A Simple Visual Analog Scale is a Valuable Tool to Assess Self-Reported Adherence in HIV-Infected Patients on Antiretroviral Treatment in a Resource-Limited Setting

S Erb[1*], E Letang[2-4], TR Glass[3], A Natamatungiro[2], D Mnzava[2], H Mapesi[2], M Haschke[5], U Duthaler[5], B Berger[5], L Muri[3], J Bader[6], C Marzolini[1], L Elzi[1,7], T Klimkait[6], W Langewitz[8], M Battegay[1*] and KIULARCO Study group

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland
[2]Ifakara Health Institute, Ifakara branch, Tanzania
[3]Swiss Tropical and Public Health Institute of Basel, Switzerland
[4]ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain
[5]Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Switzerland
[6]Division of Molecular Virology, Department Biomedicine, Petersplatz, University of Basel, Switzerland
[7]Ospedale Regionale di Bellinzona e Valli, Bellinzona, Switzerland
[8]Institute of Psychosomatic Medicine, University Hospital Basel, Switzerland

Abstract

Background: Adherence assessment in HIV-infected individuals under antiretroviral therapy (ART) is essential. The assessment tool should be reliable and easy to apply in routine clinical practice. The goal of this study was to evaluate a pictogram-enhanced visual analog scale (VAS) suitable for illiterate patients to assess self-reported adherence in ART-treated HIV-infected individuals in a resource-limited setting.

Methods: Adherence of 299 HIV-infected individuals on ART for ≥ 6 months attending an HIV-clinic in rural Tanzania was prospectively assessed 1-3 months (visit V1) and 6-9 months (V2) after a healthcare provider training in patient-centered communication by various measures: 1) 1-10 pictogram-combined Likert VAS, 2) standardized questionnaire, 3) therapeutic drug monitoring (TDM) of ART-compounds and 4) plasma HIV-RNA.

Results: 94% of the study population had no formal or only primary education. Individuals with non-adherence were detected in 17.2% by VAS (score ≤ 9) and in 10.7% by questionnaire (≥ 1 missed ART-dose/4weeks) at V1. The detection rate declined to a lesser extent with VAS (11.7%, p=0.06) compared to the questionnaire (5.7%, p=0.016) at V2. VAS strongly correlated with the questionnaire (kappa>0.50, p<0.0001). Test agreements between TDM and VAS (kappa ≤ 0.200) and between HIV-RNA and VAS (kappa ≤ 0.220) were weak to fair, but slighly superior compared to the questionnaire (kappa ≤ 0.180 and ≤ 0.060, respectively).

Conclusion: The VAS is a valuable tool for assessing self-reported adherence in illiterate HIV-infected individuals. It is inexpensive, rapid, and easier to apply than the questionnaire. Its use should be considered in resource-limited countries where more complex measures may not be feasible.

Background

Good adherence assessment is crucial for detecting HIV-infected individuals under antiretroviral treatment (ART) with suboptimal adherence, since non-adherence is associated with treatment failure [1-4]. Although no real gold standard exisits for adherence assessment, self-reported adherence assessed by standardized questionnaire is most commonly used because of its low cost and ease of use in almost all settings [5-7]. Yet, it critically depends on the healthcare providers' ability to assess adherence [8] and therefore tends to overestimate compliance [3,9-13]. Another, even simpler and faster tool to measure self-reported adherence is a visual analog scale (VAS). However, studies on the use of VAS for the assessment of adherence particularly in illiterate patients and in resource-limited setting yielded mixed results [14].

The goal of this study was to evaluate the value of an easy-to-use pictogram-enhanced visual analog scale (VAS) to assess self-reported adherence in HIV-infected individuals under ART with low literacy in a rural resource-limited setting in sub-Saharan Africa, and to compare it with a standardized and validated adherence questionnaire.

Methods

The data of this study were collected as part of an interventional cohort study published previously and conducted at the Chronic Diseases Clinic of Ifakara (CDCI), an HIV-clinic at the St. Francis Referral Hospital in rural Tanzania, from October 2013 until September 2014 [8].

