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Adherence and Readiness to Antiretroviral Treatment

BJÖRN SÖDERGÅRD

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Abstract

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Antiretroviral therapy places extraordinarily high demands on adherence, since non-adherence affects both individuals and society due to the spread of resistant viral strains. The aims of the thesis were to investigate the prevalence of adherence in Swedish HIV-infected patients, changes in adherence over time, and factors associated with adherence, including patients' readiness to adhere. Further, to investigate the collaboration between nurses, doctors and pharmacists after the introduction of a HIV-clinic satellite pharmacy. Data were collected via two cross-sectional patient surveys in 1998 and 2002, qualitative interviews with health care personnel at a major HIV clinic, and a nation-wide, cross-sectional patient survey in 2003-2004.

The level of adherence improved from 28% in 1998 to 57% in 2002, possibly due to simplified treatment and a new multi-professional treatment model at the clinic. The proportion of adherent patients was 63% in the nationwide survey. Factors associated with adherence were high age, high quality patient-provider relationships, no drug or alcohol problems and shorter time on treatment.

A hypothesized structural equational model, using readiness and adherence as separate latent concepts, was tested and found to support readiness as a distinct factor influencing adherence.

The health care personnel believed that conventional pharmacies had several disadvantages in serving the HIV infected population. They found the HIV-clinic satellite pharmacy valuable, since it contributed to increased communication and trust between the health care professions, and improved teamwork in medication management.

In conclusion, the level of adherence increased over time, and several factors associated with adherence were identified. Improved collaboration between health care professionals may enhance treatment support, and increased attention should be given to interventions that focus on the individual's readiness for behavioural change in order to optimize treatment outcomes.

Keywords: Adherence, Readiness, HIV, Pharmacy

Björn Södergård, Department of Pharmacy, Box 580, Uppsala University, SE-75123 Uppsala, Sweden

Original Papers

This thesis is based on the following papers:

I

Södergård B, Halvarsson M, Lindbäck S, Sönnerborg A, Tully M. P., Kettis Lindblad Å. "Differences in adherence and motivation to HIV therapy - Two independent assessments in 1998 and 2002".
Pharmacy World & Science (In Press)

II

Södergård B, Halvarsson M, Tully M. P., Mindouri S, Nordström L, Lindbäck S, Sönnerborg A, Kettis Lindblad Å. "Adherence to treatment in Swedish HIV infected patients".
Journal of Clinical Pharmacy and Therapeutics (In Press)

III

Södergård B, Höfer S, Halvarsson M, Sönnerborg A, Tully M. P., Kettis Lindblad Å. "A structural equation modeling approach to readiness and adherence".
Patient Education and Counceling (submitted)

IV

Södergård B, Baretta K, Tully M. P., Kettis Lindblad Å. "A qualitative study of health care personnel's experience of a satellite pharmacy at a HIV clinic".
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Contents

Abbreviations

AACTG	Adult AIDS Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
CFI	Comparative Fit Index
FDA	Food and Drug administration
GFI	Goodness-of-fit index
HAART	Highly Active Antiretroviral Treatment
HIV	Human Immunodeficiency Virus
MARS	Medication Adherence Report Scale
MEMS	Medical Event Monitoring System
MMAS	Morisky Medication Adherence Scale
PI	Protease inhibitors
RMSEA	Root mean square error of approximation
SEM	Structural Equation Modeling
TTE	Theory of Trigger Events
TTM	Transtheoretical Model of Change
WMT	Wellness Motivation Theory
WHO	World Health Organization

DEFINITIONS OF KEY CONCEPTS

Compliance

The term compliance was first used within the medical context in 1976 (1) and the most cited definition of compliance is from 1979 (2); *"the extent to which a person's behaviour (in terms of taking medications, following diets or executing lifestyle changes) coincides with medical or health advice"*

Compliance can further be divided into dose, timing and food restriction compliance. Dose compliance is focusing on the doses missed, timing compliance is the extent to which the patient is following the prescribed dosing schedule and food restriction compliance is whether the patient takes the drugs according to prescribed food restrictions.

In recent literature the term compliance has been replaced by the term adherence, since compliance represents an authoritarian way of looking at how patients and health care personnel decide on actions and behaviours (3) where the patient has a passive approach toward health-care (4).

Adherence

The definition of adherence used by the World Health Organization (WHO) is; *"the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* (5).

The term adherence is viewed to be less judgemental and the major difference compared to compliance is that patient's agreement with the recommendations, or advice, is needed (5). These two terms, compliance and adherence, are still, however, used interchangeably in research although they are different in definition (4).

Adherence can also be divided into dose, timing and food restriction adherence in the same way as compliance (6).

Concordance

A third term used in this area is concordance, which was introduced in 1997 (7). Concordance underscores the need for shared decision making between doctor and patient. The assumption is that good concordance has a positive impact on adherence to treatment. The definition of concordance is (7); *"...the intention is to assist the patient to make as informed a choice as possible about the diagnosis and treatment, about benefits and risks and to take full part in a therapeutic alliance. Although reciprocal, this is an alliance in which the most important determinations are agreed to be those that are made by the patient..."*

Readiness

The term "readiness" is often used in relation to behavioural change but researchers using the term seldom define it (8). For nurses in AIDS care, readiness has been defined as; *"a conscious awareness on the part of the individuals that they, of their own will, have considered and determined that a particular change will be beneficial. In addition, the individual has identified barriers that may prevent this behaviour from occurring and has accepted responsibility for initiation of the behaviour. Finally, a sense of control and impending action on the part of the individual must be present"* (8).

Viral load

Viral load is measured in number of HIV RNA copies per millilitre blood plasma. The viral load decreases with optimal treatment. The aim of the antiretroviral treatment is to have as low a viral load as possible i.e. an undetectable number of HIV RNA copies. The measuring method has become better over time and hence also the detection limit for viral load has decreased and is currently 20 HIV RNA copies per millilitre blood plasma. Virological failure is usually defined as a measurable amount of HIV RNA copies in blood plasma in two consecutive measurments.

CD4+ T-lymphocyte count

By monitoring the CD4+ T-lymphocyte count it is possible to assess the level of immunosuppression in HIV patients. The CD4+ T-lymphocyte count increases with optimal treatment. The definition of AIDS is partially based on the CD4+ T-cell count.

INTRODUCTION

HIV and AIDS

In 1981 the Centre for Disease Control in the United States published a report describing five previously healthy young homosexual men suffering from *Pneumocystis carinii* pneumonia (9). This was unusual since *Pneumocystis carinii* pneumonia was typically limited to severely immunosuppressed patients. Over the months to come, hundreds of new cases were diagnosed and not only homosexual or bisexual males were infected but also intravenous drug users, heterosexuals and haemophiliacs (10). This was the first evidence of an epidemic that to date has killed more than 25 million people worldwide (11).

The disease was called Acquired Immune Deficiency Syndrome (AIDS) and was, in 1983, found to be caused by a virus later called Human Immunodeficiency Virus (HIV) (12, 13) or HIV-1. In 1986, a second type of HIV was isolated, consequently called HIV-2 (14). HIV has been found in old blood samples from 1959 (15) but it possibly dates as far back as the 1930s (16).

AIDS is the fourth most common cause of death in the world (17) and is estimated to have killed 3.1 million individuals and infected 4.9 million persons in 2005 alone (11). The number of people infected by HIV is steadily rising and sub-Saharan Africa is the region in the world mostly affected (11).

HIV can be transmitted if infected body fluids, such as semen or blood, get in contact with the blood stream directly or through mucous membranes. The main route of transmission is through sexual intercourse (vaginally (18), anally (18) or orally (19)). HIV can also be transmitted by intravenous drug use (20), by occupational exposure (i.e. needle stick) (21), by transfusion (22) or from mother to child (23).

The HIV virus replicates at a high rate in untreated patients (24). When replication occurs during treatment, this leads to the development of genetic variation, which in turn leads to the emergence of variants that might be resistant to antiretroviral treatment (25).

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The Swedish situation

The first cases of HIV in Sweden were reported in the gay population of Stockholm in 1979-1980 (26). Up until the end of 2004, 6705 people have been reported infected with HIV, about 3500 of whom were believed to be still alive at that time (27). In Sweden, as in the rest of the world, the sexual route of transmission is dominant (11, 27). Of the 392 new HIV cases reported in 2005 (27), the proportion infected by HIV due to heterosexual contacts was 49% while transmission due to sexual contact between men was 25%. Unknown transmission accounted for 17% of the cases and intravenous drug was the transmission route for 6% of the cases (27). Mother to child transmission accounted for 3% of the new cases and one case was attributed to transmission by blood products (27).

Treatment of HIV infection

Untreated HIV infection leads to severe immunosuppression and death (28). The first antiretroviral drug was introduced in the United States and Sweden in 1987 (17). Further, more drugs became available in the early 1990´s but their effects were limited (29).

Highly Active Antiretroviral Treatment

The Food and Drug Administration (FDA) in the United States approved the first protease inhibitor (PI) in 1995 and more PIs were later approved. In Sweden, a PI was given in March 1995 for the first time to a patient at Huddinge University Hospital (A. Sönnerborg, personal communication). Besides this new group of drugs, a shift in therapy also occurred, when triple combinations of antiretroviral drugs replaced dual therapy (30, 31). PIs given in combination with at least two other drugs have lead to dramatic improvements in the patients´ health (32-34). The so called highly active antiretroviral treatment (HAART) was formed.

Medical research has continued to develop and new classes of drugs have been introduced, giving a total of four classes of antiretroviral drugs today (35) and a fifth class became available in a "Named patient programme" in October 2006 (A. Sönnerborg, personal communication). All classes affect HIV through different mechanisms and in total 29 antiretroviral drugs (including combinations) have been approved in the USA by the FDA (36), the corresponding number is 24 in Sweden (37).

