Factors Affecting Patient Adherence to Highly Active Antiretroviral Therapy

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OBJECTIVE: To determine the clinical and demographic variables related to adherence to highly active antiretroviral therapy (HAART) in patients treated in our hospital and identify the characteristics of nonadherent patients.

METHODS: Outpatients receiving treatment with HAART (n = 283) were asked about variables related to adherence and to complete the APGAR (family support), State-Trait Anxiety questionnaire (STAI) (emotional situation), and IAS (social support) questionnaires. Patients were classified in 2 groups depending on whether adherence was ≥95% or <95%. Adherence was defined as the percentage of dosage forms prescribed that were obtained by the patient at the hospital pharmacy. A multivariate analysis was created to analyze how each significant variable affected adherence.

RESULTS: Our data showed significant nonadherence for patients with the following factors: low level of education, unemployed, emotional situation, and abuse of substances including intravenous drugs. All significant variables were included in a logistic regression model to optimize the results. This model considered 4 variables: age (95% CI 0.89 to 0.99), number of antiretroviral drugs (95% CI 1.05 to 2.11), STAI Anxiety/Trait test (95% CI 2.02 to 6.02), and abuse of drugs (95% CI 1.20 to 3.95).

CONCLUSIONS: We recommended special intervention to reinforce adherence for younger patients, patients taking a high number of antiretroviral drugs, those who have a history of intravenous drug use, and those with high anxiety status.

KEY WORDS: adherence, antiretroviral treatment, adherence.

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ecent advances in highly active antiretroviral therapy (HAART) have resulted in delayed disease progression, improved survival, and decreased incidence of opportunistic infection and hospital admission in HIV-infected patients. Several factors may affect the success of this therapy including clinical condition, infectious viral strain,

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previous antiretroviral treatments, baseline viral load, and pharmacokinetic variability. Among these factors, inadequate HAART adherence is of concern because of its predictive relevance, both in controlled clinical trials and cohort studies.²⁻⁴

Using viral response (plasma viral load) as an effectiveness indicator, Paterson et al.⁵ showed that 81% of patients with adherence >95% maintained an undetectable viral load; however, when adherence was 90–95%, only 64% of patients showed an undetectable viral load. This percentage decreased from 50% to 25% to 6% when adherence was 80–90%, 70–80%, and <70%, respectively. The relationship between HAART adherence and other variables has been demonstrated by correlating mortality with

adherence. For every 10% decrease in adherence, mortality increases by 16%. Expert groups currently recommend an adherence percentage ≥95% to achieve optimal results, 7

Several factors may prevent HAART adherence from being optimal. However, demographic issues, such as age, gender, and race, fail to correlate consistently with inadequate adherence, and studies reported to date show conflicting results. 8-10 Older patients have been reported to exhibit better adherence to treatment except for subjects >75 years of age, for whom comorbidity worsens adherence. 11 Likewise, women and black patients have demonstrated a lower adherence to HAART. 12

Psychosocial factors may also influence adherence to antiretroviral treatment. Anxiety and depression, pathologies that are relatively frequent in HIV-infected patients, are usually linked to inadequate adherence. ^{10,11} Using different measures to evaluate the emotional condition of patients, Singh et al. ¹³ showed that subjects with higher emotional stability exhibit higher adherence levels. The influence of social factors on antiretroviral treatment has also been assessed; as a result, it has been reported that having a stable home and family support might be linked to better adherence. ¹⁴ On the other hand, alcohol consumption, most frequently related to concomitant abuse of other drugs, is related to inadequate adherence. ^{8,14}

With respect to the antiretroviral treatment itself, it is assumed that adherence decreases as the complexity of the therapeutic regimen increases. For these reasons, establishing factors related to satisfactory HAART adherence, together with their combined influence upon HIV-infected patients, is of interest. This would permit recognition of nonadherent patients and to introduce, from the early stages of clinical follow-up, support programs aimed at diminishing the possibility of nonadherence. Based on this profile, selected patients would benefit from enhanced interventions directed toward improving adherence to antiretroviral treatment.

Hence, the aim of this study was to establish variables related to inadequate HAART adherence in patients of the 11th Health Area, Madrid, Spain, in an attempt to identify the profile of the nonadherent patient.