All consecutive adult HIV-patients ≥ 16 years under antiretroviral therapy (ART) for at least 6 months, presenting at the CDCI between

*Corresponding author: Dr. Stefan Erb, MD, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland; Tel: +41-61-565 50 53; Fax +41-61 265 31 98; E-mail: stefan.erb@usb.ch

Prof. Manuel Battegay, MD, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland; Tel: +41-61-265 50 53; Fax +41-61 265 31 98; E-mail: manuel.battegay@usb.ch

October and November 2013, were included. In December 2013, all Tanzanian healthcare providers (n=13) working at the CDCI with direct patient contact including all six HIV-physicians received a 2 day training in basic elements of patient-centered communication and adherence assessment. At 1-3 months (visit 1) and 6-9 months (visit 2) after the intervention, the HIV-physicians assessed adherence with the help of an adherence assessment checklist [8] using several methodologies: 1) visual analog scale (VAS), 2) standardized questionnaire, 3) therapeutic drug monitoring of ART compounds, and 4) plasma HIV-RNA. Self-reported adherence was assessed in an interview format using basic elements of patient-centered communication including a non-judgemental manner to actively address problems with non-adherence.

The VAS was a 1-10 Likert scale enhanced with 3 pictograms (a thumb pointing downwards, horizontal, and upwards) for illiterate patients (Figure 1) and was used to assess self-reported adherence by asking: "How much of your HIV-medication have you taken in the last 4 weeks: Point with the finger on the line ranging from 0 to 10 to indicate where you think you are. 0 (thumb pointing downwards) means you have taken none of the pills, 5 (thumb is in a horizontal position) means you have taken half and 10 (or thumb is pointing upwards) means you have consistently taken every single pill".

The adherence questionnaire consisted of 2 validated questions as per standard procedure in the CDCI [4,15,16]: 1) "How often have you missed a dose of your HIV medication in the past 4 weeks: daily, more than once a week, once a week, once every second week, once a month, never?" and 2) "Did you miss ART ≥ 2 days in a row in the last 4 weeks: yes or no?".

Self-reported non-adherence was defined as admitting to have missed ≥ 1 dose of ART medication in the last 4 weeks by questionnaire and a VAS score ≤ 9. We evaluated other less strict definitions of non-adherence: missed ≥ 2 doses and drug holidays (≥ 2 consecutive doses of ART medication) in the last 4 weeks determined by questionnaire and a VAS score of ≤ 8, ≤ 7, ≤ 6 and ≤ 5 points.

In addition to self-reports, adherence was assessed by measuring plasma ART drug concentrations (=therapeutic drug monitoring) of efavirenz, nevirapine, lopinavir and atazanavir and by determining HIV-RNA as described previously [8]. An inadequate subtherapeutic drug concentration as a marker for non-adherence was defined as any concentration below the 2.5th percentile of published population based pharmacokinetic models for efavirenz 600 mg once daily [17], nevirapine 200 mg twice daily [18], lopinavir/ritonavir 400/100 mg twice daily [19] and atazanavir/ritonavir 300/100 mg once daily [20]. Virologic failure was defined according to WHO 2014 guidelines as a detectable HIV-RNA of ≥ 1'000 copies/mL [21].

Kappa test were used to analyze the agreement between different adherence measurements. Test performance between the visits was analyzed by McNemar's test for categorial and paired t-test for continuous variables. A p-value below 0.05 was considered significant. All analyses were performed using STATA™ software version 11 for Windows (Stata Corp, College Station, Texas, USA).

Research and ethical clearance was obtained from the Ifakara Health Institute Institutional Review Board (IHI/IRB/No.28-2013), the Medical Research Coordination Board of the Tanzanian National Institute for Medical Research (NIMR/HQIR.8a/V01.IXlI762) and the Tanzanian Commission for Science and Technology (No.2014-276-NA-2014-195). Written informed consent was obtained from all participants prior to enrolment in the study.

Results

Two hundred and ninety-nine HIV-patients were included in the study. Baseline characteristics have been published previously [8]. In brief, the median age was 41 years (interquartile range [IQR]: 35-48) and 28.8% were male. Most patients lived <5 km from the CDCI (72.9%) and worked as farmers (85.9%). 84.6% had completed primary school, only 6.3% had a higher degree and 9.1% never went to school. Sixty-five percent of the patients started ART due to WHO-stage IV or CD4+ cell count <200 cells/μL. Median time on ART at baseline was 43 months (IQR 22-64). 67% of the patients were on an efavirenz-based and 36.8% on a one-pill fixed-dose-combination ART regimen (efavirenz, tenofovir disoproxil fumarate, and emtricitabine or lamivudine). Nine percent were on a second-line protease inhibitor-based ART regimen with lopinavir/ritonavir. Median CD4+ cell count at study inclusion was 413/μL (IQR 268-610). Median time from the healthcare provider communication training (=intervention) to visits 1 and 2 was 63 (IQR 51-77) and 246 days (IQR 234-260), respectively. Adherence assessment by VAS was done for 261 and 240 and by questionnaire for 291 and 280 patients at visit 1 and 2, respectively.

