ORIGINAL ARTICLE

Adherence to treatment in Swedish HIV-infected patients

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SUMMARY

Objectives: The objectives were to assess the prevalence of adherence to antiretroviral treatment in Swedish human immunodeficiency virus (HIV)-infected patients and to evaluate factors associated with adherence.

Methods: All HIV-treated patients, who attended one of 30 (of a total of 32) Swedish infectious diseases clinics, during 7 months, were asked to complete an anonymous questionnaire containing the 9-item Morisky Medication Adherence Scale (MMAS) and questions about other factors potentially affecting adherence. The summary score of MMAS ranges from 1 to 13, where 13 indicates perfect adherence; patients scoring 11 or above (corresponding to 95% adherence level) were classified as 'adherent'.

Results and discussion: In total 946 patients participated (response rate 97·5%). The proportion of patients who reported not missing a dose during the day prior to the completion of the questionnaire was 97% and the proportion classified as 'adherent' was 63%. 'Adherent' patients were more likely to have a good relationship with their health care professionals ($P < 0.05$) and not have problems with drugs or alcohol ($P < 0.01$). Being older ($P < 0.01$) and having a shorter time on current treatment ($P < 0.01$) and on treatment in total ($P < 0.05$) were factors also associated with good adherence.

Conclusion: Factors modifiable for interventions by health care professionals are patient–provider relationship, drug or alcohol problems and patients with long treatment periods.

Keywords: acquired immunodeficiency syndrome, highly active antiretroviral therapy, human immunodeficiency virus, patient compliance, Sweden

INTRODUCTION

Like many other western countries, the impact of human immunodeficiency virus (HIV) has been relatively small in Sweden compared with the developing countries. Up until the end of 2003, 6299 people had been infected by HIV in Sweden and, at that time, about 3200 individuals were living with HIV (1). No reliable data, however, are available on how many HIV-infected patients are currently on treatment.

Highly active antiretroviral therapy (HAART) offers the possibility of remarkable clinical improvement and increased survival for HIV-infected patients (2–6). HAART is, however, demanding since 95% of the prescribed doses have to be taken in order to avoid virologic failure, a declining immune system and reduced survival (7). Although such high levels of adherence are of crucial importance for the success of HAART, the

level of adherence is still often sub-optimal in the HIV-infected population. The percentage of doses taken as prescribed varies between 53% and 93%, according to different studies (8–12). A range of factors is believed to influence adherence to HIV therapy:

- Treatment regimen [complexity of the regimen (13–15), amount and severity of side-effects (15–20)].
- Clinical setting [access to health care (21)].
- Patient–provider relationship [patient–provider relationship (22–24), support from health care professionals (11, 15, 16, 25, 26)].
- Patient variables [knowledge regarding the disease and the treatment (16), psychological function (25, 27–30), intravenous substance use and excessive alcohol use (20, 31), health beliefs (15, 20, 32) and social support (11, 15, 16, 25, 26)].

There appears to be no international report characterizing HIV-infected patients in a western country. Usually, adherence assessments have been carried out on inner-city clinic populations; and ethnic minorities, who speak languages other than the principal one, are usually excluded. Adherence assessments performed in the Swedish setting have only been small-scale research projects conducted at HIV clinics in Stockholm, the capital of Sweden (33–35). No systematic adherence assessment data are available for the entire Swedish HIV-infected population.

OBJECTIVES

To assess the prevalence of adherence to antiretroviral treatment in Swedish HIV-infected patients and to evaluate factors associated with adherence.

METHOD

The study was carried out at 30 out of the 32 infectious diseases clinics currently treating HIV-infected patients in Sweden. One of the three clinics in Stockholm (treating mainly gay and bisexual men) did not participate due to lack of time for a research project. The final clinic, a small infectious diseases clinic in a rural area of Sweden, had only three patients on treatment and declined to give a reason for refusing to participate.

All HIV-infected patients over 18 years of age, with ongoing antiretroviral treatment for the previous 4 months and who visited the participating clinics, from December 2003 until the end of June 2004, were eligible for inclusion in the study. Patients considered unable to fill out the questionnaires as judged by their health care providers, because of illiteracy, severe mental illness or poor general health status were excluded. The questionnaire was available in Swedish and also English, French, Spanish and Thai (the other main languages); patients who did not understand any of these languages (and did not have an interpreter present) were also excluded. The total number of patients visiting the clinics within this time period were 1056 and 91·9% (970 patients) of these fulfilled the inclusion criteria. Brief details were collected regarding the patients that did not meet the inclusion criteria and those declining to participate.