Methods

The sample comprised patients recruited from the HIV Unit at the Doce de Octubre Hospital between November 2000 and January 2001 who had been on HAART for at least 6 months. The recruitment period lasted 3 months, assessing an average of 100 possible subjects per month in order to achieve precise estimations as explained below.

The following variables were investigated: age, gender, education level (no/primary education vs. higher education), labor situation (employed/unemployed), family status (alone/accompanied), family support, anxiety, social support, drug abuse, mode of transmission, and characteristics of the combination antiretroviral treatment (number of drugs, dosage forms, daily doses).

Patients were asked about variables concerning age, education level, labor situation, and family status. Then, after being instructed, they completed several specific tests, which took about 15 minutes. Data related to drug use, mode of transmission, clinical stage of HIV infection, and HAART features were collected from the patients' medical history data. Patients were classified according to Centers for Disease Control and Prevention (CDC) criteria. 15

Social support was measured by the IAS test, a questionnaire derived from the ISS test (measures perceived social support index) according to variations. ¹⁶ An ISS score <10 points indicates insufficient perceived social support. We used that cutoff of 10 points, which would allow us to recognize the absence or presence of adequate social support.

Anxiety was measured using the State-Trait Anxiety Questionnaire (STAI).¹⁷ This instrument covers differentiated self-assessment scales that measure 2 independent conceptions of anxiety: state (S) and trait (T). Anxiety/state (A/S) is defined as a subject's temporary emotional state or condition characterized by subjective feelings of stress and apprehension consciously perceived, together with autonomic nervous hyperactivity. This situation may vary with time and fluctuate in intensity. Anxiety/trait (A/T) is the relatively stable anxious tendency of a subject to perceive situations as threatening and consequently have his or her A/S increased. STAI has demonstrated usefulness in clinical practice, since the score is a sensitive index of the temporary anxiety level in patients committed to psychiatric facilities or undergoing psychotherapy or behavioral therapy. It can also be employed to measure changes observed in these cases in the A/S variable. The fundamental features evaluated by A/S are stress, nervousness, concern, and apprehension. The 75th percentile of scores obtained by the population employed to validate the test was used in both cases.17

Family support was evaluated by means of the APGAR test, ¹⁸ which attempts to establish to what extent the patient is satisfied with his or her family circle. This test comprises 5 variables defining a family circle considered as reasonably satisfactory: adaptation, companionship, growth, affection, and resolution capacity.

Patients were classified as adherent or nonadherent according to an indirect method based on correlating the dosage of every antiretroviral drug prescribed with the number of dosage forms dispensed by the Pharmacy Department and the dispensation interval. Doses dispensed and intervals were recorded in a computer-controlled database. The percentage of fulfillment was assessed for every drug and for the total number of antiretroviral agents in the 4-6 months prior to a patient's inclusion in the study. Patients showing adherence ≥95% were considered adherent. while those showing adherence <95% were considered nonadherent. If a patient stated problems related to HAART adherence when interviewed, he or she was considered to be nonadherent even if the aforementioned indirect method revealed that his or her adherence indicator was ≥95%. All of the subjects were ambulatory and their antiretroviral drugs were dispensed monthly, free of charge, by the Pharmacy Department. If during the study period any of these patients required hospitalization, his or her adherence was considered 100% during that time.

Qualitative variables were defined by their percentages, while quantitative variables were defined by mean \pm SD for normal distribution and by interquartile range otherwise. A χ^2 test was used to compare percentages; means were compared using Student's *t*- or Mann–Whitney's U-tests.

A multivariate predictive model was built with a logistic function whose dependent variable was nonadherence. The software used to build the function was the Statistical Package for Social Sciences (SPSS 8.0). All independent variables were considered in a first step. A second model then took into account only variables that were relevant in the first model and did not show colinearity. The monotonic relationship of variables was also considered. With 10 independent variables, this multivariate analysis would require 100–150 nonadherent subjects. For a nonadherence prevalence of 50% and according to the recruiting rate observed in a pilot stage, recruitment was extended to 3 months to include 300 treated subjects.

All ranges were calculated for a 95% confidence interval and a significance level of 0.05. This study was approved by an investigational review board.

