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Adherence to ARV medication in Romanian young adults: self-reported behaviour and psychological barriers

Running title: Barriers to ARV adherence in Romanian youth

Alexandra L. Dima^{a1}, Ana-Maria Schweitzer^b, Ruxandra Diaconiță^b,
Eduardo Remor^c and Richard Sebastian Wanless^d

^a*Department of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, UK;* ^b*Baylor Black Sea Foundation at the Centrul Clinic de Exceelență - Spitalul Clinic de Boli Infecțioase Constanța - Baylor College of Medicine - Texas Children's Hospital – Abbott Fund, Str. Prelungirea Liliacului nr.10, Constanța, Romania;* ^c*Departamento de Psicología Biológica y de la Salud, Facultad de Psicología. C/ Ivan Pavlov n 6, Universidad Autónoma de Madrid, 28049 Madrid, España;* ^d*Baylor International Pediatric AIDS Initiative, 1102 Bates St., FC-630 Houston, Texas 77030 USA*

¹ Corresponding author. Email: A.Dima@southampton.ac.uk

Adherence to antiretroviral (ARV) treatment during adolescence and young adulthood is a significant clinical issue for the current management of the HIV/AIDS epidemic in Romania. Understanding patients' own perceptions of their adherence behaviours and related psychological barriers is instrumental for developing robust interventions, and developing psychometrically sound instruments is essential for measuring adherence in this population. We adapted to Romanian an internationally validated questionnaire for the evaluation of ARV treatment adherence. We subsequently conducted a cross-sectional survey to examine its psychometric properties and investigate the relations between self-reported aspects of adherence and established indicators of adherence and health status: pill count, doctor's assessment of patient's adherence, and viral load. Results suggest that low self-reported adherence is particularly associated with experiencing side effects and emotional distress, as well as perceptions of high treatment difficulty and time demands, low self-efficacy, low treatment efficacy, and low treatment satisfaction. Perceptions of improvements in health status were overall associated with increased adherence, but feeling good physically sometimes preceded non-adherence behaviours. The questionnaire proved psychometrically sound according to classical test theory criteria (e.g., Cronbach's $\alpha = .77$, significant associations with adherence and health status indicators). Addressing adherence barriers in clinical practice with this population may help reduce their potential impact on behaviours.

Keywords: ARV adherence; self-reported adherence; barriers to adherence; HIV/AIDS; HAART; PLWHA

Introduction

As a consequence of nosocomial infection in the late 1980's, a relatively large and geographically concentrated number of HIV-infected young adults now live in Constanța, Romania, and receive support services from the Baylor Black Sea Foundation (BBSF) via a public-private partnership. This population is representative of the HIV/AIDS epidemic in Romania, where adolescents and young adults represent 70% of the total known population living with HIV/AIDS and are long-term survivors (Buzducea, Lazăr, & Mardare, 2010). The transition to adulthood raises specific issues of medication adherence due to the shift from carer-managed adherence to self-management. These issues are particularly important for HIV treatment due to its low tolerance for non-adherence (Conway, 2007). Little research, however, has been conducted so far on adherence to HIV medication in Romania and no validated instruments exist for this population. Perceived treatment-related barriers may predict low adherence in people living with a chronic illness (Remor, 2011), but their specific content and relationships with adherence behaviours and health status might vary substantially across sociocultural contexts, requiring careful investigation in new settings (Ware, Wyatt, & Bangsberg, 2006).

To begin investigating adherence in this population, we translated and adapted a short measure of ARV adherence: the CEAT-VIH ("Cuestionario para la Evaluación de la Adhesión al Tratamiento Antirretroviral en Personas con Infección por VIH y Sida" in original, Remor, 2002a, 2002b, 2008). We subsequently conducted a cross-sectional survey on BBSF service users to examine the psychometric properties of the adapted CEAT-VIH, and to investigate the relations between self-reported adherence behaviours and psychological barriers as measured by this questionnaire, and established indicators of adherence and health status. We expected CEAT-VIH to show good psychometric properties and its scores to be significantly associated with pill count, doctor's assessment of patient's adherence, and viral load. The remaining analyses were exploratory and aimed at identifying associations relevant for future research and clinical practice.