The questionnaire was translated by official translators into English, French, Spanish and Thai, allowing the majority of the patients from a non-Swedish background to complete the questionnaire in their native tongue. The proportion of HIV-infected patients in Sweden of non-Swedish origin is 37% (data from 1988–2003) (1) but no data were available on the proportion of these, speaking Swedish.

The patients were given oral and written information regarding the study when asked to participate. The questionnaires were handed out, by health care personnel at the clinics, together with a preaddressed envelope. The patients were asked to fill out the anonymous questionnaire, before their appointment with the doctor or nurse, and to put the questionnaire in the envelope and seal it before handing it over to the health care personnel. The envelopes were then sent unopened to the first and second authors (B.S. and M. H.). All eligible patients attending the clinics (whether or not they participated) received a pill-box as an incentive.

The ethics committee at Karolinska Institutet gave approval for this study.

Questionnaire

The questionnaire asked about socio-demographic background, drug abuse, contacts with psychiatric health care, belief in medication effectiveness, social support and adherence (see below). Part of the questionnaire formed part of one previously used (35), and questions regarding substance abuse

and contacts with psychiatric health care were added for the purpose of this study. The final version was piloted with HIV-infected patients ($n = 5$) to check for any ambiguity.

Morisky Medication Adherence Scale. The 9-item Morisky Medication Adherence Scale (MMAS) (D. Morisky, personal communication) was used to measure adherence, with scores ranging from 1 to 13, where 13 indicates perfect adherence. The MMAS is a further development of the Morisky–Green test (36). MMAS measures adherent behaviour rather than dose adherence. Internal consistency reliability, measured by Crohnbach α, had a value of 0·89 for the English version of the MMAS (37), which is superior to the Morisky–Green test, which had a Crohnbach α value of 0·61 (36). MMAS has previously been used to measure adherence to antiretroviral treatment (35, 38, 39). The Swedish version of the MMAS has a Crohnbach α value of 0·74 (35). An adherence summary score was calculated for respondents who had fully completed the MMAS. Patients scoring 11 or above in the summary score were classified as adherent and those scoring below were classified as non-adherent. This definition of adherence is based on how patients theoretically would have completed the MMAS if they had taken at least 95% of prescribed doses.

Social support assessment. The assessment of social support for medication-taking consisted of two questions. The first asked whether the patients had friends or relatives to talk to about their treatment, and the second whether the patients had friends or relatives who reminded them to take their medicine. The second question was inspired by an item in the Adult Aids Clinical Trials Groups adherence questionnaire (40). Patients answering no to both of these questions were regarded as lacking social support. This definition was chosen as a patient can still have social support without the need to have someone reminding them about taking their drugs.

Statistical analysis

The data analysis was carried out using SPSS for Windows version 12.0.1 (2003, SPSS Inc, Chicago, IL, USA). When comparing adherent with non-adherent patients, in the univariate analysis, chi-squared test was used to analyse categorical data and the independent t-test was used to compare means (as the groups were large).

Logistic regression analysis was used to identify factors associated with adherence, while adjusting for covariates. Variables in the univariate analysis with a P-value $<0·1$ (41) were included in the logistic regression model.

RESULTS

In this study, 946 of the 970 eligible patients completed the questionnaire (response rate 97·5%) (Fig. 1). Over 90% of the respondents filled out the questionnaire in Swedish.