Results

The study included 357 patients. Nevertheless, during recruitment, 6 patients refused to participate, 54 did not return for clinical follow-up at the HIV-Infection Consultation, and 14 were unable to complete the tests or completed them improperly, thus preventing their evaluation. Therefore, at the end of the recruitment period, variables studied were analyzed for 283 patients. An adequate adherence could

be observed for 51.9% of the patients (95% CI 46.0% to 57.9%).

Table 1 describes patients according to their clinical condition, gender, age, education, labor situation, family status, drug abuse, anxiety test result, social and family support, and mode of transmission. Percentile distribution of results from the STAI test was similar to that of the Spanish population. Social support could be perceived by 78% of patients, while a high percentage of patients affirmed that they drank alcohol (used alone or with other drugs) in excess (>280 g/wk). Most patients had been infected with HIV parenterally. The HAART features for these patients as median (range) were: number of drugs, 3 (2–6); number of dosage forms/day, 12 (3–27); and number of doses/day, 6 (2–17).

Results from the univariate analysis of discrete variables are shown in Table 2. Patients with lower adherence are more likely to have no academic degree or to have only primary education than adherent patients. Nonadherent patients were more likely to score >75% on the anxiety scales

Table 1. Clinical Characteristics of Subjects (r	n = 283
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Characteristic	Value n (%)
Clinical status	
AIDS	173 (61)
Gender	` '
male	194 (68.6)
female	89 (31.4)
Median age (y)	36
range	25-72
Education	
no/primary studies	186 (65.7)
secondary or higher	97 (34.3)
Labor situation	
unemployed	87 (30.7)
employed, student, or retired	196 (69.3)
Family status	
alone	29 (10.2)
accompanied	254 (89.8)
APGAR test	
≤8 points >8 points	74 (26.4) 206 (73.6)
•	200 (73.6)
STAI test A/S < percentile 75	4D4 (CD C)
A/S ≥ percentile 75	194 (68.6) 82 (29)
no answer (A/S)	7 (2.5)
A/T< percentile 75	169 (59.7)
A/T ≥ percentile 75	107 (37.8)
no answer (A/T)	7 (2.5)
IAS test	
<10 points	52 (18.4)
≥10 points	221 (78.1)
no answer	10 (3.5)
Drug abuse	00 (00 0)
no alcohol and others	80 (28.3) 203 (71.7)
	203 (71.7)
Mode of transmission intravenous drug use	100 (00 0)
others	196 (69.3) 87 (30.7)
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APGAR = Family Support Test; A/S = anxiety/state; A/T = anxiety/trait; IAS = social support test; STAI = State-Trait Anxiety questionnaire.

than the general population (STAI A/S, p < 0.001; STAI A/T, p = 0.000). Consumption of drugs or alcohol and parenteral infection were more likely in nonadherent patients (p < 0.002, p = 0.002, respectively).

On average, nonadherent patients were prescribed 3.47 drugs, while the mean for adherent subjects was 3.18 (95% CI for a difference of means 0.12 to 0.47; p = 0.001). No difference was found between these groups regarding both family status and support. Social support perception was also the same in both groups (p = 0.062). Gender, clinical condition (CDC classification), number of daily doses, and number of daily dosage forms in the combination antiretroviral therapy regimen failed to show any connection with adherence.

The selected model accounts for 20% of variance and allows 67% of patients to be classified properly. Presenting a score on the anxiety trait test 75% greater than that of the general population means nonadherence risk increased 3.49-fold (95% CI 2.02 to 6.02). Drug or alcohol consumption increased the nonadherence risk by a factor of 2.18 (95% CI 1.20 to 3.95), while every new drug prescribed entailed an increase of 54% in the probability that the treatment was not used correctly (95% CI 1.05 to 2.11). Age was shown to be a protective factor, since every year decreased the chances of inadequate adherence by 7% (95% CI 0.89 to 0.99). No other independent variables were predictive of nonadherence.

