Schechter, M., Montaner, J.S., Schooley, R.T., Jacobsen, D.M., et al. (2006). Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *Journal of the American medical association*, 296(7), 827-843.
5. Portsmouth, S.D., Osorio, J., McCormick, K., Gazzard, B.G., & Moyle, G.J. (2005). Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. *HIV medicine*, 6(3), 185-190.
6. Ironson, G., O'Cleirigh, C., Fletcher, M.A., Laurenceau, J.P., Balbin, E., Klimas, N., et al. (2005). Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. *Psychosomatic medicine*, 67(6), 1013-1021.
7. Molassiotis, A., Nahas-Lopez, V., Chung, W.Y., Lam, S.W., Li, C.K., & Lau, T.F. (2002). Factors associated with adherence to antiretroviral medication in HIV-infected patients. *International Journal of STD & AIDS*, 13(5), 301-310.
8. Halkitis, P.N., Kutnick, A.H., & Slater, S. (2005). The social realities of adherence to protease inhibitor regimens: substance use, health care and psychological states. *Journal of health psychology*, 10(4), 545-558.

For Peer Review Only

9. Carrieri, M.P., Raffi, F., Lewden, C., Sobel, A., Michelet, C., Cailleton, V., et al. (2003). Impact of early versus late adherence to highly active antiretroviral therapy on immuno-virological response: a 3-year follow-up study. *Antiviral therapy*, 8(6), 585-594.

10. Fumaz, C.R., Munoz-Moreno, J.A., Molto, J., Negredo, E., Ferrer, M.J., Sirera, G., et al. (2005). Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. *Journal of acquired immune deficiency syndromes*, 38(5), 560-565.

11. Lucas, G.M., Wu, A.W., & Cheever, L.W. (2004). Adherence to antiretroviral therapy: an update of current concepts. *Current HIV/AIDS reports*, 1(4), 172-180.

12. Tuldrà A, Fumaz CR, Ferrer MJ, Bayés R, Arnó A, Balagué M et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to Highly Active Antiretroviral Therapy. *J Acquir Inmune Defic Syndr* 2000;**25**: 221-228.

13. Paterson, D.L., Swindells, S., Mohr, J., Brester, M., Vergis, E.N., Squier, C., et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of internal medicine*, 133(1), 21-30.

14. Molto, J., Blanco, A., Miranda, C., Miranda, J., Puig, J., Valle, M., et al. (2006). Variability in non-nucleoside reverse transcriptase and protease inhibitor concentrations among HIV-infected adults in routine clinical practice. *British journal of clinical pharmacology*, 62(5), 560-566.

15. González de Requena, D., Bonora, S., Canta, F., Marrone, R., D'Avolio, A., Sciandra, M., et al. Atazanavir Ctrough is associated with efficacy and safety: definition of therapeutic range. 12th Conference on Retroviruses and Opportunistic Infections. Boston, February 2005. [abstract 645]

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16. Back, D.J., Blaschke, T.F., Boucher, C., Burger, D., Fletcher, C., Flexner, C., et al. Optimising TDM in HIV clinical care: a practical guide to performing therapeutic drug monitoring (TDM) for antiretroviral agents. Available at: http://www.hivpharmacology.com. Accessed 10 January 2005.

17. Rosenstock, I.M. (1974). Historical origins of the Health Belief Model. *Health Education Monographs*, 2, 328-335.

18. Becker, M.H. (1974). The Health Belief Model and Personal Health Behavior. *Health Education Monographs*, 2, 354-386.

19. Zak-Place, J., & Stern, M. (2004). Health belief factors and dispositional optimism as predictors of STD and HIV preventive behavior. *Journal of American college health*, 52(5), 229-236.

20. Ajzen, I., & Fishbein, M. (1975). *Belief, Attitude, Intention and Behavior: An Introduction to Theory and Research*. Reading, Mass: Addison-Wesley.

21. Ajzen, I., & Fishbein, M. (1980). *Understanding Attitudes and Predicting Social Behavior*. Englewood Cliffs, NJ: Prentice-Hall.

22. Schultz, J.R., Butler, R.B., McKernan, L., & Boelsen, R; Haemophilia Behavioral Intervention Evaluation Project. (2001). Developing theory-based risk-reduction interventions for HIV-positive young people with haemophilia. *Haemophilia*, 7(1), 64-71.

23. Glass, T.R., De Geest, S-, Weber, R-, Vernazza, P.L., Rickenbach, M., Furrer, H., et al. (2006). Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. *Journal of acquired immune deficiency syndromes*, 41(3), 385-392.

24. van Servellen, G., Chang, B., Garcia, L., & Lombardi,, E. (2002). Individual and system level factors associated with treatment nonadherence in human

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immunodeficiency virus-infected men and women. *AIDS patient care STDS*, 16(6), 269-281.

25. Halkitis, P.N., Kutnick, A.H., & Slater, S. (2005). The social realities of adherence to protease inhibitor regimens: substance use, health care and psychological states. *Journal of health psychology*, 10(4), 545-558.