The sample completing the questionnaire was compared with the total patient population in Sweden (1). The national data (1) is based on all reported HIV cases from 1988 until the end of 2003 and hence also included deceased patients, thus
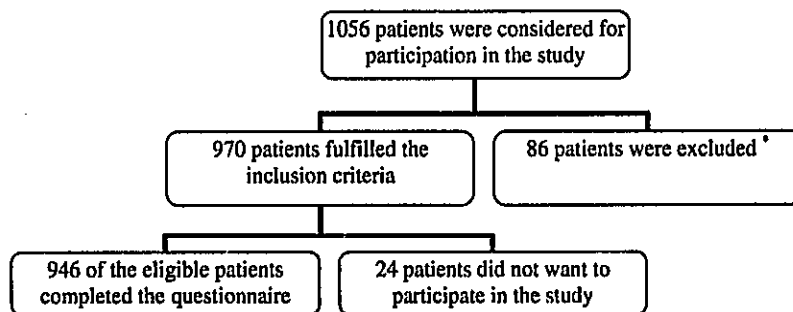
Fig. 1. Distribution of the number of included and excluded respondents in the study. *Exclusion due to: not on current antiretroviral treatment or been on treatment for <4 months ($n = 34$); could not read ($n = 7$); did not understand any of the five questionnaire languages ($n = 25$); were not mentally capable of participating ($n = 15$) or under the age of 18 years ($n = 4$).

not representing totally comparable data. The comparison revealed that the sample completing the questionnaire was slightly less male dominated than the national data (63% (n = 598) vs. 73% (n = 4552)). Sexual transmission was reported less frequently in our sample compared with the national data [62% (n = 568) vs. 78% (n = 4872)], as was intravenous drug use [7% (n = 65) vs. 15% (n = 904)]. Transmission through blood products was more frequently reported in our sample [6% (n = 52) vs. 4% (n = 221)] and this was also the case for the unknown route of transmission [25% (n = 225) vs. 4% (n = 228) in the national data].

Background characteristics

Background characteristics of the respondents are presented in detail in Table 1. The majority of the respondents were male and the mean age was 45 years (range 18–79). According to the respondents, sexual transmission and unknown transmission were the two most common modes of transmission. Most respondents were European and had stable housing. More than one in six respondents reported problems with drugs or alcohol, whereas one in four of the respondents stated they had contacts with psychiatric health care. Almost 90% considered their contact with health care to be good. Mean time on any treatment was almost 7 years and time on current treatment was slightly <3 years. Most respondents had a twice-daily treatment regimen and over 80% reported viral loads below the detection limit (at the time, the normal detection limit in Sweden was 50 copies/mL). According to the majority of the patients, the most demanding aspect of the HIV treatment was hiding their HIV status from others. One-third of the respondents believed that the antiretroviral treatment would absolutely prevent them from getting sick.

Self-reported adherence

The responses to the items in the MMAS are presented in Table 2. The mean summary score was 11 (on a scale ranging from 1 to 13, where 13 indicates perfect adherence). Nineteen per cent of the respondents scored 13, whereas 63% scored 11 or above, and were thus categorized as being adherent.

Social support assessment

Almost three quarters (73%) of the sample had friends or family to talk to about their treatment, whereas 46% of the respondents reported that they had friends or family who reminded them to take their drugs. Almost one quarter (23%) of the respondents were categorized as not having social support for medication taking (i.e. having no friends or relatives to talk to about the treatment, in combination with having no friends or relatives who remind you to take the treatment).

Background characteristics associated with adherence

The univariate analysis is presented in Table 3. Adherent patients had a higher mean age (45·2 years vs. 43·7 years) and were more likely to consider their contacts with health care to be very good (91% vs. 81%). Adherent patients also had a shorter time on any treatment (6·3 years vs. 7·5 years) as well as a shorter time on their current antiretroviral treatment (2·5 vs. 3·2 years). Viral load was more likely to be undetectable among the adherent patients compared with the non-adherent patients (84% vs. 77%).

Multivariate analysis

The results of logistic regression analysis of factors associated with adherence (MMAS summary score ≥11), adjusted for covariates are presented in Table 4. The variables included in the analysis were age, drug or alcohol problems, contacts with psychiatric health care, perceived contacts with health care, time on treatment in total, time since start of current treatment and viral load. Full data were available for 659 respondents (70%), who were included in the logistic regression analysis. There were significant differences between included and excluded respondents in the logistic regression regarding gender, mode of transmission and origin. The following factors remained independently associated with adherence; age, drug or alcohol problems, perceived contacts with health care, time on treatment in total and time since start of current treatment.