Discussion

Use of HAART therapy has allowed a dramatic decrease in the mortality rate and incidence of opportunistic diseases in HIV-infected subjects. In clinical trials, between 80% and 90% of patients reach and maintain undetectable viral loads. Nevertheless, in daily clinical practice, <50% of patients are able to accomplish that clinical condition.20 Inadequate adherence to HAART is unanimously considered to be the main reason for therapeutic failure in both treated and untreated patients. This circumstance becomes complicated due to the fact that, while for other pathologies an adherence of 80% is considered suitable, efficacy against HIV infection, as mentioned above, is achieved only with adherence levels >95%. In our study, only 51.9% of the patients showed adherence ≥95%, a low value, which is in agreement with that reported in other studies.21

With respect to demographic issues, gender could not be established as a predictive factor of nonadherence. Despite the fact that some studies have reported that women tend to be less adherent than men, no agreement has been found to date. 9,22,23 We can also conclude that adherence improves with age. The influence of these factors on HAART adherence is under discussion; some studies based on univariate models have found that factors such as age, gender, and race are unrelated to adherence. 8,9,13 Using a multivariate model, Paterson et al. 10 reported similar results with respect to age. However, other studies have established that age ≤40 years is associated with inadequate adherence, 22 while older

patients show better adherence. 10,21 Our results indicate that, in middle-aged individuals, adherence increases with age regardless of emotional conditions and drug consumption habits.

The analysis of psychosocial factors in our patients has allowed us to detect relevant differences between adherent and nonadherent patients. Patients who have secondary or higher education and are employed appear to exhibit adherence significantly >95%. Comparable results have been reported.²¹ Nevertheless, other trials^{10,13} found that these variables are not determining factors in the prediction of poor adherence to antiretroviral treatment. Concerning

anxiety and emotional situation, we detected significant differences between the groups of patients. It is noteworthy that A/T is a predictive factor of improper adherence while A/S is not. This may be due to the fact that these parameters, as stated above, measure different aspects of the emotional situation. It should be also taken into account that a temporary situation has more influence on personality traits and could be explained by a high correlation between these 2 variables. To date, several authors have agreed to establish a marked influence of psychological factors, such as depression and anxiety, on adherence.^{13,21} Paterson et al.¹⁰ stated that a lower psychiatric morbidity can be re-

Characteristic	v	Value n (%)	Total
Education	no/primary education	secondary or higher	
nonadherent adherent TOTAL	100 (35.3) 86 (30.4) 186 (65.7)	36 (12.7) 61 (21.6) 97 (34.3)	136 (48.1) 147 (51.9) 283 (100)
		p = 0.008	,
Labor situation	unemployed	employed, student, or retired	
nonadherent adherent TOTAL	51 (18.0) 36 (12.7) 87 (30.7)	85 (30.0) 111 (39.2) 196 (69.3) p = 0.018	136 (48.1) 147 (51.9) 283 (100)
Family status	living alone	living accompanied	
nonadherent adherent TOTAL	14 (4.9) 15 (5.3) 29 (10.2)	122 (43.1) 132 (46.6) 254 (89.8) p = 0.980	136 (48.1) 147 (51.9) 283 (100)
Family support	APGAR ≤8 points	APGAR >8 points	
nonadherent adherent TOTAL	41 (14.6) 33 (11.8) 74 (26.4)	94 (33.6) 112 (40.0) 206 (73.6) p = 0.149	135 (48.2) 145 (51.8) 280 (100)
Emotional status A/S	STAI A/S <75 percentile	STALA/S ≥75 percentile	
nonadherent adherent TOTAL	81 (29.3) 113 (41.0) 194 (70.3)	52 (18.8) 30 (10.9) 82 (29.7) p = 0.001	133 (48.2) 143 (51.8) 276 (100)
Emotional status A/T	STAI A/T <75 percentile	STALA/T ≥75 percentile	
nonadherent adherent TOTAL	61 (22.1) 108 (39.1) 169 (61.2)	71 (25.7) 36 (13.0) 107 (38.8) p < 0.001	132 (47.8) 144 (52.2) 276 (100)
Social support	IAS <10 points	IAS ≥10 points	
nonadherent adherent TOTAL	31 (11.4) 21 (7.7) 52 (19.0)	100 (36.6) 121 (44.3) 221 (81.0) p = 0.062	131 (48.0) 142 (52.0) 273 (100)
Alcohol and/or drug abuse	no	yes	
nonadherent adherent TOTAL	27 (9.5) 53 (18.7) 80 (28.3)	109 (38.5) 94 (33.2) 203 (71.7)	136 (48.1) 147 (51.9) 283 (100)
Mode of transmission	intravenous drug use	p = 0.002 other	
nonadherent adherent TOTAL	106 (37.5) 90 (31.8) 196 (69.3)	30 (10.6) 57 (20.1) 87 (30.7)	136 (48.1) 147 (51.9) 283 (100)