At visit 1, 17.2% of the patients reported a VAS score ≤ 9, indicating adherence problems. At visit 2 this percentage declined to 11.7%, however this was statistically not significant (p=0.06). With lower VAS cut-offs the detection rate continuously declined, however, the dfferences between visit 1 and visit 2 were not statistically significant as well (Table 1).

Using a cut-off of ≤ 9 VAS identified more individuals with adherence problems than by the questionnare which detected 10.7% of patients who reported "any adherence problem" (≥ 1 ART dose
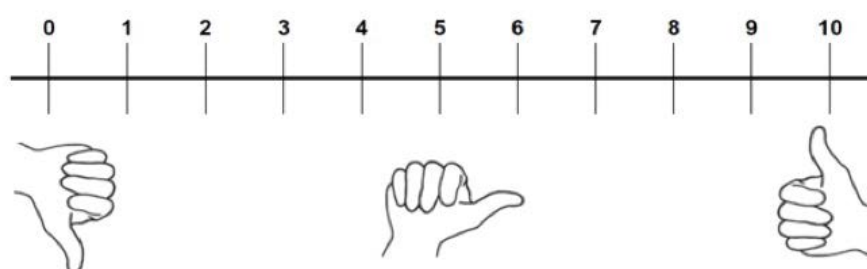
Figure 1: Pictogram-enhanced visual analog scale (VAS).
The following question was asked to the patient when showing the VAS: "How much of your HIV-medication have you taken in the last 4 weeks: Point with the finger on the line ranging from 0 to 10 to indicate where you think you are. 0 (thumb pointing downwards) means you have taken none of the pills, 5 (thumb is in a horizontal position) means you have taken half and 10 (or thumb is pointing upwards) means you have consistently taken every single pill"

	Visit 1		Visit 2		p-value [a]
Adherence self-reported VAS (n, %)	**n=261**		**n=240**		
VAS ≤ 9	45	17.2%	28	11.7%	p=0.06
VAS ≤ 8	23	8.8%	13	5.4%	p=0.18
VAS ≤ 7	7	2.7%	9	3.7%	p=0.56
VAS ≤ 6	4	1.5%	5	2.1%	p=0.71
VAS ≤ 5	3	1.1%	3	1.3%	p=1.00
VAS median (range)	10	(0-10)	10	(0-10)	p=0.12
VAS mean (± SD)	9.65	(1.08)	9.73	(1.03)	p=0.42
Adherence self-reported questionnaire (n, %)	**n=291**		**n=280**		
≥ 1 dose missed	31	10.7%	16	5.7%	p=0.02
≥ 2 doses missed	16	5.5%	11	3.9%	p=0.30
≥ 2 consecutive doses missed	8	2.7%	9	3.2%	p=0.81
Therapeutic drug monitoring[§] (n, %)	**n=275**		**n=255**		
Subtherapeutic drug concentrations all ART compounds	20	7.3%	12	4.7%	p=0.23
HIV viral load (n, %)	**n=286**		**n=284**		
HIV-RNA ≥ 1'000 copies/mL	26	9.1%	26	9.2%	p=1.00

VAS: Visual Analog Scale; n: number of patients available for analysis; SD: Standard Deviation; ART: Antiretroviral Therapy
§Subtherapeutic drug concentration was defined as any concentration below the 2.5th percentile of published population based pharmacokinetic models for efavirenz [17], nevirapine [18], lopinavir/ritonavir [19] and atazanavir/ritonavir [20]
[a]p-value refers to differences between visit 1 and visit 2 (Mc Nemar Test and paired t-test where appropriate)
Self-reported adherence assessment by VAS and questionnaire refers to a adherence period of the last 4 weeks

Table 1: Adherence assessment with VAS, questionnaire, therapeutic drug monitoring and HIV viral load.

missed in last 4 weeks) at visit 1. Until visit 2 the detection rate by questionnaire significantly decreased to 5.7% (p=0.02). When using alternative cut-offs for defining non-adherence (≥ 2 missed ART doses and drug holidays in the last 4 weeks), the reported non-adherence was only 5.5% and 2.7% at visit 1, respectively, but with a similar rates at visit 2 (Table 1).