Table 1. Characteristics of the respondents ($n = 946$)

Characteristics	Value	Missing (n)
Male, %	63·4	3
Mean age ± SD	44·7 ± 10·2	45
Mode of exposure, %		36
Sexual exposure	62·4	
Intravenous exposure	7·1	
Blood transfusion	5·7	
Unknown exposure	24·7	
Homeless, %	6·0	18
European origin, %	62·2	9
Problems with drugs or alcohol, %	15·5	7
Contacts with psychiatric health care, %	24·5	10
Perceived contact with health care, %		6
Very good	87·0	
Good	10·5	
Neutral	1·8	
Bad	0·4	
Very bad	0·1	
Mean years since start of any treatment ± SD	6·8 ± 4·2	60
Mean years since start of the current treatment ± SD	2·8 ± 2·4	118
Number of daily doses of HIV drugs, %		11
Once daily	7·3	
Twice daily	79·5	
Three times daily	12·5	
Viral load below detection limit, %	81·5	107
The most demanding issue with the treatment, %		234
Hide the HIV status from others	33·6	
Side effects	24·7	
Fear of the drugs stop working	13·1	
The number of tablets	11·7	
Dosage	8·6	
Other	8·4	
Will treatment prevent getting sick, %		15
Yes, absolutely	30·2	
Yes, probably	39·6	
Maybe	24·4	
No, probably not	3·9	
No, absolutely not	1·9	
Language of the questionnaire, %		0
Swedish	90·3	
English	4·3	
Thai	2·9	
French	1·5	
Spanish	1·1	
Questionnaire response rate	97·5%	

DISCUSSION

The objectives of the study were to assess the prevalence of adherence to antiretroviral treatment in Swedish HIV-infected patients and to evaluate the factors associated with adherence. In this sample 68% of the respondents were classified as adherent. Factors associated with high adherence were good relationship with their health care professionals, no drug or alcohol problems, being older, a shorter

Items and summary score	Total	%
Have sometimes forgotten medicines	933	39·4
Have forgotten medicines during the last two weeks	936	17·0
Have reduced doses without the doctors knowledge	938	8·5
Have forgotten medicines when travelling	935	21·1
Took medicines yesterday	937	97·4
Have reminder system for medicines	933	55·2
Have had treatment interruptions because he or she considers the infection under control	940	3·6
Consider it a difficult treatment	925	37·7
Difficulty remembering the treatment	937	
Never/rarely	589	62·9
Occasionally	261	27·9
Sometimes	71	7·6
Usually	5	0·5
Always	11	1·2
Summary score	883	
<5	6	0·7
5–8	97	11·0
9–10	219	24·8
11–13	561	63·5
Mean summary score	10·8[a]	

Table 2. Individual items in the Morisky Medication Adherence Scale and its summary score (n = 946)

[a]Only respondents completing all the 9 items are included when calculating the mean summary score.

time on current treatment and treatment in total. As nearly all infectious-disease clinics in Sweden participated in this study, we have an unselected group of respondents from both inner-city areas and rural areas and this is, to our knowledge, unique. As the questionnaire was also available in four additional languages, participation of patients of non-Swedish origin was encouraged and hence people from many ethnic groups were included. The response rate of the study was exceptionally high and we have no reason to believe that the patients participating in the study would differ from the small proportion of patients not included.

According to this study, higher age, no drug or alcohol problems, better-perceived contacts with health care and shorter time on treatment (both total treatment and current treatment) were factors associated with high adherence.

There is conflicting evidence in the literature on whether age influences adherence in HIV-infected patients. Some studies have found no association between age and adherence (42, 43) whereas others, as in our study, found that increasing age positively influences adherence (16, 44–47).

Drug or alcohol problems have also been reported to reduce the level of adherence (20, 31) and this is in line with our results. This empirical finding also fits well within the theoretical framework for achieving readiness to adhere in HIV [reviewed in (48)]. These theories have a stage where the patients take charge over their life and eliminate barriers for adherence such as drug and alcohol dependency (49, 50).

Good patient–provider contacts have previously been reported to enhance adherence (22–24, 46, 51). Again, the theory of trigger events attempts to explain how patients become ready to adhere (49). Trigger events are changes either in health status or in personal life status (such as disease progression because of non-adherence), which may result in patients wanting and feeling that they deserve to live. One of the components of the subsequent process is the patient finding the right health care provider (49).