26. Braitstein, P., Justice, A., Bangsberg, D.R., Yip, B., Alfonso, V., Schechter, M.T., et al. (2006). Hepatitis C coinfection is independently associated with decreased adherence to antiretroviral therapy in a population-based HIV cohort. *AIDS*, 20(3), 323-331.

27. Bangsberg, D.R. (2006). Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clinical infectious diseases*, 43(7), 939-941.

28. Shuter, J., Sarlo, J.A., Kanmaz, T.J., Rode, R.A., & Zingman, B.S. The "95% adherence rule" may not apply to lopinavir/ritonavir (LPV/r) based HAART regimens [abstract TUPE0110]. Presented at the XVI International AIDS Conference; 2006; Toronto, Canada.

29. Ruiz, L., Paredes, R., Gómez, G., Romeu, J., Domingo, P., Pérez-Alvarez, N., et al. (2007). Antiretroviral Therapy Interruption Guided by CD4+ Counts and Plasma HIV-1 RNA Levels in Chronically HIV-1-Infected Patients. *AIDS*, 21(2), 169-178.

30. Locadia, M., van Grieken, R.A., Prins, J.M., de Vries, H.J., Sprangers, M.A., & Nieuwkerk, P.T. (2006). Patients' preferences regarding the timing of highly active antiretroviral therapy initiation for chronic asymptomatic HIV-1 infection. *Antiviral therapy*, 11(3), 335-341.

31. Murri, R., Ammassari, A., Gallicano, K., De Luca, A., Cingolani, A., Jacobson, D., et al. (2000). Patient-reported nonadherence to HAART is related to protease

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inhibitor levels. *Journal of acquired immune deficiency syndromes*, 24(2), 123-128.

32. Beach, M.C., Keruly, J., & Moore, R.D. (2006). Is the quality of the patient-provider relationship associated with better adherence and health outcomes for patients with HIV? *Journal of general internal medicine,* 21(6), 661-665.

33. Nettles, R.E., Kieffer, T.L., Parsons, T., Johnson, J., Cofrancesco, J. Jr, Gallant, J.E., et al. (2006). Marked intraindividual variability in antiretroviral concentrations may limit the utility of therapeutic drug monitoring. *Clinical infectious diseases*, 42(8), 1189-1196.

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APPENDIX

Spanish items used to assess the dimensions of the Health Belief Model and Theory of Reasoning Action

Perceived Susceptibility

1. *Después de tantos años viviendo con el VIH, creo que mi estado de salud empeorará en el futuro.*

2. *Es lógico pensar que en algún momento desarrollaré una enfermedad oportunista.*

3. *Es probable que mi estado de salud sufra altibajos en los próximos años.*

Perceived Severity

1. *Creo que tengo una enfermedad.*

2. *La infección por VIH sigue siendo un problema de salud grave.*

3. *Mi estado de salud necesita de cuidados importantes y continuos.*

Perceived Benefits

1. *Tomar mi medicación mejora mi calidad de vida.*

2. *La medicación me permite seguir una vida prácticamente normal.*

3. *Tomar mi medicación disminuye la posibilidad de desarrollar infecciones oportunistas*

Perceived Barriers

1. *La toxicidad de la medicación afectará a mi salud a largo plazo.*

2. *Tomar mi medicación es incómodo y molesto.*

3. *Tomar mi medicación empeora mi calidad de vida.*

Cues for Action

1. *El apoyo de mi familia y amigos me ayuda para tomar la medicación.*

2. *La información que me dan en mi hospital me ayuda para tomar la medicación*

Self-efficacy

1. *Me siento capaz de tomar la medicación de forma adecuada.*

2. *Creo que puedo seguir las recomendaciones que recibo de mi médico sin ninguna dificultad.*

Attitude

1. *Creo que la infección por VIH puede controlarse con medicación antirretroviral.*

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2. *Creo que la medicación me ayuda a evitar el progreso de la infección.*

Subjective Norms

1. *Mi familia y amigos me animan a tomar la medicación de forma adecuada.*

2. *Mis seres queridos creen que la medicación es fundamental para controlar la infección por VIH.*

Intention

1. *Tengo la intención de tomar mi medicación tal como me lo ha indicado mi médico.*

2. *Tengo la intención de cuidar mi salud.*

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Table 1. Baseline sociodemographic and clinical characteristics of the patients