APGAR = family support test; A/S = anxiety/state; A/T = anxiety/trait; IAS = social support test; STAI = State-Trait Anxiety questionnaire. *There are discrepancies in some total percentages due to rounding.

garded as a predictive factor of good adherence (OR = 1.7). Likewise, Tuldra et al.²⁴ reported significant differences, which may compromise adherence, between adherent and nonadherent patients in a study with 65 patients regarding the emotional state. Both family status and support (as measured by the IAS test) have failed to be predictors of adherence to antiretroviral therapy in our study; nevertheless, other results have associated having fixed housing and structured family and friends with good adherence to HAART.¹¹ This disagreement may be due to the fact that our study distinguished only between living alone or with others, and failed to take into account either the relationships with the other people who live with the patient or possession of fixed housing.

On the other hand, alcohol and/or drug abuse has been clearly associated with inadequate adherence to antiretroviral therapy. 12,13,25-27 Our present work supports the high predictive capacity of this feature, which increases the risk of nonadherence 2.18-fold.

Intravenous drug use has been identified as a predictive factor of improper adherence. One investigation established that patients who have not consumed drugs parenterally show a significantly better adherence to HAART.¹³ The probability of intravenous drug users showing proper adherence to zidovudine treatment decreased 3.7-fold with respect to nonusers. Other results support this observation and assess that alcohol or drug users exhibit lower CD4+levels, viral load decrease, and are significantly less adherent.⁸ This situation calls for the intervention of clinicians to improve adherence, since results indicate that patients who have stopped drug abuse eventually show the same adherence as those who have not abused drugs.²⁸

Mode of HIV transmission is apparently related to adherence as revealed by univariate analysis; this observation is supported by other results,²³ but such association is not maintained in the multivariate analysis. This discrepancy may be due to the fact that subjects who had been infected parenterally tend to maintain drug abuse habits more frequently than those who were infected in other ways.

The influence of treatment characteristics on adherence is also controversial. In the 1990s, when combination therapies started to be used, some studies reported that patients receiving only 1 drug were more adherent than those receiving double therapy with reverse transcriptase inhibitors.14,29 It is now commonly accepted that adherence decreases when the number of dosage forms, doses, or drugs increases.30,31 In this regard, the PACTA study31 revealed that, according to the patient's perspective, reducing the number of dosage forms during HAART would be the most effective way of improving adherence (12.1 dosage forms were prescribed on average in that study). Conversely, other authors have reported that adherence remains unaffected by the number of drugs that the patient is prescribed^{25,32-34}; Singh et al.³² and Walsh et al.³³ indicated that the number of daily and retroviral drugs that the patient is prescribed is not related to adherence.

We failed to find any relationship between dosage (number of dosage forms, number of daily doses) and adherence;

nonetheless, according to our results, every new drug prescribed augments by 54% the risk of improper adherence. This observation can be explained by an increase in the occurrence of minor adverse effects, interference in the patient's everyday life, or increased difficulty in adherence.^{14,35}

Among the limitations inherent in our work, it should be noted that it was a cross-sectional study measuring adherence indirectly; nevertheless, the quality of patient records, along with the fact that drug administration was centralized, diminishes bias when estimating adherence. However, results attained in this way could be overestimated, since it is possible for a patient to discontinue the prescribed drug, while there is no chance for underestimation.

On the other hand, the circumstances under which drugs are taken, as well as the relationship with food ingestion and whether the drugs are properly stored, have not been investigated. A subject considered as adherent in our study could be regarded as nonadherent should all of these factors be taken into account. Adherence to a treatment involves factors other than simply discontinuing drugs³⁴; however, indirect measurements, despite their drawbacks, have been largely recommended, employed, and compared in numerous studies. ^{1,10,21,23,25,34,35}

Other limitations are related to the debated capacity of the instruments employed to measure anxiety levels, social support, and family support, an issue that might influence our findings. Despite this, utilization of similar instruments with acceptable reliability should lead to similar results, and the instruments at hand will continue to be used until more reliable tools are developed.