Methods

Sample

A random sample of 312 patient records was extracted from the BBSF database (Figure 1) and checked against inclusion criteria: aged 18-25, HIV+ status, currently receiving ARV therapy, likely to remain in the care of BBSF for the next year, no psychological or psychiatric issues that warrant urgent intervention, and no resistance to current treatment. The eligible patients (207) were invited to participate during their next scheduled visit; 184 patients gave written informed consent and underwent study procedures. Twenty-two patients did not complete the study (e.g. abandoned therapy, death, moved abroad, withdrawal).

Insert Figure 1 about here

Measures and procedures

The CEAT-VIH² was used to measure self-reported ARV adherence behaviours and barriers; it is a 20-item patient-reported outcome instrument developed and validated in Spain, and subsequently validated in Brazil (Remor, Milner-Moskovics, & Preussler, 2007), Colombia and Mexico (Remor, 2008), Portugal (Reis, Lencastre, Guerra, & Remor, 2009), and Peru (Tafur-Valderrama, Ortiz, Alfaro, García-Jiménez, & Faus, 2008). It understands adherence as a multifaceted and complex behaviour; items target behavioural indicators and determinants of adherence: antecedents of non-adherence behaviours, doctor-patient interaction, beliefs regarding adherence-related effort, time, degree of difficulty, self-efficacy and outcome expectations, side effects intensity, treatment knowledge, satisfaction, improvements in health, and strategies to remember taking medication. Most items have a 5-point Likert scale

² Researchers interested in the CEAT-VIH and user's manual should contact the original author at ceat.vih@gmail.com

response format, with one item on a 3-point scale and 2 dichotomous items (Appendix 1).

The CEAT-VIH adaptation included back-translation (Maneesriwongul & Dixon, 2004), examination of source language and back-translated versions regarding *comparability of language* and *similarity of interpretability* (Sperber, 2004), and piloting via cognitive interviews. A professional translator first translated the questionnaire from Spanish to Romanian; a different professional translator then translated back to Spanish. To identify problem-items, three fluent source-language speakers (two translators and one researcher, E. R.) compared the original and back-translated items regarding the formal similarity of sentences and the degree to which they might lead to the same response, using 7-point Likert scales (from 'extremely similar' to 'not at all similar'). Three items received mean scores above 2.5 (threshold recommended for item revision) and were revised.

We conducted face-to-face cognitive interviews with 11 service users (convenience sample; aged 18-22 years; 5-14 years of education). Participants responded to the questionnaire and assessed item clarity and comprehensibility, suggested rephrasing problematic items, and made additional comments. Numerous words were reported as difficult to understand (e.g., “qualify”, “effort”, “strategy”); twelve items were simplified (e.g. “How do you qualify the relationship with your doctor?” became “How do you get along with your doctor?”). Moreover, the words “medicines”, “medication”, “antiretrovirals”, “treatment” were replaced with “pills”, reported as most comprehensible. Two items (regarding the patient's perception of the effort required for and difficulty of maintaining adherence) were interpreted similarly by respondents, and were thus simplified to the same format (“How hard is it for you to take your pills?”), but with different response formats.

Pill count and the doctor's assessment were also used to measure adherence. Pill count was computed as a percentage: $(\text{total number of tablets dispensed} - \text{number of tablets returned}) / \text{total number of tablets dispensed} \times 100$. Three clinically relevant ordered categories were recorded: >95% (good adherence), 65-95% (high risk of developing resistance), and <65% (very poor adherence, unlikely to develop resistance due to low drug levels). During their next scheduled visit to the clinic for obtaining refills, participants were instructed to use only pills from their current refill. BBSF community social workers made unannounced home visits within two weeks and counted the number of pills in their pill boxes. The physicians consulting the

participating patients were asked to complete a global adherence evaluation for each patient (3 ordered categories: <80%, 80-95%, and >95%). Viral load was recorded dichotomously based on the standard Romanian clinical criterion as detectable (≥ 400 copies/ml) versus undetectable (<400 copies/ml).

Sociodemographic and treatment-related variables were included from patient files: age, gender, location (dichotomous: rural versus urban), educational level (3 ordered categories: less than high school; high school or equivalent; more than high school), educational history (dichotomous: abandoned versus ongoing/completed), number of children, ARV treatment duration and current ARV treatment complexity (number of ARV pills taken per day).