HAART has dramatically reduced mortality and morbidity (38, 39). It is effective because it reduces HIV replication and hence allows the regenera-

tion of CD4+ T-lymphocyte mediated immune responses (29, 33). HAART cannot, however, totally eradicate HIV (40, 41) and hence prolonged viral suppression is essential for long-term efficacy of HAART (42, 43). Prolonged viral suppression is only achievable if the virus does not get the chance to replicate and develop drug-resistant HIV variants (25). The virus has the chance to replicate not only if the patient is untreated (24) but also if the viral replication is not completely inhibited by the treatment (i.e. due to sub-optimal drug exposure) (44).

The level of virologic failure has decreased over time during the HAART era. In the largest cohort study, over 22 000 patients, starting antiretroviral treatment between 1995 and 2003, were included. The proportion of patients with viral loads over 500 copies after 6 months of treatment decreased from 42% in 1995-1996 to 17% in 2002-2003 (45) and this trend has also been found in other cohort studies (46, 47). The definition for virological failure has also changed over time with improved viral load measurements.

The importance of adherence to HIV therapy

One of the main factors contributing to sub-optimal drug levels and resistance is non-adherence to treatment (48, 49). It has been reported that the patient needs to take a minimum of 95% of prescribed antiretroviral doses in order to avoid resistance development (48). Patients taking 95% or more of their doses only had a documented virologic failure (i.e. over 400 virus copies/mL in blood) in 22% of the cases compared to 80% of the patients taking less than 80% of their doses (48).

However, high levels of adherence do not totally prevent HIV drug resistance mutations occurring (50) and lower adherence levels than 95% might also result in successful virologic suppression (51). There is, hence, an ongoing discussion regarding the level of viral suppression needed to avoid resistance development. Most evidence supports the finding that continuing viral replication in the presence of therapy will lead to resistance development and later to virologic failure (52). Stressing one single adherence threshold might, however, no longer be optimal (51).

The consequences of non-adherence are not limited to the patient, which is usually the case in most other chronic diseases. If a patient with a resistant virus infects another person, the resistant virus is transmitted. This is hence a risk for society in a wider sense, since these patients have limited treatment options. The proportion of patients newly infected with a resistant virus has been reported to be 8-17%, depending on the population (53-56).

Besides poor adherence, several other factors contribute to sub-optimal drug exposure or otherwise affect the virological response to HAART;

- already having a resistant virus (57)
- prior treatment with sequential monotherapy (58)
- drug interactions that result in lower drug exposure (59)
- altered drug metabolism (60)
- low drug absorption (61-63)
- advanced disease stage (42)
- low pre-treatment CD4+ T-lymphocyte count (64)
- high pre-treatment viral load (64)

Several of the factors that affect the virological response to HAART are the consequences of previous antiretroviral treatment. Patients with prior treatment are therefore at higher risk for development of resistance. The initial treatment has, as a consequence, the highest success rate (65).

Consequences for treatment initiation

Since the initial treatment is the most successful treatment, it is important to carefully consider treatment initiation. The time for treatment initiation has been continuously debated and different approaches have been used throughout the HAART era (30, 31, 66-68). In Sweden, the attitude has generally been conservative during the years (69). The first approach was to "hit hard, hit early" (i.e. to start treatment early with as effective treatment as possible). However this was replaced by the approach "hit hard, hit later", since side-effects, meal restrictions and high requirements on adherence were too demanding for the patients. Treatment initiation was hence postponed until the HIV infection cause symptoms or other complications due to a deteriorating immune system (17). This trend might change again since, today, the antiretroviral drugs are more forgiving when it comes to the demands for high adherence and have better side-effect profiles (70) but the treatment recommendations have not changed (17, 68, 71).

Level of adherence to HIV therapy

The level of adherence in the HIV population is higher than in most other chronic diseases (5). In the international literature the percentage of HAART doses taken as prescribed varies between 53-93% according to different assessments (72-74).

Usually, adherence assessments have been carried out on inner-city clinic populations. Further, ethnic minorities, who speak languages other than the

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principal one, are usually excluded. To our knowledge, no systematic adherence assessment data are available for the entire Swedish HIV-population, or any other country's HIV-population. Adherence assessments performed in the Swedish setting have only been small-scale research studies conducted at HIV clinics in Stockholm (75-77). The proportion considered adherent (>95% of prescribed doses taken) was in one of these studies 80-83% (75) while in another study, 12% reported missing doses in the 4 days prior to completing the questionnaire (76). During a 2-year longitudinal study by the same authors (77), 61% of the 144 patients remained fully dose adherent during all measuring periods.

Measuring adherence

One reason for variation in adherence levels between different studies is the variety of methods used for measurement. Measuring adherence is complex and difficult since there is no optimal approach available. The approaches are divided into direct and indirect methods (78). The direct approach is to measure the plasma concentrations of the antiretroviral drugs (79), while indirect methods rely on less objective measures. The indirect methods mainly include self-reported adherence (80), pill count (81), pharmacy refill records (82), medical event monitoring systems (MEMS) (48), and assessment of adherence by doctor or nurse (83). Other indirect methods include reviews of patient charts (documented patient report of adherence to provider), missed clinic visits, direct observed therapy (DOT) and therapeutic outcomes (i.e. viral load, CD4 lymphocyte count, stage of disease progression (as defined by Centres for Disease control) and mortality) (80). The most widely used approach is, however, self-reported adherence (84).

Self-reported adherence

By the use of questionnaires, interviews or diaries, the patients report how many doses they have taken or forgotten to take during a specified time-interval. Alternatively, they can be asked about different aspects of their adherent behaviour. The advantages of self-report are low cost, low participant burden, ease and speed of administration, and flexibility with regard to mode of administration and timing (5, 78, 85, 86). The latter offers possibilities to gain specific information regarding timing of doses and adherence to food restrictions (5, 78, 85, 86).

The specificity and sensitivity of self-reported adherence is high (83). The patients reporting to be non-adherent are usually actually non-adherent (i.e. high specificity) according to pill count (83). The sensitivity is the probability that patients actually being adherent will be categorized as adherent according to the assessment (87). According to a recent meta-analysis (84), the pooled association between self-reported adherence and viral load was statis-

tically significant despite many different self-reporting measurement approaches being used.

Self-reported adherence has 10-20% higher estimates of adherence than MEMS (73, 88) thus overestimating adherence. The disadvantages with the method are that the results are easily affected by recall error (i.e. the patients do not remember how many doses they have taken) and social desirability (i.e. they report the behaviour they think is correct according to the social norms (89) or in other words they report the behaviour their health-care personnel want to hear). Another problem is the many different questionnaires developed to measure adherence making the study results difficult to compare. The other methods mainly used to measure adherence, besides self-report, are summarized in Table 1.

The use of multiple methods for measuring adherence has been proposed but is believed only to be necessary when it comes to intervention trials or when there is a ceiling effect of self-reported perfect adherers (80). Reporting bias is worrying in intervention studies as it might be hard to distinguish which of the patients reporting perfect adherence that might need adherence support.

Table 1. Advantages and disadvantages of adherence measuring methods (based on (5, 78, 85, 86))

Adherence measuring method	Description	Advantages	Disadvantages
Drug concentrations	The drug concentrations in plasma is measured to see whether the patient has used their drugs.	• Objective way of measuring adherence. • Standard	• Expensive • Time of last dose might be uncertain. • "White coat adherence" (i.e. the patients are more adherent prior to a clinic visit). • Not all available antiretroviral drugs can be measured in plasma. • Level of the drug in plasma is also depending on other factors besides adherence.
Pill count	The patients are asked to bring back their remaining drugs to the hospital when they get a new prescription and the remaining drugs are counted.	• Objective • Easy to perform • Perceived as inexpensive • Information collected regarding the number of pills taken • Standard tool (especially in clinical trials)	• Time-consuming approach • Patients can easily throw away drugs before visiting the hospital for the pill count (i.e. easy to produce biased information). • Overestimate adherence
Pharmacy records	Depending on pharmacy system, the pharmacy records (data regarding dispensed drugs) can be used for assessing refill adherence.	• Objective • Easy to obtain data	• Requires a closed pharmacy system. The Swedish pharmacy system did not have data regarding dispensed drugs stored for more than two months until the data was anonymized. Recently a new registry was created where pharmacy records are anonymized but linked and are now available for research purposes (90). • No information regarding the proportion of the dispensed drugs that the patient actually has used.

Method	Description	Advantages	Disadvantages
MEMS	Medical Event Monitoring System (MEMS) is an electrical device consisting of a micro chip in a pill-bottle lid and the micro chip registers each time the lid is opened.	• Difficult for the patient to consistently bias the measure • Recall error is minimized • The impact of social desirability is reduced • Data regarding exact timing of doses • Considered a standard	• Expensive • Only gather data regarding number of doses not number of pills taken. • Patients are instructed to remove only one dose at a time and also to open the lid only when the dose is taken however this might not always be the case so there are also practical limitations to MEMS (91). • Pill boxes (e.g. Dosett) can not be used. • Adherence might be underestimated by the use of MEMS (72, 91). • Can not be used to measure if the doses removed from the container has been ingested • MEMS has been suggested to be the preferable choice before self-reported adherence when conducting intervention trials (92). • Requires that the patient returns for a follow up visit and download data. • MEMS caps can be lost.
Assessment of adherence by doctor or nurse	Doctors or nurses make an assessment regarding the level of adherence.	• Convenient	• Biased • Inaccurate

Factors influencing adherence to HIV therapy

Theories used to explain adherence

Adherence has been thoroughly examined but still no clear-cut solution to low adherence has been found. It remains a significant problem in the clinical reality of the HIV treatment (48) as in other chronic treatments (5). There is no consensus about the theoretical framework for adherent behaviour and several theories have been proposed (93). The theories mainly used have not been exclusively developed to explain adherent behaviour to drug treatment but rather health behaviour in general, e.g. the Health Belief Model (94), and the Theory of Reasoned Action/Theory of Planned Behaviour (93).