Subtherapeutic ART drug concentrations were found in 7.3% and 4.7% and virologic failure in 9.1% and 9.2% of the patients at visit 1 and 2, respectively (Table 1).

Test agreement between VAS and questionnaire was strong for all different cut-offs. Test agreement between VAS and therapeutic drug monitoring showed the best performance at the first visit and with a VAS score ≤ 7, but was in general rather weak (kappa ≤ 0.20). Similar test agreement was found between questionnaire and therapeutic drug monitoring (kappa ≤ 0.18). Virologic failure (HIV-RNA ≥ 1'000 copies/mL) significantly correlated with subtherapeutic ART drug concentration levels at visit 1 and 2 (kappa 0.25 and 0.36, respectively, p<0.0001 for both, not shown in the table, to a lesser extent also with VAS at visit 2 (kappa 0.216 with VAS ≤ 7, p<0.001; kappa 0.171 with VAS ≤ 8, p=0.003), but not with the questionnaire (Table 2).

Discussion

Our in-depth study compared different methods of adherence measurements, including therapeutic drug monitoring. It shows that a simple pictogramm-enhanced 1-10 Likert-based VAS is a useful tool to assess self-reported adherence in ART treated HIV-infected patients with generally low literacy in a rural Sub-Saharan African setting. The VAS strongly correlates with a validated self-report questionnaire, but seems to be 1) more sensitive in the detection of patients with potential adherence problems, 2) easier to apply, and 3) less dependent on healthcare providers' communication and adherence assessment ability. Although test agreement between VAS and therapeutic drug monitoring (kappa ≤ 0.200) as well as between VAS and viral load (kappa ≤ 0.220) was rather weak, it seemed to be slightly superior than the respective correlations with a questionnaire.

Similar findings have been reported by other studies, in which VAS had exhibited a great strength of association with other self-report measures like questionnaires, but on average only minor correlation with viral load [14,22-25], irrespective if the study was done in a high- or a low-income setting.

Patients' self-reported adherence or non-adherence critically depends on the communication ability of the healthcare provider to empower HIV-infected individuals to talk about their adherence problems and the applied assessment method. Adherence assessment approaches using an interview format and attempting to address the problem of adherence in a non-judgemental way usually showed a larger effect size in the detction of adherence problems [22,26,27]. In our study, the rate of self-reported non-adherence (assessed by questionnaire and VAS) varied between 5.2% and 17.1%, and was higher at visit 1 compared to visit 2. This suggests that the detection rate could be improved by training healthcare providers appropriately in adherence assessment and patient-centered communication. However, the effect of the intervention on the detection of self-reported adherence problems seemed to wean over time even though objective adherence measures of adherence like therapeutic drug monitoring and viral load did not change over time.

Notably, only few patients showed virologic failure and/or inaedequate drug concentration during the study (both <10%) suggesting that a good standard of medical care was provided for the study population by the healthcare providers at the CDCI.

Our study has several limitations. First, the study - like any study on the topic of adherence - suffers from the lack of a commonly accepted gold standard for the assessment of adherence. We have used therapeutic drug monitoring and viral load as objective and clinically useful surrogate markers for adherence to the ART regimen. Previous reports have described a fairly good correlation between therapeutic drug monitoring of protease inhibitors and self-reported adherence measures [28-34]. In our study, however, this correlation was rather fair to weak, both for VAS and questionnaire. This might partly be explained