The evidence of the impact of treatment duration on adherence is conflicting. It has been reported both not to effect adherence (25, 45, 52) and to be associated with higher adherence (53). Our result

Table 3. Univariate analysis of background factors with respect to adherence ($n = 946$)

	Not adherent		Adherent		
	n	%	n	%	Total
Male	207	64·5	354	63·2	881
Mean age*[a]	43·8		45·3		843
Mode of transmission					853
Sexual	192	61·1	345	64·0	
Intravenous	24	7·6	31	5·8	
Blood transfusion	24	7·6	24	4·5	
Unknown	74	23·6	139	25·8	
European	191	59·7	357	64·1	877
Homeless	17	5·4	32	5·8	866
Trouble with drugs or alcohol*[a]	62	19·5	72	12·8	879
Contacts with psychiatric health care[a]	87	27·4	123	22·0	878
Perceived contact with health care**[a]					880
Very good	259	80·9	507	90·5	
Good	47	14·7	45	8·0	
Neutral	10	3·1	6	1·1	
Bad	3	0·9	2	0·4	
Very bad	1	0·3	0	0·0	
Mean years since start of any treatment***[a]	7·5		6·3		826
Mean years since start of current treatment**[a]	3·2		2·5		775
Number of daily doses of HIV drugs					874
Once daily	25	7·9	39	7·0	
Twice daily	250	78·6	448	80·6	
Three times daily	43	13·5	69	12·4	
Viral load below detection limit*[a]	222	77·1	418	83·8	787
The most demanding issue with the treatment					667
Hide the HIV status from others	74	31·0	153	35·7	
Side effects	58	24·3	108	25·2	
Fear of the drugs stop working	30	12·6	58	13·6	
The number of tablets	29	12·1	45	10·5	
Dosage	26	10·9	29	6·8	
Other	22	9·2	35	8·2	
Will treatment prevent getting sick					871
Yes, absolutely	79	24·9	185	33·4	
Yes, probably	131	41·3	210	37·9	
Maybe	87	27·4	126	22·7	
No, probably not	13	4·1	22	4·0	
No, absolutely not	7	2·2	11	2·0	
Patients with social support regarding medicines	240	75·2	426	77·2	871

[a] Included in multivariate analysis ($P < 0·1$).
*$P < 0·05$.
**$P < 0·01$.
***$P < 0·001$.

seems to differ from these previous findings with antiretroviral treatment. However, longer time on treatment is generally associated with a decreased level of adherence in other chronic diseases (54).

Sexual transmission (i.e. both hetero- and homosexual subjects) is the dominant mode of transmission in Sweden according to national data (1). The national data (1), however, have several

Variable[a]	Odds ratio	(95% CI)	P-value
Age**	1·03	(1·01–1·04)	0·002
Trouble with drugs or alcohol**			
Yes	1*		
No	1·89	(1·18–3·01)	0·008
Contacts with psychiatric health care			
Yes	1*		
No	0·96	(0·64–1·43)	0·838
Perceived contact with health care*[b]			
Very good	1*		
Other	0·59	(0·37–0·95)	0·031
Years since start of first treatment**	0·94	(0·90–0·98)	0·003
Years since start of current treatment*	0·92	(0·85–0·99)	0·035
Viral load below detection limit			
Yes	1*		
No	0·85	(0·56–1·29)	0·448

Table 4. Logistic regression analysis of factors associated with adherence (MMAS summary score ≥ 11)

[a]Including all variables with $P < 0.1$ in the univariate analysis.
[b]The variable was collapsed into a dichotomous variable with the options; very good contacts with health care and other (good/neutral/bad/very bad), because of few responses in the original categories (good/neutral/bad/very bad).
*$P < 0.05$.
**$P < 0.01$.

limitations, making the comparison with our results difficult. The national data is based on all patients reported as infected from 1988 to 2003 and hence deceased patients are included. Because patients are not reported to the registry with their full social security number, some patients might be reported several times and some of the included patients might have moved from the country. According to the respondents in this sample, the proportion of sexual transmission as well as the proportion transmitted through intravenous drug use was smaller than that in the national data. The proportion of respondents claiming transmission through blood products was, on the other hand, larger than in the national data. The very high proportion of patients who reported an unknown transmission, in comparison with national data, might explain these differences.