The key concepts of the *Health Belief Model* are perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy (93). According to the model, patients will take action to prevent ill-health conditions, if they feel that they are susceptible to the condition (i.e. they feel that low adherence will result in treatment failure), if the condition is believed to have serious consequences for the patient (i.e. treatment failure is perceived as bad), if the patient feels that the action they can take will reduce their susceptibility to the condition (i.e. they feel that adherence will reduce the risk for treatment failure) and if the patient feels that the anticipated barriers to taking the action are outweighed by the perceived benefits (93). Cues (bodily or environmental events that trigger action) and self-efficacy i.e. "the conviction that one can successfully execute the behaviour required to produce the outcome" (95), are other concepts that have been added to model.

The Theory of Reasoned Action can be divided into three areas where the first area is intention. According to this theory, intention, is the main predictor and influencer of behaviour (i.e. without intention behaviour will not likely occur). Intention is however influenced by two concepts, attitudes toward the behaviour and subjective norms. Attitudes toward the behaviour are a result of the weighting (by the individual) regarding the beliefs about the possible outcomes of the action and whether the patient finds these outcomes positive or not. In other words, an individual that strongly believes that the outcomes of the behaviour will be negatively valued will have negative attitudes toward the behaviour. Subjective norms are influenced by normative beliefs and motivation to comply. Normative beliefs are a result of the perceived approval (or disapproval) regarding performing the behaviour of people important to the individual (i.e. referents). Normative beliefs are then weighted by the individual's motivation to comply with these referents (i.e. the perceived social pressure) (93).

The Theory of Planned Behaviour is an extension of the theory of reasoned action. Besides the concepts of attitudes toward the behaviour and subjective norms it also includes the concept of perceived behavioural control since not all factors influencing intention and behaviour are under the control of the individual. Perceived behavioural control is influenced in turn by control beliefs and perceived power. Control beliefs regards whether there are factors that can facilitate or impede the planned behaviour and these factors are weighted by their perceived power (93).

Empirical evidence of factors associated with adherence

A range of factors have been found to be related to adherence to chronic diseases. WHO has suggested a taxonomy for grouping these factors (5). The factors are divided into social and economic factors, health care team and system related factors, condition-related factors, therapy-related factors and patient-related factors.

Factors specifically influencing adherence to HIV-therapy corresponds well to these categories. Age (6, 96) and social support (96, 97) are part of the social and economic factors associated with adherence. The health care team and health care system is also associated with adherence and especially the relationship between the patient and provider (98, 99), together with access to health care (100). Condition related factors (i.e. symptoms due to the infection (101)) are associated with adherence. The complexity of the therapy (102) and side-effects (103-105) are therapy related factors. Patient specific factors such as knowledge (103) and beliefs about the treatment (101, 105, 106), psychological (97, 107) and drug or alcohol abuse related factors (108-110) together with motivation (82, 111, 112) are also associated with adherence.

Strategies for improving adherence

According to a Cochrane review which focused on adherence in chronic disease, several individual interventions or factors have a positive impact (albeit small) on adherence to long term treatment. These factors are more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy and other forms of additional supervision or attention by a health care provider (physician, nurse, pharmacist or other) (113). The interventions found to have the greatest impact on adherence for long-term treatments were multi-faceted, although still leading to only relatively minor improvements (113).

Many adherence promoting interventions have also been tested in the HIV infected population specifically (114). Some randomized controlled trials

have evaluated the impact of interventions on adherence (115-119). Two of the studies found no improved adherence (115, 116). One of these studies used a multidisciplinary intervention focusing on social support, information and behaviour (115) while the other attempted to improve self-efficacy (116). One intervention (117) used cue-dose training (i.e. counsellors trained the patients to find personalized cues for their medicines taking) and money incentives. This intervention enhanced adherence during the intervention but not during the follow up (117). An intervention focusing on couples where education about treatment and adherence was the main focus had an impact on adherence during the first period after the intervention but showed no difference after 6 months (118). In a multidisciplinary intervention, with pharmacists and nurses focusing on education and helping to integrate the treatment in the patients daily life (119), a significant improvement in the adherence level was found during the 28 day follow up.

Readiness for treatment

Although adherence is very important in the treatment of HIV it can only be assessed during an ongoing treatment and by the time the interventions to promote adherence have been initiated, the virus might already have developed resistance due to suboptimal adherence. It is hence equally important, or possibly even more important, to focus not only on adherence (i.e. drug taking behaviour once the treatment is initiated), but also on the patient's readiness before embarking on the treatment. Readiness for HIV therapy can be assessed prior to treatment initiation and hence timely measures can be taken before initiation of therapy. Sometimes postponement of treatment may be preferable in order to motivate and increase the degree of readiness, and hence, hopefully, increase the success rate of the initial treatment.

Readiness to initiate treatment is simply put that the patient himself/herself feels ready to initiate, take responsibility for, and to maintain (including being adherent to) a prescribed treatment.

Table 2. Instruments used so far to assess readiness and the main results of the studies.

First author, year published	Topic	Instrument	Population	Main result
Willey, 2000 (120)	Prospective readiness measure (with patients already on treatment)	Willey's 2-item scale (based on TTM[1])	161 HIV-positive patients, and 731 hypertensive patients	Statistically significant association between baseline stage of change and adherence (as measured by MEMS) to protease inhibitors during the next 30 days was found in a sub-sample of 85 patients. The scale can be used to match communication strategies with readiness for adherence.
Highstein, 2006 (121)	Prospective readiness measure (with treatment naïve patients and with patents already on treatment).	A further development of Willey's 2-item scale (based on TTM[1]) and a decisional balance measure.	103 HIV-positive female patients.	An association between degree of readiness and starting antiretroviral treatment was found. In addition, there was also an association between degree of readiness and viral suppression.
Södergård, 2006 (122)	Cross-sectional readiness measure (with patients already on treatment)	Willey's 2-item scale (based on TTM[1])	111 HIV-positive patients.	Patients categorized in the action or maintenance stage according to the Swedish version of Willey's 2 item scale had to significantly higher degree viral loads below detection limit.

Kennedy, 2000 (123)	Readiness instrument used in HIV	Kennedy's 26-item scale (based on literature, not based on a specific theory)	8 HIV-infected patients	The construct validity of this questionnaire was tested on students, treatment providers and HIV patients on treatment. Two of the items in the questionnaire were to be used as a predictive scale to assess readiness prior to treatment initiation, but were never evaluated. The small-scale pilot test seemed to show promise for further exploration
Enriquez, 2004 (124)	Prospective readiness measure (with patients who had previously failed antiretroviral treatment and started a new antiretroviral combination)	Index of readiness (125) (based on WMT^2)	19 HIV-infected men	Patients with viral suppression had scored significantly higher on the Index of Readiness, suggesting its predictive validity This prospective pilot study concluded that readiness seems to be an important component in successful adherence, and that the Index of Readiness might be appropriate for assessing readiness for adherence in HIV-infected patients. (as measured by MEMS)

[1] Transtheoretical Model of Change (TTM)
[2] Wellness Motivation Theory (WMT)

Factors influencing readiness

Readiness theories

Theories used to explain readiness more generally include the *Transtheoretical model of change* (126) (TTM) and the *Wellness Motivation Theory* (127) (WMT). One theory has been specifically developed regarding the disease progression in HIV and the stages the patient moves through (128). A process of events, grounded in empirical evidence, was by Enriquez et al (129) suggested to constitute the phenomenon of readiness in HIV. We refer to this process as the *Theory of Trigger Events* (TTE). Since TTE is the only theory that describes the phenomenon of readiness specifically in HIV, this theory was chosen as the theoretical basis for the assessment of readiness in this thesis.

Although several different theories (126-129) have been used to explain how a patient becomes ready to adhere to the treatment, they all exhibit similarities. Initially, the patient is unaware of the need for a change of the undesired behaviour (126, 128). This stage can be equivalent to the crisis stage that have been suggested to follow after a HIV diagnosis (128), since it is a stage of emotional turmoil and the HIV infected patient might not even be able to comprehend health care advice given by the health care professionals. After this, a period of indecisiveness follows, when the patient is weighing up the pros and cons of change (124, 126, 127). Something in the patients´ life, however, needs to happen (i.e. a trigger or cue) for the pros to out weigh the cons of changing, resulting in the patient taking action to change the undesired behaviour (126-129). The first part of taking action is that the patient will smooth the way for the change (128, 129) and try to coordinate different aspects of the lifestyle (i.e. find the right health care provider, finding the right support system and so on) in order to be able to change (128, 129). The second part of this stage is to actually initiate the change (126-129). Maintaining the change in the undesired behaviour requires individual approaches (126). If the patient has maintained the change for long enough time, the change will be incorporated in the lifestyle (126, 127). The concept of self-efficacy (126) and temptation (126) is also present.

The Theory of Trigger Events

The TTE was based on a phenomenological approach to readiness (129), in which 13 men and women with HIV were interviewed. The interviewees had failed at least two treatment regiments previously and had, after this, sustained an adherent behaviour for at least one year without a formal intervention. Enriquez et al (129) found that, during this period of non-adherence, all

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patients experienced a specific "trigger event" that lead to a powerful feeling of wanting and deserving to live, which broke the non-adherent behaviour. These trigger events could be a change in health status, such as illness progression, that the patients perceived as life-threatening or a change in personal life status that the patients felt could only be sustained if they became adherent. The trigger event led to a process consisting of five components that all the interviewed patients had experienced, but not necessarily in a specific order. The five components were changing attitudes toward HIV medication, finding the right health care provider and the right medication regimen, creating the right support system, getting control of life and finally the component of having goals. Enriques et al (129) believed the trigger event and the following process to be the phenomenon of readiness for HIV treatment adherence.

Empirical Evidence
Only one study has quantitatively investigated factors influencing readiness for antiretroviral treatment, using an investigator-developed questionnaire (130). Emotional responses following diagnosis such as anger, hopelessness, denial, anxiety and confusion were found to significantly affect readiness, while gender and racial factors had no impact (130).

Two qualitative studies (131, 132) have explored reasons for refusing to initiate HIV therapy. A variety of factors were identified but the only reason found in both studies was fear of side effects (131, 132). Other treatment related factors included that the patients did not feel ready for adherence (131), refused the particular type of treatment (PIs) (131), distrusting conventional medical approaches to treatment (132) and having practical problems with therapy (132). Psychological aspects included factors such as fear of the emotional responses that being on therapy might raise (132), accepting the thought of dying (132) and religious beliefs (131). Feeling well without HAART (131), active drug use (131) and homelessness (131) were other factors found to have an impact on readiness in these studies.