Ethics approval was obtained from the Bucharest Institute of Virology and the Baylor College of Medicine Institutional Review Boards. Data collection began with obtaining informed consent, followed by completion of self-report measures, global adherence evaluation by the physician, documentation of sociodemographic and treatment-related variables recorded from patient files, documentation of viral load test results from patient files or venipuncture for viral load test (if no results were recorded within the last 6 months), and home visit for pill count. Feedback regarding the assessment was given within the next scheduled visit. As data collection aimed for minimal interference with standard patient care, the time intervals between the various adherence-related assessments fluctuated considerably despite efforts to minimize these intervals. The dates of all adherence-related assessments were recorded.

Statistical analyses

Data analysis was performed using R (R Development Core Team, 2009). Psychometric properties were examined within classical test theory (reliability and external criterion validity), which was also used for previous CEAT-VIH validation studies. Item analyses were performed to identify areas of questionnaire improvement. Associations with sociodemographic variables were also examined. Since no theoretical claims exist regarding the structure of self-reported adherence in relation to CEAT-VIH, structural validity was not examined (e.g. factor analysis).

Correlations between adherence determinants and adherence and health status indicators were computed (applying Bonferroni correction for multiple testing) to

identify the barriers to adherence most relevant for our cohort at group level. A sensitivity analysis (G*Power 3.1.2.; Faul, Erdfelder, Lang, & Buchner, 2007) indicated that with the present sample size a correlation test can detect a minimum effect size of .22 with .80 power at a .05 alpha level, and a minimum effect size of .32 at a .05 Bonferroni corrected alpha level for 60 simultaneous tests (.0008). As the data are nonparametric, Kendall τ^3 and Wilcoxon tests are reported.

Results

Participants

From the 162 participants aged 18-24, 52.5% were female, 49.4% from urban areas, 90.7% unemployed (of which 26.5% currently studying), 13.6% with children. The majority were either currently studying or had finalized their education level (66%); 44.4% had an education level below high school, 40.7% were attending or had attended high school or equivalent, while 14.9% had a higher education level. Treatment duration ranged from 1 to 22 years (mode 11 years). Participants took between 2 and 11 ARV pills daily (mode 6 pills). Non-detectable viral load was identified for 46.3% of participants. Pill count indicated good adherence levels (i.e., >95%) for 59.9% of participants, while doctors considered only 36.4% participants adherent above 95% (Table 1). The most frequently used strategy to remember taking pills was using phone alarms (n=20), followed by being reminded by others (family, friends, partners; n=16), associating medication with food intake (n=5) and placing medication in a visible location (n=2).

Insert Table 1 about here

Psychometric analysis of the adapted CEAT-VIH

³ Kendall τ is reported to provide better estimates of the population parameters compared to Spearman's ρ (Field, 2005; Howell, 2010). We also computed Spearman's ρ and Pearson's r where appropriate, and the results were extremely similar.

CEAT-VIH total scores ranged 50-88 (possible range 17-89), showing the expected skewed distribution (median 78, mean 76.5, SD 7.55, skewness -.79, SE .19). As 85% of respondents scored <84, a score ≥ 84 could be interpreted as strict adherence in our population according to the threshold used in previous CEAT-VIH versions. Notably, this value is higher than the cut-off score for strict adherence in the original Spanish population (79; Remor, 2002b). The instrument showed acceptable reliability (Cronbach's $\alpha = .77$) and construct validity related to established indicators of adherence and health status (Table 1)⁴. Doctor's assessment of adherence was significantly associated with pill count ($\tau = .23$, $p < .001$) and viral load ($\tau = .30$, $p < .001$), which were also significantly related ($\tau = .17$, $p < .05$). Only 25.3% of participants were adherent according to both pill count and doctor's assessment, 8% were adherent according to all three adherence criteria (i.e., pill count, doctor's assessment, and CEAT-VIH self-report items) with only 6.8% also having a non-detectable viral load.

CEAT-VIH scores were not related to gender, age, education level and duration of treatment. Participants living in rural areas had slightly lower scores (means 75.37 and 77.71; $W = 2714$, $p = .06$), and those who had abandoned education had lower scores than people currently studying or with studies completed (means 74.44 and 77.60; $W = 2196$, $p < .01$). Higher treatment complexity (number of ARV pills taken daily) was unexpectedly related to slightly higher self-reported adherence levels ($\tau = .13$, $p < .05$). Pill count was not significantly associated with any sociodemographic characteristics. Patients with lower education levels or abandoned education were assessed as less adherent by doctors ($\tau = .20$ and $.22$, $p < .01$).