VAS and adherence questionnaire	Visit	Agreement	Kappa	p-value
VAS ≤ 9 and missed ≥ 1 ART dose	V1	90.80%	0.633	
	V2	90.76%	0.408	
VAS ≤ 8 and missed ≥ 1 ART dose	V1	92.34%	0.588	
	V2	95.38%	0.536	
VAS ≤ 8 and missed ≥ 2 ART doses	V1	95.79%	0.696	<0.0001*
	V2	96.65%	0.584	
VAS ≤ 7 and missed ≥ 1 ART dose	V1	90.04%	0.285	
	V2	96.22%	0.552	
VAS ≤ 7 and missed ≥ 2 ART doses	V1	95.79%	0.503	
	V2	98.33%	0.742	
VAS and therapeutic drug monitoring				
VAS ≤ 9 and subtherapeutic drug concentration**	V1	79.1%	0.062	0.14
	V2	84.6%	-0.011	0.57
	V1/V2	81.7%	0.039	0.17
VAS ≤ 8 and subtherapeutic drug concentration**	V1	87.2%	0.130	0.02
	V2	91.4%	0.050	0.23
	V1/V2	89.1%	0.106	0.01
VAS ≤ 7 and subtherapeutic drug concentration**	V1	92.0%	0.198	<0.001
	V2	93.2%	0.083	0.10
	V1/V2	92.5%	0.152	<0.001
VAS and HIV-RNA				
VAS ≤ 9 and HIV-RNA >1'000 copies/mL	V1	78.2%	0.040	0.25
	V2	83.1%	0.107	0.048
	V1/V2	80.6%	0.069	0.058
VAS ≤ 8 and HIV-RNA >1'000 copies/mL	V1	83.7%	-0.044	0.76
	V2	88.6%	0.171	0.003
	V1/V2	86.0%	0.052	0.12
VAS ≤ 7 and HIV-RNA >1'000 copies/mL	V1	88.3%	-0.044	0.80
	V2	90.3%	0.216	<0.001
	V1/V2	89.3%	0.088	0.01
Adherence questionnaire and therapeutic drug monitoring				
Missed ≥ 1 ART dose and subtherapeutic drug concentration**	V1	84.7%	0.079	0.09
	V2	90.1%	0.022	0.36
	V1/V2	87.3%	0.063	0.07
Missed ≥ 2 ART doses and subtherapeutic drug concentration**	V1	89.1%	0.110	0.03
	V2	92.2%	0.052	0.20
	V1/V2	90.6%	0.089	0.02
Missed ≥ 2 consecutive ART doses and subtherapeutic drug concentration**	V1	92.0%	0.180	<0.001
	V2	92.6%	0.058	0.17
	V1/V2	92.3%	0.128	<0.001
Adherence questionnaire and HIV-RNA				
Missed ≥ 1 ART dose and HIV-RNA ≥ 1'000 copies/mL	V1	82.4%	0.010	0.43
	V2	86.2%	0.025	0.33
	V1/V2	84.3%	0.016	0.35
Missed ≥ 2 ART doses and HIV-RNA ≥ 1'000 copies/mL	V1	86.0%	-0.023	0.66
	V2	88.3%	0.057	0.15
	V1/V2	87.2%	0.014	0.36
Missed ≥ 2 consecutive ART doses and HIV-RNA ≥ 1'000 copies/mL	V1	88.1%	-0.045	0.82
	V2	88.3%	0.01	0.42
	V1/V2	88.2%	-0.017	0.68

VAS: Visual Analog Scale; V1: Visit 1; V2: Visit 2; V1/V2: Cumulative Analysis of Sample Pairs from Visit 1 and 2
* For all analysis p<0.0001
**<2.5th percentile of published population based pharmacokinetic models
Self-reported adherence assessment by VAS and questionnaire refers to a adherence period of the last 4 weeks

Table 2: Test agreements between VAS, adherence questionnaire, therapeutic drug monitoring and HIV-RNA.

by the long half life time of efavirenz, the ART drug most frequently used in our study, which makes the detection of non-adherence in the days prior to blood sampling for drug concentration measurements more difficult. Second, the extensive adherence assessment, including

both questionnaire and in addition VAS for every patient, could have influenced patients' reporting of non-adherence. Third, understanding a Likert VAS requires some ability in abstract thinking and reasoning and some degree of literacy as well. Both might be impaired in patients with only limited formal education. To overcome this inherent drawback we combined the VAS Likert-scale with pictograms, which had previously been used successfully for adherence assessment in illiterate patients [35].

Our study also has important strengths: it was prospective and comprehensive, evaluating various subjective and objective adherence assessement measures longitudinally at different time points. With this approach we were also able to demonstrate that self-reports of non-adherence might vary according to a healthcare provider's communication skills. The focus on patients with low literacy in a resource-limited setting may provide new insights into this vulnerable and so far rarely investigated population [14]. Finally, the sample size of our study was relatively large compared to many earlier studies on the topic [22,25-27,36].

Conclusion

In conclusion, we showed that HIV-infected patients can be successfully treated with high virologic response and adherence rates in rural Tanzania. A pictogramm-combined VAS is effective for the assessment of self-reported adherence and should be considered as a sole or at least adjunct measure of adherence. With its single item-structure and visual-graphical format, the VAS is a fast and inexpensive adherence screening tool. It appears easier to apply for healthcare providers and is therefore particulary appealing in settings where more complex measures may not be feasible, including resource- or time-constrained environments such as busy clinical care settings in sub-Saharan Africa.

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