Measuring readiness in HIV

There is currently no tool used to assess readiness in clinical practice. Available tools have so far only been used for research purposes. Several instruments have been used in other health behaviour changes (e.g. addiction, dieting and anorexia nervosa) (133-137). Only three instruments have yet been used to assess readiness in the HIV population to our knowledge (120, 123, 125) (see table 2). Two of these instruments are based on different theoretical frameworks (120, 125) and the third instrument is based on the literature but without a specific theory as a base (123). The instrument mainly used so

far is the Willey´s 2-item scale (or further developments of this scale) which is based on the TTM (120-122)

Strategies for improving readiness

If the stage of readiness can be established for individual patients, it may be possible to make individualized treatment decisions for the patients. There have been attempts made to arrange strategies for achieving readiness for antiretroviral therapy into a logical order and adapting them to the patient's current stage, resulting in stage tailored treatments (131, 138-140). Motivational interviewing is a counselling approach that has been used in the health care setting in general (141) and in the HIV setting (142) as a means of increasing readiness based on knowledge of the patient's current stage of change.

The relationship between adherence and readiness for treatment

There is preliminary evidence that the level of readiness for treatment influences the subsequent level of adherence. Although there are few published studies, and they have used different methods to assess readiness (based on different theories), a significant association between the level of readiness and the level of adherence has been found (120). There are also preliminary evidence of an association between the level of readiness and viral load (121, 122, 124). However, it is still unclear whether factors commonly thought to influence adherence actually have a direct relationship with adherence, or if changes in adherence are mediated through influences on other concepts, such as readiness for treatment. The TTE postulates that some factors, that appear to influence adherence, are actually influencing readiness (129). Based on this, it can be hypothesized that some factors influence adherence directly, while others influence adherence through the mediating effect of readiness.

Collaboration between health care professions – the case of pharmacy

According to the existing body of literature on adherence and readiness, the relationship with the provider is one of the key elements (99, 129, 143). There is also evidence of treatment outcomes being improved if different health care providers collaborate effectively in areas such as depression (144), diabetes (145, 146) and Chronic Obstructive Pulmonary Disease

(147). Although the interventions are considered promising, the evidence is so far lacking regarding the case of HIV (148).

Barriers for multi-professional teamwork have been identified by community pharmacists. Barriers identified in a Canadian study, (149) included limited time available for team activities, limited possibilities to meet and get to know the other team members, lack of proximity to other professions in the team, financial considerations, and tendency for the different professions to protect their own profession.

Studies exploring attitudes of doctors toward an expanded role of the community pharmacists are found in the international literature. Studies from the beginning of their clinical pharmacy era in the 1980´s in the UK and USA indicate that doctors in these countries generally support pharmacists giving patient information (150-152), reporting adverse reactions (150, 153) and helping the physicians regarding drug related questions (150, 152-154). Factors found to have a negative impact on the doctors´ acceptance of clinical pharmacy, in the 1980´s, included doctors being of older age, belonging to a speciality at high risk for malpractice suits and writing large number of prescriptions (152). In some situations doctors today still do not know what to expect of pharmacists in the USA, although younger doctors have been reported to have greater expectations (155).

Studies exploring attitudes of doctors toward an expanded role of the community pharmacists have not been found for the Swedish setting. Clinical pharmacy is today still in its infancy in Sweden (see box 2 – Paper IV) and can be compared with the situation in the UK and USA in the beginning of their clinical pharmacy era in the 1980´s.

Decentralization of pharmaceutical services

Decentralization of pharmaceutical services has been shown to increase the nurses´ satisfaction with pharmacy services in the USA (156). When satellite pharmacies were established on some of the in-patient wards at a hospital in the USA, the nurses` attitudes toward pharmaceutical services improved on these wards, whereas it did not in other areas of the hospital during the same time (157). Decentralization of pharmaceutical services to HIV clinics has been described in the USA (158-161), but not in Sweden.

The multidisciplinary treatment model at a HIV clinic in Sweden

Since 1999, the largest HIV clinic in Sweden, the HIV clinic at Karolinska University Hospital, Huddinge, has tried to improve adherence by means of a multi-professional treatment model, where doctors, nurses, counsellors,

pharmacists, psychiatrists and dieticians collaborate in patient centred teams. The aim of the treatment model (see Box 1 – Paper IV) was to increase the patients' motivation to follow the treatment regimen. The model combines several of the interventions found to impact on adherence (i.e. information, reinforcement, counselling and additional attention by health care provider).

In parallel to the introduction of the treatment model, a satellite pharmacy was opened at the HIV clinic. At the satellite pharmacy, patients can get in depth information (both oral and written) about their HIV-treatment while their prescriptions are dispensed in private. The pharmacy staff also help the patients in their contacts with other pharmacies and offer personalised advice on how to increase the level of adherence. The pharmacist was also involved in the adherence promoting activities at the HIV clinic.

AIMS OF THE THESIS

The aims of this thesis were to;

- investigate the prevalence of adherence to antiretroviral treatment (ARV) in Swedish adult HIV-infected patients
- investigate changes in adherence to ARV over time
- investigate factors associated with adherence to ARV
- test a developed hypothesized readiness-adherence model, based on the theory of trigger events.
- investigate the collaboration between nurses, doctors and pharmacists after the introduction of satellite pharmacy in a Swedish HIV clinic

MATERIAL AND METHOD

In table 3 a short methodological summary of the papers included in this thesis is provided.

Table 3. Overview of papers included in the thesis

	Design	Ethical approval	Study population	Assessments	Analysis
I	Two cross-sectional surveys at one HIV clinic	Not required, classified as quality assurance (DNR 163/02)	60 and 53 HIV infected patients respectively with ongoing treatment	• Sociodemographic factors • Adherence • MMAS (only 2002) • Motivation	• Crohnbach α • Chi Square (Fisher's exact) • Independent T-test • Mann-Whitney • Cohen's Kappa
II	National cross-sectional survey	Approved (DNR 03-384)	946 HIV infected patients with ongoing treatment for at least the previous 4 months.	• Sociodemographic factors • Adherence • Drug or alcohol use • Contacts with psychiatric health care • Belief in medication • Social support • MMAS	• Chi Square (Fisher's exact) • Independent T-test • Logistic regression
III	Secondary analysis of a national cross sectional survey (Paper II)	Approved (DNR 03-384)	828 HIV infected patients with ongoing treatment for at least the previous 4 months.	• Adherence (latent) • Readiness (latent) • Drug or alcohol use • Contacts with psychiatric health care • Age • Time on treatment (on current treatment)	• Structural Equation Modeling, • Chi Square
IV	Qualitative interview study	Not required, classified as quality assurance (DNR 02-104)	5 nurses and 2 doctors working at the HIV clinic	• Interviewer guide (Appendix 3)	• The phenomenographic approach • Consensus analysis

Study population

Paper I

All adult (≥ 18 years of age) HIV-patients on antiretroviral treatment, attending the HIV clinic at Karolinska University Hospital – Huddinge, were included in this study. The inclusion periods were three weeks in 1998 and seven weeks in 2002 and patients were consecutively asked to participate. In 1998, 72 patients agreed to consider participating in the study and were given questionnaires to fill out; in 2002, 77 patients agreed to consider participating.

Paper II and III

All adult (≥ 18 years of age) HIV-patients who had an ongoing antiretroviral treatment for a minimum of the previous four months were included in this study. The recruitment period was seven months. Patients attending 30 out of the 32 HIV-clinics in Sweden were consecutively asked to participate. If they could not understand Swedish, or any of the other languages the questionnaire was translated into (i.e. English, French, Spanish and Thai) and did not have an interpreter present they were excluded. Patients were also excluded due to illiteracy, severe mental illness or poor general health. The number of patients visiting the clinics during inclusion was 1056 and 91.9% (970 patients) fulfilled the inclusion criteria (see Figure 1 – Paper II). Brief details were collected regarding the patients that did not fulfil inclusion criteria and those declining to participate. All patients, regardless of completing the questionnaire or not, received a pill organizer (dosett) during the study period.

Paper IV

All doctors and nurses who, at the time of the study, had regular contacts with HIV patients and the HIV satellite pharmacy were approached to participate in the study. In total, six nurses met the inclusion criteria and five of these were interviewed (one was on sick leave). Three doctors were eligible for inclusion and two were interviewed (one was on a vacation and could not be recruited).

Methods

Paper I

The study compared two cross-sectional, anonymous adherence assessments carried out in 1998 and 2002. The majority of the questionnaires were handed out in the reception area by the clinic's receptionists. One research nurse and the author also occasionally handed out questionnaires. The questionnaires were anonymously returned by the respondents to a sealed box in the reception area.

Papers II and III

The study was a cross-sectional, anonymous survey carried out for seven months in 2003-2004. The questionnaires were translated by official translators into English, French, Spanish and Thai, allowing the majority of the non-Swedish patients 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) (162) but no data is available on the proportion of these speaking Swedish fluently. Health care personnel at the participating clinics handed out the questionnaires to the patients. The patients were asked to fill out the anonymous questionnaire, preferably before their appointment with the doctor or nurse, and to put the questionnaire in the pre-addressed envelope and seal it before returning it to the personnel again, who sent it to the researchers responsible for the study.

Paper IV

Data collection was carried out by means of semi-structured qualitative interviews. Before the interviews, the interviewer emphasized that the interview was going to focus on the health care professional's opinions about the pharmacy service at the HIV clinic and how it could be improved. Open questions were used, allowing the respondents to freely discuss issues concerning pharmaceutical services considered most important to them.