Most items were skewed towards reporting adherence (Appendix 1). Only two items had nonsignificant item-total correlations (reporting medication labels and use of strategies to remember taking pills). None of the items would considerably improve the reliability if deleted, therefore no items were excluded in this analysis (questionnaire improvement will be considered consistently for all CEAT-VIH versions in a dedicated study).

Psychological barriers to adherence

⁴ Time intervals between study procedures ranged from 0 to 479 days, therefore criterion validity was also examined via partial correlations controlling for time intervals between measurements (Table 1).

We examined the associations (Table 2) between fifteen CEAT-VIH items targeting adherence determinants and pill count, doctor's assessment of adherence, viral load, and self-reported adherence. The latter was computed by summing four CEAT-VIH items (1, 12, 17, and 19) measuring adherence behaviours (SR, Cronbach's $\alpha = .60$)⁵.

Insert Table 2 about here

Most items were significantly associated with self-reported adherence, except items addressing health status (10), the doctor-patient relationship (6 and 13), information and use of strategies (8 and 20). The latter four were unrelated to any adherence indicators. Doctors' assessments showed a pattern of associations similar to self-reported adherence, except a lack of association with patient's outcome expectations (9). Thus, adherence behaviours (according to both self-reports and doctor's assessment) seemed to be particularly at risk when the patients felt physically better or worse or emotionally distressed, if they perceived adherence as difficult and requiring time and effort, if they had less confidence in their ability to perform these behaviours, if they felt less satisfied with their treatment, and if they experienced more side effects. Pill count was significantly associated only with perceived self-efficacy (11), which was also related with viral load, together with the perceived difficulty of adherence and side effects (7, 15, 18) and the health status-related items (10 and 14). However effect sizes were generally small to medium, and correcting for multiple testing resulted in a lower number of significant associations (Table 2).

Discussion

Our findings contribute to the existing literature in two important ways. First, they represent a more detailed characterisation of adherence behaviours and determinants in Romanian HIV-infected young adults, adding to the limited information on this population and representing a starting point in developing behaviour change interventions. Second, they indicate that the translation and adaptation of the CEAT-

⁵ Item no. 5 had low item-total correlation (.18, $p=.03$) and low correlations with the other 4 items (-.04 to .13), reducing the subscale's Cronbach's α to .55. It was therefore excluded from this analysis.

VIH to Romanian produced a questionnaire with reliability and validity comparable to versions in other languages and countries (Reis et al., 2009; Remor, 2002a, 2002b; Remor et al., 2007; Tafur-Valderrama et al., 2008). Similar associations between adherence self-report and different indicators of HIV-related health and treatment markers have been reported as evidence of validity (e.g. Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; Muñoz-Moreno et al., 2007; Segeral et al., 2010).

Our sample had higher self-reported adherence levels relative to the original Spanish sample, as indicated by the difference in cut-off scores for strict adherence (84 versus 79). Although other studies assessing adolescents and young adults have reported higher adherence levels (e.g. Belzer, Fuchs, Luftman, & Tucker, 1999), this may have been due partly to social desirability and sampling, especially excluding patients who abandoned or were resistant to current treatment. Nevertheless, pill count and doctor's assessments indicate that numerous participants were non-adherent, which highlights the need for improving current services.

Only 8% of participants could be considered adherent according to all three measures, suggesting that each indicator constructs adherence differently. While CEAT-VIH classifies strict self-reported adherence relative to the sample (scores higher than 85% of the study participants), pill count computes adherence as medication use relative to the quantity prescribed, and doctor's assessment is a global subjective rating which considers various patient behaviours and medical data. These differences highlight the multifaceted nature of adherence and the need to assess it on multiple levels (see Bangsberg, 2008, for a comparative analysis of adherence assessment methods).

The differences between the adherence and health status indicators are also revealed by their different patterns of association with adherence barriers. Consistent with previous studies (e.g., Segeral et al., 2010; Wiener, Riekert, Ryder, & Wood, 2004), self-reported adherence and doctors' assessments were associated with most barriers, suggesting that both patients' and doctors' judgements of adherence may rely partly on patients' reports of their perceptions of these barriers. The correlation between perceptions of treatment efficacy and viral load could be partly due to respondents assessing treatment performance also based on current health status indicators, including symptoms and results of medical tests. The associations of viral load and pill count with patient's perceptions of self-efficacy, and of viral load with perceptions of adherence difficulty and side effects support established health

behaviour theories regarding the role of behavioural and control beliefs in guiding behaviour. For example, they support the role of perceived behavioural control (self-efficacy) and attitudes toward behaviour (negative appraisals of difficulty and harm) in predicting adherence, as stipulated in the Theory of Planned Behaviour (Ajzen, 1991). However causal relations are likely bidirectional and need to be further explored in longitudinal research.