The mean adherence summary score (MMAS) was 10·8 in this sample. A sample from a single HIV clinic in Sweden (Karolinska University Hospital, Huddinge) had, in 2002, an almost identical mean MMAS summary score of 10·7 (35).

In this sample, 82% of the respondents reported that they had viral loads under the detection limit. It has previously been reported that 85% of the

patients on treatment at the HIV clinic at Karolinska University Hospital had a viral load below detection limit (50 copies/mL) in 2002 (55) and 2003 (56). There are no similar results from other clinics in Sweden to support this high level of treatment success. Data available elsewhere indicate that 37–70% of patients on HAART have viral loads below 400–500 copies/mL (16, 57, 58). These treatment results could be attributed to a treatment model described by Sodergard et al. (59), where the HIV clinic works multi-professionally and each patient is allocated their own doctor, nurse and counsellor. The aim of the model is that the patient should become motivated enough to take responsibility for their own treatment and hence avoid treatment interruptions and resistance. Other clinics in Sweden also have counsellors and work in ways similar to those of the Huddinge clinic. Other differences in the health care systems might also explain the differences in treatment success between Sweden and countries where the other studies have been performed [USA (57), Switzerland (58) and Italy (16)].

The most demanding personal issue in HIV treatment, according to the majority of the respondents, was hiding their HIV status from

others. In the HIV-Problem Detection Study carried out in 1998 in Sweden (60), several of the top 10 perceived problems for HIV-infected people concerned how the public have reacted, or possibly might react, when finding out about a person's HIV status. Six years later, the fear of stigmatization because of HIV status still seems to exist in Sweden.

Limitations

Selection bias is likely to be limited as the proportion of non-responders was small (24 of 970). A response rate of almost 98% is exceptionally good and the proportion of eligible patients was also high. The internal attrition because of unanswered questions was, however, relatively high, with 659 respondents (70%) included in the logistic regression analysis and there were differences between the included and excluded respondents in this analysis. However, the overall effects are unlikely to be qualitatively different since none of the non-significant findings had borderline *P*-values.

When considering the relationship between background factors and adherence it is also important to remember that a temporal relationship cannot be established in a cross-sectional survey.

The methods available for measuring adherence all have different strengths and weaknesses (61); however, because of the complexity of adherence behaviour and problems with bias, none is optimal. When conducting large-scale cross-sectional adherence assessments, self-reporting was deemed to be most suitable because of its inexpensiveness and possible breadth of distribution.

It would be an advantage to be able to assess the validity of the self-reported adherence assessment by comparing it with the individual patients' documented treatment results. However, to maximize the response rate (because of the sensitive nature of the questions) and to reduce bias because of socially desirable responses, the questionnaires were distributed anonymously and hence no such information could be obtained from the respondents' medical records.

To limit the impact of social desirability the patients were provided with preaddressed envelopes and could themselves seal the envelope directly after filling out the questionnaire and before handing over the envelope to the health care personnel. By this approach the patients would hope-

fully have felt reassured that their anonymity would be preserved and hence answered truthfully. It can of course not be ruled out that some patients might not have been totally reassured on this. Patients might for example have felt a need to consult the staff while filling out the questionnaire and hence staff might have inadvertently influenced the patient's responses although instructed not to do so.

It would be valuable to evaluate how factors found to be associated with adherence interact with each other and create a multidimensional model to describe adherent behaviour. Many of the factors found to influence adherence seems to fit well within the readiness theories (48) and there is a need to further explore the readiness concept, as this might contribute to the understanding of adherent behaviour.

CONCLUSION

Adherence to HAART seems to be influenced by several factors amendable to change according to this cross-sectional study of a Swedish nationwide sample of HIV-infected patients. Good relationship between health care provider and patient seems to be associated with good adherence whereas drug or alcohol problems are associated with low adherence. Low adherence is associated with longer time on treatment and younger age. This implies that although the initiation of HAART is extremely important, to ensure good treatment results, follow-up and motivation of the patients throughout the treatment are also important. Continuous measurement of the patients' readiness to maintain treatment adherence, to identify when interventions are required, seems to be an approach worth further investigation.

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