All interviews were conducted in May 2002 and were held in a private room at the HIV clinic. The active contact time was up to 30 minutes, while the shortest interview was 9 minutes (mean; 16 minutes). Although a private and non-stressful interview situation was sought, one of the interviewees was interrupted twice by short cellular phone calls. Since the author of this thesis was working at the satellite pharmacy, a pharmacy student, not involved in either the clinic or the pharmacy, was chosen to conduct the interviews. All interviews were taped and later transcribed verbatim by the interviewer.

Questionnaires and interview guide

Questionnaire Paper I

The questionnaire was specifically developed for the 1998 study (Paper I) and contained questions about socio-demographic factors, adherence and level of motivation at start of treatment and at the time of the study (see Appendix 1). The development of the questionnaire was informed by clinical experience of caring for HIV-infected patients and empirical evidence from the litterature. The questions pertaining to adherence were based on two items in the Adult Aids Clinical Trials Groups adherence (AACTG) questionnaire (163). The final version was piloted on a few patients (n<5) to check for any ambiguity.

Questionnaire Paper II

The questionnaire (Papers II-III) contained questions regarding socio-demographic background, drug abuse, contacts with psychiatric health care, belief in medication, social support and adherence (see Appendix 2). The social support assessment was in part based on the AACTG questionnaire (163). Part of the questionnaire had been used previously (Paper I), but the questions regarding substance abuse and contacts with psychiatric health care were added for the purpose of the present study. Clinicians, researchers and pharmacists were given the opportunity to comment on the length and content of the questionnaire. The final version of the questionnaire was piloted with HIV-infected patients (n = 5) to check for any ambiguity.

Interview guide

An interviewer guide was used in Paper IV, as a reminder to cover relevant issues (see Appendix 3). The main issues in this guide were the health care professionals´ collaboration with pharmacy staff (regarding the satellite pharmacy and conventional pharmacies) and how they perceived the pharmacists role and importance, particularly concerning adherence promotion.

Assessments

Adherence

Paper I (1998 and 2002)

Data from two items in the questionnaire were combined to achieve an adherence assessment (Paper I). The first asked whether the respondents had missed any doses the day prior to completing the questionnaire, and the second asked how often doses were missed in general (ranging from every day to never). Respondents, who reported that they had not forgotten a dose the day prior to the completion of the questionnaire and who also responded that they never forget doses were in this study categorized as adherent. This strict definition of adherence was chosen, since the respondents providing us with these answers would theoretically reach an adherence level of at least 95%.

Paper I (2002) and Papers II-III

The Swedish version of the 9-item Morisky medication adherence scale (MMAS) became available after 1998 and was used in Paper I (in the 2002 assessment) and Papers II-III. The MMAS was initially added to allow for validation of the in-house adherence assessment used in 1998. The scores of the 9-item MMAS (164) ranges from 1-13, where 13 indicates perfect adherence. The MMAS is a further development of the Morisky-Green test (165) often used in the HIV population (119, 166-170). The MMAS and the Morisky-Green test measures adherent behaviour rather than dose adherence. Internal consistency reliability (measured by Crohnbach α) has been reported to be 0.89 for the English version of the MMAS (164), which is superior to the Morisky-Green test (Crohnbach α 0.61 (165)). MMAS has been used internationally to measure adherence to antiretroviral treatment (171, 172). The Swedish version of the MMAS has a Crohnbach α value of 0.74 (Paper I).

An adherence summary score was calculated for all respondents who had fully completed the MMAS. Patients scoring 11, or above, in the summary score were classified as adherent in papers I and II. This definition of adherence is based on how we believe the patients theoretically would have completed the MMAS if they had taken at least 95 % of prescribed doses.

Social support for medication taking

An assessment of social support for medication taking was created and consisted of two items (Papers II-III). The first asked whether the patients had friends or relatives to talk to about their treatment, and the second concerned

if the patients had friends or relatives who reminded them to take their medicine. Patients answering no to both of these items were considered as lacking social support. This definition was chosen as a patient can still have social support regarding treatment without having the need for someone to remind them about taking their drugs.

Latent variables in the readiness-adherence model in Paper III

Adherence
The individual items from MMAS (except item 6) and self-reported viral load were used as indicators for the latent variable of adherence.

Readiness
Four out of the five components in the TTE was used as indicators of the latent variable of readiness.

- *Changing attitudes towards HIV medication* was assessed by asking the patients if they thought that their present treatment would prevent them from becoming ill as a result of their HIV infection.
- *Finding the right health care provider* was assessed by asking the patients how they perceive their contacts with health care staff.
- *Creating the right support system* was measured by a two-question assessment of social support for medication taking (described on pages 24 and 25 in the thesis).
- *Getting control over life* was assessed by item six in MMAS. This item measured whether the patient has a special system to remember the medication. This can be considered to be an indicator for this component, since it indicates some treatment related structure in the patient's life.
- *Having goals* could not be assessed in this study since no relevant data were available. The tested model hence differs from the hypothesized model in this aspect.

Additional variables included in the readiness-adherence model

The variables found to influence adherence according to the primary analysis of the data (Paper II) were also included to control for the direct impact of these on the latent variable of adherence. These variables were drug or alcohol problems, contacts with psychiatric health care, age, time on treatment in total and time on the current treatment.

Drug or alcohol problems were assessed by asking whether the patient had existing or previous problems with drugs or alcohol. Contacts with psychiatric health care were assessed by asking whether the patient were in contact

with or had been in contact with the psychiatric care services. Information on age, time on treatment and time on current treatment were also used.

The readiness-adherence model and the two comparative models

The hypothesized readiness-adherence model (Model 1)

Model 1 (see Figure 1 – Paper III) with two latent variables (readiness and adherence) is based on TTE. The TTE contains several components (i.e. changing attitudes towards HIV medication, finding the right health care provider, creating the right support system, getting control of life and having goals). These components could be used as indicators of readiness and four of the five were included in this model. The latent variable of readiness in turn was hypothesized to be one of the factors that influence the latent variable of adherence. Other factors that were believed to directly influence adherence included age, time on treatment, drug or alcohol problems and contacts with psychiatric health care.

To improve the fit of model 1, some variables were allowed to correlate. These were chosen if they were considered theoretically and/or logically sound and had high modification indices. The indices of model fit reported were based on the model after correlations had been allowed. The variables time on treatment and time on current treatment were allowed to correlate as were the variables age and time on treatment. The variables of drug or alcohol use and contacts with psychiatric health care were also allowed to correlate. The error variance of MMAS items 1 and 4 were also allowed to correlate, as were the error variance of items 3 and 7.

Comparative Model (Model 2)

Model 2 is presented in Figure 2 (Paper III). The only difference between Model 1 and Model 2 is that the latent variable of readiness had been eliminated; hence adherence was the only latent variable in the model. The former indicators of readiness now influenced adherence directly. All other factors were the same and the same correlations were allowed.

Comparative Model (Model 3)

Model 3 is presented in Figure 2 (Paper III). Only variables included in the logistic regression model of the primary analysis (Paper II) were included (see Table 4 – Paper II). No correlations were allowed and the model was

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identical to the logistic regression model in that there was a direct path between all independent variables and adherence. No error co-variances were allowed in this model, since this was not done in the logistic regression analysis.

Analysis of quantitative data (Paper I-III)

The data analysis was carried out using SPSS for Windows version 10 (SPSS Inc, Chicago, 2000). The level of significance was set at 0.05 and two-sided tests of significance are reported in this thesis and no adjustment for multiple testing was done.

- Cronbach´s α was used to measure internal consistency reliability (Paper I).
- Chi Square (or Fisher's exact test) was used to assess categorical data (Paper I-II) and was also used to compare the fit of the three models (Paper III)
- Independent T-test was used when comparing means in normally distributed samples (Paper I-II).
- Mann-Whitney test was used when comparing means where the measurements were not normally distributed and when analysing ordinal data (Paper I).
- Cohen's kappa was used when assessing agreement between adherence assessments (Paper I).
- Logistic regression was used to identify factors associated with adherence, while adjusting for covariates (Paper II).
- Structural equation modelling was used to determine if a hypothesized adherence-readiness model's covariance matrix fitted was consistent with collected data (Paper III).

Cronbach´s α

Cronbach´s α is a coefficient that measure internal consistency (173). Cronbach´s α indicate how well a set of items or variables measure a single (unidimensional) latent construct (i.e. the variables are positively correlated). If the items measure a multidimensional construct the Cronbach´s α value will be low. A value over 0.70 is considered satisfactory for comparing groups in research settings (173).

Chi Square test (or Fisher's exact test)

Chi square test was used to analyse categorical data (174, 175). Fisher's exact test was used when the expected frequency was less than 5 (174, 175).

Independent T-test

The assumptions of this test are that the variables tested are sampled from a normally distributed population, and equal population variance (174). This test is fairly robust to violations regarding normality assumptions in large samples (174, 176). Samples were classified as large if more than 50 observations (174, 177). Levene's test for equality of variances was used to determine whether the variance was equal or not in the groups and based on this the appropriate independent t-test was chosen (178).

Mann-Whitney test

Mann-Whitney test is the non-parametric equivalent to the independent t-test (179) and was thus used when the samples were not normally distributed. The test can also be used for ordinal data (180).

Cohen's kappa

Cohen's kappa measures the interrater reliability taking random correlation into account (181). Values of Cohen's kappa between 0.4 and 0.75 are considered fair to good agreement (182), although other cut-offs have been suggested (175, 177).

Logistic regression

Logistic regression is used when the dependent variable is dichotomous and is valid for binary, continuous or categorical covariate values (176). Variables in the univariate analysis with p-values less than 0.1 were included in the logistic regression model (175). No factors were excluded due to multi-collinearity since a conservative approach was taken (if multicolinearity is present it is more difficult to obtain statistical differences (182)).

Structural Equation Modeling

SEM is a statistical methodology that combines factor analysis and path analysis, and is considered a confirmatory rather than exploratory technique (183). The technique allows a hypothesized model to be tested statistically, in a simultaneous analysis of all the variables included in the model, in order to determine if the model's covariance matrix is consistent with the collected data. SEM is confirmatory, provides explicit estimates of measurement errors, and can incorporate not only observed but also unobserved (latent) variables in the analysis. Due to this, SEM was most applicable for testing whether a model with two latent variables (readiness and adherence) fitted existing, previously collected data. However, the SEM technique does not

allow us to rule out that other possible models might fit the data equally well as the tested models.