Most barriers account for a significant proportion of variance in adherence behaviours, highlighting the importance of focusing counselling interventions on common difficulties (e.g., changes in physical and emotional states as antecedents of non-adherence, perceived adherence self-efficacy, concerns regarding difficulty, time, effort, side effects). However the low to medium effect sizes of these associations (Table 2) indicate that most adherence barriers have minor contributions to adherence behaviours at group level. Indeed, when controlling for multiple comparisons, fewer barriers show significant associations and only to self-reported and doctor-assessed adherence. This exposes the need to also identify difficulties relevant to individual patients when providing adherence support.

Notably, knowledge of medication labels and use of strategies to remember taking pills were unrelated to adherence or health status indicators, suggesting that these items may be deleted or reviewed to improve validity. This may equally reflect the lower relevance of these two aspects for adherence in our group. Similarly, sociodemographic factors had a minor impact on self-reported and doctor-assessed adherence, and no impact on actual pill use. However, the high unemployment rate (90.7%) reveals a difficult socioeconomic situation. Although the impact of employment status on adherence is not consistently supported in the literature, unemployment may impede adherence via the stress of job insecurity and lower control over daily schedule (Falagas, Zarkadoulia, Pliatsika, & Panos, 2008). This suggests a need for including services such as vocational counselling and training within the psychosocial support programmes offered.

The results of this study should be considered in light of its limitations. First, the sample size was reduced by logistical restrictions aimed at minimizing interference with clinical care, and thus limited our ability to test associations with smaller effect sizes while controlling adequately for Type I errors. Second, given the brevity of the CEAT-VIH, these results certainly do not exhaust the range of barriers

to adherence in this population. Therefore it would need to be complemented with additional assessments in clinical practice.

Conclusion

Our results suggest several avenues of investigation regarding the psychological barriers to ARV adherence in Romanian young adults. They indicate that low self-reported adherence is more likely when patients feel physically better or worse or emotionally distressed, and if they perceive adherence as difficult and requiring time and effort, have less confidence in their ability to adhere to the medication schedule, feel less satisfied with their treatment, experience more side effects and have lower outcome expectations. These relationships may provide a good starting point for investigating ARV adherence in this population.

Moreover, this study represents an important advancement towards reliable adherence measurement for both research and clinical practice with Romanian young adults. While the total score can be considered a good overall indicator of treatment adherence, examining responses to individual items may prove useful for identifying specific targets for intervention.

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Appendix 1

Insert Table 3 here

Figure 1: Consort diagram of study participation.

Table 1. Evidence for CEAT-VIH construct validity (Kendall τ).

External criterion	Frequencies	Correlation coefficients with CEAT-VIH score	Partial correlation with CEAT-VIH score (controlling for time intervals between measurements)
Pill count	<65% = 26 (16.1%) 65-95% = 39 (24.1%) 95-100% = 97 (59.9%)	.12, p<.05	.13 p<.05
Doctor's assessment	<80% = 54 (33.3%) 80-95% = 48 (29.6%) >95% = 59 (36.4%)	.31, p<.001	.31, p<.001
Viral load	>400c/ml = 71 (43.8%) ≤400c/ml = 91 (56.2%)	.18, p<.01	.17, p=.001

Note: N represents sample size.

Table 2. Barriers to adherence – correlations (Kendall τ) with adherence indicators and viral load