Characteristics	Total n=87	Adherent patients* n= 54	Non-adherent patients† n=26	*P* value
Age‡ (y)	44 (29-62)	44 (34-62)	41 (29-55)	0.014§
Sex‖				0.005§
Male	55 (63.2)	41 (75.9)	11 (42.5)	
Female	32 (36.8)	13 (24.1)	15 (57.7)	
Infection route‖				0.1
Men who have sex with men	37 (42.5)	28 (51.9)	7 (26.9)	
Injection drug use	29 (33.3)	13 (24.1)	13 (50)	
Heterosexual	18 (20.7)	11 (20.4)	5 (19.2)	
Haemophilia	1 (1.1)	1 (1.9)	-	
Unknown	2 (2.2)	1 (1.9)	1 (3.8)	
Job status‖				
Employed	56 (64.4)	34 (63)	18 (69.2)	0.581
Years since HIV diagnosis‡	15 (8-23)	14.5 (8-23)	15 (11-21)	0.682
Years on antiretroviral treatment‡	13 (10-19)	14 (11-19)	13 (10-16)	0.257
CD4 count (cells/mm^3)¶	558 (296)	588 (313)	537 (272)	0.480
Nadir CD4 count (cells/mm^3)¶	177 (113)	175 (119)	177 (109)	0.934
Plasma HIV-1 RNA copies/ml‡	50 (4920-31 400)	50 (50-300 000)	50 (50-77)	0.652
HIV-1 RNA<50 copies/ml‖	58 (66.6)	39 (72.2)	19 (73.03)	0.078
Current substance abuse†	30 (34.4)	12 (22.2)	14 (53.8)	0.004§
Methadone‖	5 (5.7)	–	5 (19.2)	1.000
HCV coinfection‖	32 (36.8)	12 (22.2)	17 (65.4)	<0.001§
Current interferon therapy‖	5 (5.7)	2 (3.7)	3 (11.5)	0.323
Lipodystrophy‖	55 (67.8)	34 (63)	17 (65.4)	0.695

Deleted: situation

* Patients with self-reported adherence to antiretroviral treatment ≥95% upon entry

† Patients with self-reported adherence to antiretroviral treatment <95% upon entry

‡ Data are median (interquartile range)

§ Statistically significant difference

‖ Data are number (%)

¶ Data are mean (standard deviation)

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Table 2. Current antiretroviral drugs in patients taking HAART at the study entry

Drugs	Total* n=80	Adherent patients*† n= 54	Non-adherent patients*‡ n=26	*P* value
Nucleoside reverse transcriptase inhibitors				
Zidovudine	5 (6.2)	3 (5.6)	2 (7.7)	0.658
Didanosine	21 (26.2)	13 (24.1)	8 (30.8)	0.591
Lamivudine	46 (57.5)	33 (61.1)	13 (50)	0.469
Stavudine	6 (7.5)	4 (7.4)	2 (7.7)	1.000
Abacavir	18 (22.5)	11 (20.4)	7 (26.9)	0.572
Trizivir	4 (5)	2 (3.7)	2 (7.7)	0.592
Emtricitabine	2 (2.5)	2 (3.7)	–	1.000
Tenofovir	36 (45)	28 (51.9)	8 (30.8)	0.096
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine	22 (27.5)	13 (24.1)	9 (34.6)	0.423
Efavirenz	11 (13.7)	10 (18.5)	1 (3.8)	0.093
Protease inhibitors				
Ritonavir	11 (13.7)	10 (18.5)	1 (3.8)	0.093
Lopinavir/ritonavir	29 (36.2)	16 (29.6)	13 (50)	0.088
Amprenavir	1 (1.2)	1 (1.9)	–	1.000
Nelfinavir	7 (8.7)	3 (5.6)	4 (15.4)	0.206
Indinavir	1 (1.2)	1 (1.9)	–	1.000
Saquinavir	8 (10)	7 (12.9)	1 (3.8)	0.381
Atazanavir	8 (10)	5 (9.3)	3 (11.5)	0.710
Tipranavir	2 (2.5)	2 (3.7)	–	1.000
Fusion inhibitors				
T-20	4 (5)	1 (1.9)	3 (11.5)	0.103

* Data are number (%).

† Patients with self-reported adherence to antiretroviral treatment ≥95% upon entry

‡ Patients with self-reported adherence to antiretroviral treatment <95% upon entry

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Table 3. Dimensions of the Health Belief Model and Theory of Reasoned Action, thematic grouping of items and differences between adherent and non-adherent patients

Dimensions of Health Belief Model and Theory of Reasoned Action	No of items	Cronbach's α	Adherent patients agreeing or strongly agreeing (%)*	Non-adherent patients agreeing or strongly agreeing (%) †	*P* value
Perceived susceptibility	3	0.8	81.4	53.8	0.009
Perceived severity	3	0.6	62.9	54.2	0.4
Perceived Benefits	3	0.6	69.5	45.1	0.036¶
Perceived Barriers	3	0.6	22.2	38.4	0.1
Cues to action	2	0.7	77.7	42.3	0.001¶
Self-efficacy	2	0.7	76.6	54.4	0.045¶
Attitude	2	0.7	96.2	80.7	0.06
Subjective norm	2	0.9	79.6	80.7	0.9
Intention	2	0.6	98.1	73.07	0.001¶

* Patients with self-reported adherence to antiretroviral treatment ≥95% upon entry

† Patients with self-reported adherence to antiretroviral treatment <95% upon entry

¶ Statistically significant difference between adherent and non-adherent patients.

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