There are, however, assumptions that should be met or at least be approximated in order to obtain trustworthy results. The first assumption is that the data should have a reasonable sample size. Fifteen cases per measured variable has been proposed as a rule of thumb for SEM analysis (184). In the hypothesized readiness-adherence model there are 18 measured variables and more than 270 cases were included in Paper III so this assumption is met. A second assumption is that the endogenous variables (i.e. dependent variables) in the model should be continuous and normally distributed (183). All data in the dataset were treated as if they were continuous.

Model Fit

Different indices were used to measure the fit of the models tested. The statistics usually reported in SEM are Chi-square (χ^2), degrees of freedom, p-value, goodness-of-fit index (GFI), comparative fit index (CFI) and root mean square error of approximation (RMSEA) (183). The χ^2 statistic is an overall test of how well the hypothesized model fits the data and a significant χ^2 indicates a model that does not fit the data (i.e. the null hypothesis, that there is no difference between model and data, is rejected). Because the χ^2 statistic assumes multivariate normality and is affected by large sample size (i.e. a model with relatively good fit for a large dataset can still be rejected), additional indices of fit (i.e. GFI, CFI and RMSEA) must be used. The GFI and CFI should have values over .90 and the RMSEA value should be below .05 (183). These goodness-of-fit statistics only give information regarding the model's lack of fit to the data used. The statistics cannot assess if a model is plausible, hence a model should be constructed based on knowledge gained from empirical research and/or theory. Before testing the whole model, the constructs of the latent variables (adherence and readiness) were tested separately. The difference between models was tested by examining significant differences in the χ^2 values for the change in degrees of freedom.

Analysis of qualitative data (Paper IV)

The phenomenographic approach (185) (see text box 3 in Paper IV) was used to determine the variations in the health care personnel's perceptions. The aim of the approach is to describe differences in how a phenomenon is perceived by humans and to preserve the content of these perceptions. The researcher tries to find subjective categories of meaning in the interviews during analysis. The interview text was repeatedly read and statements related to the aim were coded. Next, the statements were reread and all related

statements were combined to create categories. The categories found were iteratively analysed, redefined and reduced. The text was analysed in an initial step by the interviewer. Two other researchers conducted further analyses and a consensus version based on these independent analyses was established. When the statements were translated in English, the aim was to capture the meaning of the statements, rather than giving a literal translation.

RESULTS

Paper I

In 1998, 60 patients completed the questionnaire (response rate 83%). In 2002, the response rate was 69%, with 53 patients completing the questionnaire.

Mean age ($p<0.01$), time since tested positive ($p<0.001$), time on HIV treatment in total ($p<0.001$) and time on the current treatment ($p<0.01$) were all higher in 2002 compared to 1998. Fewer respondents used adherence aids ($p<0.01$) and fewer had friends or relatives to talk to about the treatment ($p<0.05$) in 2002 compared to 1998.

In the 1998 survey, 30% of the respondents reported that they never missed a dose and in 2002, this proportion was 58% ($p<0.05$). According to the in-house adherence assessment, 28% of the respondents were considered sufficiently adherent in 1998, while in 2002, the proportion was 57% ($p<0.01$).

The Crohnbach α value for the MMAS was 0.74. The mean summary score was 10.7 in the 2002 assessment and 20% of the respondents scored 13. Almost two out of three (62%) scored 11 or above and were thus categorised as being adherent. The agreement between the two adherence assessments (the in-house assessment and the MMAS) was good with a Cohen's kappa of 0.74).

Paper II

In total, 946 patients completed the questionnaire (response rate 97.5%). The mean summary score for the respondents on the MMAS was 10.8. Nineteen percent scored 13, while 63% of the respondents scored 11 or above and were thus categorised as being adherent. Almost one in four (23.4%) of the respondents were categorized as not having social support.

Adherent patients had a higher mean age (p<0.05), were less likely to have drug or alcohol problems (p<0.05), and were more likely to consider their contacts with health care to be very good (p<0.01). Adherent patients also had had a shorter time on any treatment (p<0.001) as well as a shorter time on their current antiretroviral treatment (p<0.01). Viral load was more likely to be undetectable among the adherent patients (p<0.05).

The logistic regression analysis of factors associated with adherence, are presented in detail in table 4. Complete data were available for 659 respondents (70%), who were included in the analysis. The factors that remained independently associated with high adherence while adjusting for covariates were; increasing age (p<0.01), no drug or alcohol problems (p<0.01), better perceived contacts with health care (p<0.05), shorter time on treatment in total (p<0.01) and shorter time since start of current treatment (p<0.05).

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

Variable[1]	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†			
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

[1] Including all variables with p<0.1 in the univariate analysis

* Reference category

† The variable was collapsed into a dichotomous variable with the options; very good contacts with health care and other (good/neutral/bad/very bad), due to few responses in each of the original categories (good/neutral/bad/very bad).

Paper III

In this secondary analysis of the data described in Paper II, 118 cases (12.5%) of the original 946 cases were excluded, due to listwise deletion, and in total 828 cases were hence used in the SEM analysis.

Model 1 (our hypothesized model) had a good fit to the data. The fit of model 2 was acceptable, as was the fit of Model 3. Model 1 had a significantly better fit than Model 2 while Model 2, in turn, had a significantly better fit than Model 3.

The interpretation of the standardized model estimates presented in Figure 1 is as following. With an increasing level of readiness (indicated by more favourable attitudes towards HIV medication, having the right health care provider, having created the right social support system, and having control of life) the level of adherence (indicated by undetectable viral loads and better scores on the individual MMAS items used) also increased according to this model. Problems with drugs or alcohol or psychiatric problems decreased adherence, while higher age of the patient increased adherence. Shorter time on treatment in total (and shorter time on current treatment) increased adherence. In this model, 27% of the variability in adherence was explained by readiness.
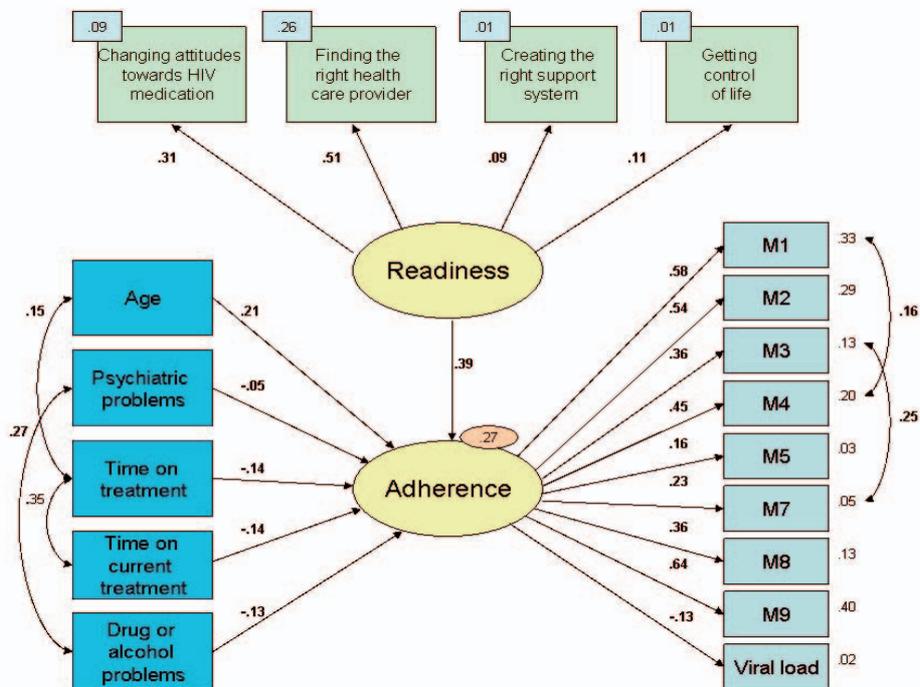

Figure 1. Standardized model estimates for Model 1.

Paper IV

Four main categories of meaning were identified during the analysis. The *availability* of the satellite pharmacy at the HIV clinic seemed in turn to form a basis for improved and more frequent *contacts between the professions* at the HIV clinic. The increased contacts lead to *knowledge sharing between the professions* and the development of *teamwork* between the staff at the satellite pharmacy and the staff at the HIV clinic.

Availability

Several drawbacks were identified regarding the availability of conventional pharmacies (e.g. the long waiting times, problems getting in contact by the phone, not to have HIV drugs in stock and lack of privacy).

The availability and proximity of the satellite pharmacy were appreciated and the pharmacy staff was considered flexible. The availability of the satellite pharmacy had several advantages (e.g. by simplifying the nurses´ work, being timesaving and allowing privacy).

Contacts with pharmacy staff

The respondents had varying contacts with conventional pharmacies and nurses had in general more contacts compared to doctors. The doctors had rarely contact with conventional pharmacies and described the pharmacy staff as "invisible". The doctors had different opinions about the quality of the contacts with conventional pharmacies. Other factors believed to influence the quality of the contacts included the number of people involved, proximity, personal contacts, and pharmacist's competence. The doctors' perception of conventional pharmacies depended on the pharmacy and the pharmacist they had been in contact with. It was believed that pharmacists should be specialized to be able to contribute effectively to medication management in HIV. Nurses, on the other hand, were positive regarding the quality of the contacts with the conventional pharmacies. The staff were expected to be professional, but concerns about not knowing how the patients were treated at the pharmacy were expressed by the doctors.

The personal relationship with the staff at the satellite pharmacy enabled direct communication. The information given to patients by the satellite pharmacy staff was therefore considered better, due to reduction in conflicting messages, and since the staff were specialized in HIV.

Knowledge sharing between professions

Lack of personal contacts between the doctors and pharmacy staff at conventional pharmacies seemed to result in little information being exchanged between the professionals, except regarding the control function where the

pharmacist assessed the appropriateness of prescriptions. The nurses, on the other hand, thought that conventional pharmacy staff generally had some knowledge about HIV drugs and were considered to give competent answers.