Item no.	Item	Correlations with			
		Adherence (SR)	Adherence (Pill count)	Adherence (Doctor)	Viral Load
2	Feeling physically better as antecedent of non-adherence	0.40** ^b	0.14	0.29** ^b	0.07
3	Feeling physically worse as antecedent of non-adherence	0.40** ^b	0.06	0.16*	0.11
4	Feeling sad or depressed as antecedent of non-adherence	0.40** ^b	0.09	0.28** ^b	0.06
6	Global assessment of the quality of the doctor – patient relationship	0.13	0.02	0.09	0.15
7	Beliefs regarding adherence-related effort	0.25** ^b	0.10	0.20**	0.18*
8	Perception of level of personal knowledge regarding medication	0.00	-0.03	0.09	-0.06
9	Outcome expectations	0.13*	0.07	0.09	-0.05
10	Improvements in health attributed to treatment	0.03	0.04	0.04	0.21**
11	Beliefs regarding adherence-related self-efficacy	0.22** ^b	0.18*	0.16*	0.15*
13	Perceived frequency of doctor's reinforcement of adherence behaviours	0.03	-0.05	0.08	0.00
14	Satisfaction with treatment	0.18** ^b	0.09	0.17*	0.20**
15	Perception of side effects intensity	0.25** ^b	0.03	0.17*	0.15*
16	Beliefs regarding adherence-related time	0.22** ^b	0.02	0.17*	0.09
18	Beliefs regarding adherence degree of difficulty	0.26** ^b	0.13	0.19**	0.19**
20	Strategies used to remember taking medication	0.03	-0.03	-0.07	-0.09

Notes: * $p < 0.05$ (two-tailed); ** $p < 0.01$ (two-tailed); ^b $p < 0.0008$ (two-tailed, reflecting Bonferroni correction for multiple comparisons for $\alpha = 0.05$)

Table 3: CEAT-VIH Item analysis

Item no.	Item (translated from Romanian to English for this publication)	Response scales & frequencies						Cronbach's α if item excluded	Item-total corrs (Kendall τ)
		0	1	2	3	4	5		
1	During the last week: did you ever skip taking pills? 1=always; 5=never		11	3	2	52	94	0.74	0.47**
2	During the last week: If you felt better, did you ever skip taking pills? 1=always; 5=never		12	5	0	27	118	0.74	0.49**
3	During the last week: If you felt worse after taking the pills, did you ever skip taking pills? 1=always; 5=never		9	1	3	19	130	0.75	0.44**
4	During the last week: If you felt sad or depressed, did you ever skip taking pills? 1=always; 5=never		10	5	0	21	126	0.75	0.48**
5	Do you remember what pills you take at present? (scored by comparison with prescription) 0=none remembered, 1=half remembered, 2=all remembered	7	7	148				0.77	0.05
6	How do you get along with your doctor? 1= bad; 5=good		0	0	25	6	131	0.77	0.20**
7	How difficult is it for you to take the pills? (reversed) 1=not at all; 5=very		3	7	13	44	95	0.76	0.45**
8	How much do you feel you know about the pills? 1=not at all; 5=very		12	15	30	74	31	0.78	0.16**
9	How much do you think the pills help you? 1=not at all; 5=very		0	2	3	20	137	0.76	0.29**

10	How much do you think your health status has improved since you started taking pills? 1=not at all; 5=very		2	2	13	33	112	0.76	0.28**
11	How confident are you that you can take the pills? 1=not at all; 5=very		1	2	14	45	100	0.75	0.40**
12	Do you usually take the pills at the recommended intervals? 1=no, never; 5=yes, always		10	43	21	43	45	0.75	0.47**
13	When your test results are good, does the doctor encourage you to keep taking the pills? 1=no, never; 5=yes, always		3	6	5	36	112	0.77	0.23**
14	How do you feel in general since you have started taking pills? 1=very unsatisfied; 5=very satisfied		4	3	9	56	90	0.77	0.36**
15	How bad do you feel after you take the pills? 1=very bad; 5=very good		1	2	28	53	78	0.75	0.46**
16	How much time do you think you need to spend with taking the pills? 1= a lot; 5=not at all		0	1	8	37	116	0.76	0.36**
17	How conscientious do you think you are in taking the pills? 1=not at all; 5=very		4	5	19	58	76	0.75	0.43**
18	How difficult it is for you to take the pills? 1=very difficult; 5= very easy		2	6	29	42	83	0.74	0.49**
19	Since you have started treatment, did it ever happen not to take the pills one entire day, or more? 0=yes; 1=no	107	55					0.76	0.32**
20	Do you do anything special to remember taking pills? 0=yes; 1=no	123	39					0.77	0.01

Notes: ** p<0.01 (two-tailed); CEAT-VIH © is protected by international copyright law, with all rights reserved to Eduardo Remor. Do not use without permission. For information on, or permission to use CEAT-VIH ©, please contact ceat.vih@gmail.com