Summary

We have confirmed that both patient- and treatment-related factors can predict inadequate adherence to HAART. Other issues pertinent to clinicians have not been recognized in this study, but it can be stated that young patients, patients abusing drugs, those taking a high number of antiretroviral agents, and those showing noticeable anxiety levels require special attention to improve adherence. Likewise, choosing a therapeutic alternative that involves the minimal number of drugs will improve adherence. This is an essential requirement for long-lasting suppression of viral replication, with consequences both for the patient's and the community's state of health.

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EXTRACTO

OBJETIVO: El objetivo de este estudio es determinar las variables clínicas y demográficas relacionadas con la adherencia al tratamiento antirretroviral de alta actividad (HAART) e identificar las características del paciente no adherente.

MÉTODOS: Se analizaron diferentes variables relacionadas con la adherencia en 283 pacientes en tratamiento con terapia antirretroviral y se cumplimentaron los cuestionarios APGAR (soporte familiar), STAI (situación emocional), e IAS (soporte social). Los pacientes fueron clasificados en 2 grupos dependiendo de si su adherencia al tratamiento antirretroviral fuera ≥95% (adherentes) o <95% (no adherentes). La adherencia se calculó correlacionando la pauta posológica con el intervalo de dispensación y el número de formas farmacéuticas dispensadas al paciente por el Servicio de Farmacia Hospitalaria. Se realizó un análisis multivariante para analizar como afectaba cada variable a la adherencia.

RESULTADOS: Los resultados muestran, de forma significativa, que los pacientes no adherentes tienen menor nivel educativo, son desempleados, tienen peor situación emocional, y presentan antecedentes de abuso de sustancias y uso de drogas por vía parenteral.

Todas las variables se incluyeron en un modelo de regresión logística para optimizar los resultados. Este modelo consideró 4 variables: edad (CI 95% 0.89 y 0.99), numero de medicamentos antirretrovirales de la combinación (95% CI 1.05 y 2.11), Test STAI Ansiedad/Estado (95% CI 2.02 y 6.02), y antecedentes de drogas de abuso (95% CI 1.20 y 3.95)

CONCLUSIONES: Sería recomendable especiales intervenciones para reforzar la adherencia en pacientes jóvenes que toman un número elevado de medicamentos antirretrovirales, tienen antecedentes de uso de drogas por vía parenteral, y presentan rasgos compatibles con ansiedad.

Ismael Escobar Rodríguez

RÉSUMÉ

OBJECTIF: Le but de cette étude est de déterminer les variables démographiques et cliniques liées à l'observance chez les patients d'un hôpital traités avec une thérapie antirétrovirale hautement active (TARHA) et identifier les caractéristiques des patients observants.

MÉTHODOLOGIE: On a interrogé 283 patients traités en externe avec une TARHA à propos de variables liées à l'observance et on leur a demandé de compléter les questionnaires APGAR (support familial), STAI (état

émotionnel), et IAS (réseau social). Les patients ont été classifiés en 2 groupes tout dépendant si leur observance a été évaluée ≥95% (observant) ou <95% (non observant). L'observance a été définie comme étant le pourcentage des différents médicaments prescrits que les patients sont venus chercher à la pharmacie de l'hôpital. Une analyse à variables multiples a été établie pour analyser de quelle façon chaque variable significative a affecté l'observance.

RÉSULTATS: Les données ont démontré une non observance significative chez les patients peu scolarisés, sans emploi, dans un état émotionnel plus grave, qui abusent de substances et qui utilisent des drogues par voie intraveineuse. Toutes les variables significatives ont été incorporées dans un modèle de régression logistique pour optimiser les résultats. Ce modèle a considéré 4 variables: l'âge (IC 95% 0.89 à 0.99), le nombre de médicaments antirétroviraux (IC 95% 1.05 à 2.11), STAI Anxiety/Trait test (IC 95% 2.02 à 6.02), et l'abus de drogues (IC 95% 1.20 à 3.95).

CONCLUSIONS: Les auteurs recommandent des interventions spéciales pour renforcer l'observance chez les patients plus jeunes qui ingèrent un nombre élevé de médicaments antirétroviraux, qui ont déjà utilisé des drogues par voie intraveineuse, et qui ont un niveau élevé d'anxiété.

Marie Larouche