However, the nurses thought it was of great importance to have a pharmacist in the clinic to consult (regarding side effects, interactions, herbal medicines and diet restrictions) when they could not find the information they needed, and when consulting a doctor was not possible. The doctors said they benefited from the knowledge of specialized pharmacists at the satellite pharmacy and took greater advantage of the pharmacist's competence. The pharmacists helped the interviewed doctors regarding several issues (e.g. by informing patients about their medicines and informing doctors regarding prescribing policies. They also contributed by qualified questioning of the doctors prescriptions by being updated on new HIV drugs and interactions and act as an additional safety control.

Teamwork in Medication Management

There seemed to be a lack of agreement about medication management in conventional pharmacies and the HIV clinic. One nurse considered that the staff interfered with the trust the doctor and nurse had established with the patient. Uncertainty was expressed about the information given at conventional pharmacies. The conventional pharmacies were also expected to act as an additional source of drug information, but the respondents were unsure if that actually occurred and the lack of personnel and time constraints at conventional pharmacies was a reason mentioned.

Most nurses and doctors introduced the pharmacist personally to new patients at the satellite pharmacy. In doing so, they let the patient know that the pharmacist was considered a competent and reliable member of the health care team, thus increasing the trust between the staff and the patients. Both doctors and nurses seemed to agree that different individuals informing the patients was better than just one, especially as long as the staff had contact with each other and gave similar information, which was believed to be the case at the satellite pharmacy. The agreement between the professionals at the HIV clinic also led to involvement of the pharmacist in adherence promoting activities. The doctors used the pharmacy staff, not only to discuss ways of improving adherence generally, but also to assess the individual patients´ level of adherence. The interviewed doctors and nurses considered that the level of adherence of the clinic's patients had improved since the opening of the satellite pharmacy. The suggested reason for this was the in-depth information delivered by the pharmacy staff in a non-stressful environment. However, all respondents were not sure that the satellite pharmacy

alone was the reason for this, since many adherence-enhancing activities had been introduced at the clinic in parallel.

Suggested improvements of the service

Expanded opening hours, drugs should be dispensed for longer periods of time than the legislation permitted and even more interaction between the pharmacy staff and health care personnel were improvements suggested.

DISCUSSION

The aims of this thesis were to investigate the prevalence of adherence to antiretroviral treatment in Swedish adult HIV-infected patients, to investigate changes in adherence over time and to identify factors associated with adherence. The secondary aims of the thesis were to test a hypothesized readiness-adherence model, and to investigate how the introduction of a satellite pharmacy at a HIV clinic impacted on the collaboration between nurses, doctors and pharmacists. The level of adherence to antiretroviral therapy was low in 1998, when 28% were considered adherent, but the level seemed to increase over time, since 57% were considered adherent in 2002. Several factors associated with adherence were identified e.g. patient-provider relationship, drug or alcohol problems and time on treatment. The fit of the hypothesized readiness-adherence model indicated that increased attention should be attached to interventions that focus on the individual's readiness for behavioural change. A shift of focus from adherence to readiness to initiate antiretroviral therapy might therefore be beneficial. One approach that might increase the patient's readiness and subsequent adherence is by enhanced teamwork in medication management of which the introduction of a satellite pharmacy at the HIV clinic is an example.

The single most important conclusion in this thesis must be that readiness is a concept that seems fruitful for further investigation, compared to the concept of adherence. The work leading up to this thesis has also reflected this. The initial research plan for the thesis was strongly geared to adherence, but over time, my evolving insights have shifted the focus towards readiness after the paper regarding the theory of trigger events was published (129). The main reason for this is that there is preliminary support for the hypothesis that the level of readiness can predict treatment adherence (120) as well as treatment outcome (121, 122, 124). If this hypothesis holds, it would be of great clinical importance, not the least in the HIV treatment context, where it is crucial that the first treatment is successful by means of adherence.

Methodological considerations

The strength of this thesis was that it was designed to represent contemporary clinical reality and hence attempts were made to include all patient

groups, treated at Swedish HIV-clinics in the studies. This strive for external validity also led to several methodological challenges to internal validity.

The limitations of the thesis can be summarized in five major areas. The data is cross-sectional and based on patient self-reports. In addition the approach to adherence was not theoretical, but rather practical based on clinical experience. As in much research based on self-report, there were, at least partially, also limitations due to low response rate and internal attrition.

Cross-sectional data

The thesis is based only on cross-sectional data (Papers I-III) and hence it is important to remember that no causal relationships can be established between independent and dependent variables in the thesis. The qualitative study (Paper IV) was also conducted at one point in time.

Self-reported data

Papers I-III are all based on anonymous self-reported data. The accuracy of these data cannot be verified as all research based on self-reported data. Anonymous self-reported data was chosen in an attempt to maximise the response rate (due to the sensitive nature of the questions) and to reduce bias due to socially desirable responses. However, the anonymity also meant that self-reported data could not be linked to the respondents´ medical records. In one of our ongoing studies (186), additional data were collected from the medical records. All 111 patients approached in that study so far have been willing to participate, meaning that our concerns were unnecessary.

Choice of method for measuring adherence

To choose a method for measuring adherence is a difficult task as all methods have their strengths and weaknesses (see table 1) and hence it might be preferable to combine different approaches. In this thesis adherence measurement based on self-reports was chosen as the only method due to a number of factors.

The first paper aimed to measure adherence in a single HIV clinic. The treatment model at this clinic, had the strive to increase the use of pill organizers, and some methods for measuring adherence are not optimal when used together with pill organizers. MEMS is one of these methods (78), as is pill count (78), since pills should preferably not be transferred from the original container in either of these two methods. In addition, the second paper had the aim to assess the level of adherence in a large population, and some of the methods for measuring adherence are resource intensive in large populations. MEMS, pill count and measuring drug concentrations were therefore

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rejected. Measuring drug concentrations is only possible for some drugs and provides information for a limited time-span (78). Pharmacy records could not be used as an approach for measuring adherence due to limitations of the Swedish pharmacy computer system at the time of data collection. The only remaining method for measuring adherence was self-reports. Although self-reported adherence leads to over estimation of adherence, it shows a strong linear relationship with viral load (187, 188). The method is less demanding than the other methods, it is inexpensive and allows patients to use pill organizers.

One of the ways to measure self-reported adherence is by using questionnaires and this was deemed the most suitable, since the other ways (i.e. interviews or diaries) would not be practically feasible in that large a population. Many adherence questionnaires are available (80) and the choice was made based on the following four criteria. The questionnaire should have a reasonably high Crohnbach α value and be easy to use regardless of the respondent's schooling or level of language skills. The questionnaire should also be as short as possible so patients with limited time would be able to complete the questionnaire. Finally, it should not be too susceptible to recall error. These criteria would theoretically enable a high response rate and, hopefully, minimize the risk for incomplete and inaccurate data.

Several questionnaires were evaluated (189) and three potential questionnaires were identified; MMAS (164), MARS (Medication Adherence Report Scale) (190) and AACTG (163). MMAS is easily understood with simple yes or no answers, brief and with a high Crohnbach´s α. MARS is even briefer, but uses Likert scales that we believed to be more difficult for patients to complete. AACTG is the most widely used adherence scale in the area of HIV (80) and had been used previously in clinical trials at the HIV clinic at Huddinge. The experience at the clinic regarding this scale was, however, that it is too complicated for the patients to understand. In a head to head comparison of MMAS and AACTG at the HIV clinic at Huddinge, AACTG had substantially larger internal attrition than MMAS (186). Others have also reported that AACTG is too complicated for patients (99). The questionnaire chosen was the MMAS since it seemed to fulfil the criteria best.

The limitations of the alternative methods meant that only one measure was used to measure adherence in Papers I - II although multiple methods would be more reliable (72). As a result, the level of adherence reported in Papers I - II might not fully correspond to the patients' actual adherence, since self-reported adherence has been reported to overestimate adherence (72). In Paper III, a combination of MMAS and self-reported level of viral load was used.

According to a recent meta-analysis of self-reported adherence, the ability to distinguish adherent from non-adherent patients, is poor, if there is a ceiling effect (i.e. when patients consistently score high on measures on adherence) (84). Although the MMAS had a rather high mean score in Paper I and Paper II it does not have as high a ceiling effect as AACTG (186). This difference might be due to the fact that AACTG measures dose adherence, while MMAS measures adherent behaviour. One possible explanation is that it might be more tempting for patients to answer questions untruthfully (due to social desirability) regarding missed doses than regarding adherent behaviour.

Selection bias and generalizability

No information was collected regarding the number of patients visiting the clinic during these two collection periods (Paper I) so hence no data is available regarding the proportion of the patients that fulfilled inclusion criteria. More motivated patients might have been more likely to accept participation and thereby be over-represented among the respondents (Paper I). The respondents in 1998 and 2002 were almost identical concerning gender and mode of transmission, but both samples differed from the total patient population at the clinic. Intravenous drug users were underrepresented in both samples, while men and those who reported transmission of HIV through sexual intercourse were overrepresented in the study populations. Selection bias can due to this not be ruled out, but both samples appear similarly effected. The comparison is therefore valid for these sub-groups but can not be generalized to all HIV patients.

Selection bias is likely to be limited in Paper II, since the proportion of non-responders was small (24 out of 970). A response rate of almost 98% is exceptionally good and the proportion of eligible patients was also high. Selection bias should also be limited regarding the study presented in Paper IV since nearly all health-care providers that fulfilled the inclusion criteria were interviewed.

Since only adult patients (i.e. over 18 years old) were included in Papers I-III, the generalizability of the results is limited to adults. Only a few patients over the age of 65 were included which limits the generalizability further. The results from Papers I-III can only be generalized to patients in a developed country similar to Sweden. All patient sub-groups in the Swedish HIV-infected population are, however, represented in this thesis. Generalizability regarding Paper IV is limited to the Swedish health care system and a pharmaceutical service as the one described in the same paper.

Social desirability

Social desirability is a major concern in most, if not all, research based on self report (191). Social desirability might have influenced the results of all the studies in this thesis. However, a number of steps were taken to reduce the impact of social desirability;

- anonymous questionnaire (Paper I-III)
- the receptionists usually handed out the questionnaires (Paper I)
- anonymous return of the questionnaire, either via a sealed box (Paper I) or in a sealed envelope (Paper II-III)
- the interviews were carried out by a interviewer not directly involved in the HIV clinic or the satellite pharmacy (Paper IV)
- the interviewer emphasized to the clinic staff that the interview was going to focus on their opinions of the pharmacy service and how it could be improved (Paper IV).

Since the involvement of health-care providers were reduced in Papers I-III the patients would hopefully have felt reassured that their anonymity would be preserved and hence answered truthfully. It cannot, of course, be ruled out that some patients might not have felt that they had the total anonymity that was intended (Paper I-III). The authors of a meta-analysis of self-reported adherence (84) reported a counter intuitive finding regarding confidentiality and social desirability. Instead of the previously believed effect of confidentiality (i.e. that confidentiality decreases social desirability bias), they suggest that by raising the question of confidentiality, the patients become aware of that the researchers consider non-adherence as an undesired behaviour and they might therefore not report non-adherence.

Patients might have felt a need to consult the staff while filling out the questionnaire (Paper I-III) and hence staff might have inadvertently influenced the patient's responses, although they were instructed not to do so. In Paper IV, negative comments were made to the interviewer about the pharmacy's opening hours, for example, and this led us to believe that the staff did not only give us the answers they thought we wanted to hear and hence social desirability was believed to be limited.

Theoretical approach to adherence

Clinical experience together with empirical research informed the development of the original questionnaire used in Paper I, but there was no explicit theoretical basis. Due to this, some variables (such as self-efficacy) are lacking. An complementary approach would have been to develop the questionnaire based on one of the available adherence theories and to measure all components of the chosen theory. The questionnaire in Paper II was expanded in relation to the questionnaire used in Paper I but still some vari-

ables that might have been helpful are missing since the aim was to keep the questionnaire as short as possible. When the questionnaire used in Paper II was created, Enriquez et al (129) had not yet published the qualitative study that TTE is based on. As a result, only four out of the five components of TTE (129) was measured in Paper III. If the fifth component, that of having goals, had been included it might have changed the fit of the hypothesized model and the concept of readiness might have explained more (or less) of the variance in adherence.

Response rate

The relatively low number of respondents in Paper I means that the study might have been underpowered to detect some significant differences. On the other hand, the differences that were detected are likely to be large enough to be clinically relevant. The decreasing response rate over time in Paper I might indicate that the selection bias was more pronounced in 2002, thereby compromising the comparison between 1998 and 2002. One of the reasons for the decrease in response rate in this paper is possibly that the patients were more exposed to research projects in 2002 compared to 1998, which might result in a lowered willingness to participate. In addition, fewer questionnaires were distributed per unit of time in 2002 compared to 1998, possibly due to a higher workload in the clinic's reception.

Internal attrition

Missing data in Papers I-III could possibly decrease the statistical power of significance testing of the parameters, i.e. there might be other variables that in fact might be significant but that could not be detected in these studies due to missing data. The internal attrition due to listwise deletion was relatively large in the logistic regression of Paper II (30%) but none of the non-significant findings had borderline p-values so we believe the statistical power was sufficient to detect differences. Due to missing data in the data-set, 12.5% of the original 946 cases were excluded by listwise deletion in the SEM analysis in Paper III. Since the response rate was extremely high in the original study (Paper II), the total number of observations was large and the missing data were assumed to be random, listwise deletion was the most appropriate choice for handling incomplete data (183). It was also the most conservative way to do so.

Other limitations

The intention was to conduct the interviews (Paper IV) in a peaceful environment, but despite this, one interview was interrupted twice. This could

have led to the interviewee loosing their train of thought and thus some perceptions relevant to the aim of the study could have been lost.

The respondents´ opinions about conventional pharmacies may have been influenced by response shift (192) in Paper IV. The respondents' views might have been more negative in retrospect, following the introduction of the new satellite pharmacy. We do not, however, consider this to be seriously affecting the findings in our study since a small unpublished study (193), carried out at the same time, explored healthcare worker's attitudes toward conventional pharmacies at another HIV clinic in Stockholm without a satellite pharmacy. The respondents in that small study had similar opinions about the conventional pharmacies as our respondents.

The prevalence of adherence

In the 1998 sample of Paper I, 30% of the respondents reported they never missed a dose, while this proportion was 58% in the 2002 sample. The proportion of patients never missing a dose has been reported as 32-41% in American studies from 1999 and 2000 (163, 188) and our data hence seems to be similar.

The mean MMAS summary score for the 2002 sample in Paper I was 10.7. In the national cross-sectional sample from 2004 (Paper II) the mean adherence summary score was almost identical with a score of 10.8. In a sample of 111 patients at the HIV clinic in Huddinge the mean adherence score was in 2006 11.1 thus even slightly higher (186). In an American cross-sectional sample of low-income HIV infected patients the MMAS *non-adherence* score was 4.9 (171) corresponding to the mean *adherence* score of 8.1. In another study, by the same authors (172), they found an identical MMAS summary score in a cross sectional convenience sample of adult HIV patients. In comparison to these two studies, the adherence rate seems to be higher in the Swedish samples in this thesis. One possible reason for this is that the Swedish patients only have had to pay 1800 SEK per year for all their prescribed medications (and today they do not have to pay anything for their antiretroviral treatment) while in the USA the patients have to pay themselves or have health insurance and lack of health insurance negatively affects adherence (78).

In Paper II, 82% of the respondents reported viral loads under the detection limit, and such a high level does not seem unlikely. According to chart reviews, 85% of the patients on treatment at the HIV clinic at Karolinska University Hospital - Huddinge, had a viral load below the detection limit (50 copies/mL) in 2002 (194) and 2003 (195). This proportion had increased to

88% in 2006 (196). No similar results have been published from other clinics in Sweden, but unpublished data support this high level in the larger clinics. Such good treatment results as these from clinical practice have not been reported elsewhere in the international literature to our knowledge. Data available indicate that 37-70% of the patients on HAART have viral loads below 400-500 copies/mL (103, 197, 198). This difference in treatment success might for instance be due to differences in health care system and drug costs for the patients.

Changes in adherence over time

The proportion categorized as adherent was 28% in 1998 and 57% in 2002 according to the in-house adherence assessment in Paper I. In 2002 the MMAS summary score was 10.7 (Paper I) and in the national cross-sectional sample from 2004 (Paper II) the mean summary score was 10.8.

There are several possible explanations for the increase in adherence at the HIV clinic in Huddinge. Since 1999, the studied HIV clinic has tried to improve adherence by means of a multi-professional treatment model (Paper I), where doctors, nurses, counsellors, pharmacists, psychiatrists and dieticians collaborate in patient-centred teams. The treatment model combines several of the interventions found to impact on adherence (i.e. information, reinforcement, counselling and additional attention by health care provider) (113). Although the model was mainly based on clinical experience from the HIV clinic, it has parallels with theoretical models (199, 200)).

In parallel with the introduction of the treatment model, a satellite pharmacy was opened at the HIV clinic. At the satellite pharmacy, the patients can get in depth information about their HIV-treatment while their prescriptions are dispensed. The pharmacy staff also help the patients in their dealings with other pharmacies and offer personalised advice on how to increase the level of adherence and other treatment related questions (Paper IV).

The treatment regimen has also changed during this period. In 1998, the majority of patients were prescribed antiretrovirals three times daily but, in 2002, twice-daily therapy was dominant and also in 2004 (Paper II). The level of adherence to HIV-treatment has been shown to increase with fewer doses (108), and the reduction in the number of daily doses over time may hence have contributed to the higher levels of adherence. However, according to one systematic review, which assessed electronic adherence monitoring in a variety of treatments (i.e. not only HIV), the difference in adherence between three times daily and twice daily regimens was not statistically significant (201).

The level of adherence has continued to increase slightly between 2002 and 2006 at the HIV clinic in Huddinge. In 2002, the proportion categorised as adherent according to MMAS was 62%, (Paper I) while it was 68% in 2006 (186).

Factors associated with adherence

To summarise the research on factors associated with adherence is difficult, since for almost any studied variable there is conflicting evidence.

According to the multivariate analysis in Paper II, 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 associated with high adherence.

There is conflicting evidence in the literature of whether age influences adherence in HIV patients. Some studies have found no association between age and adherence (107, 188) whereas others, as in Paper II, found that increasing age positively influences adherence (103, 202, 203).

Drug or alcohol problems have also been reported to reduce the level of adherence (108, 204) and this is in line with our results in Paper II but no association with adherence has also been found (205). This empirical finding also fits well within the theoretical framework for achieving readiness for treatment in HIV (reviewed in (206)). These theories have a stage where the patients take charge over their life and eliminate barriers for adherence, such as drug and alcohol dependency (128, 129).

Good patient-provider contacts have previously been reported to enhance adherence (99, 143) as it does in Paper II, although it has also been shown to have no impact on adherence (97). Again, TTE attempts to explain how patients become ready to adhere to antiretroviral treatment (129) and one of the components of the subsequent process is the patient finding the right health care provider (129).

The evidence of the impact of treatment duration on adherence to antiretroviral treatment is also conflicting. Treatment duration has been reported not to effect adherence (97, 207) but longer time on treatment has also been associated with higher adherence (50). Our result seems to differ from these previous findings with antiretroviral treatment since we found an association between shorter time on treatment and high adherence. However, longer time on treatment is generally associated with a decreased level of adherence in

other chronic diseases (208). This indicates the need to continuously follow up the patients although they previously have had good treatment results.

The hypothesized readiness-adherence model

Model 1 (our hypothesized model) in Paper III, where readiness and adherence are two separate latent concepts, fitted the data well. Model 1 also indicated that readiness influenced adherence and that variables previously found to influence adherence directly seems to be mediated by the concept of readiness. We have also shown that Model 1 fitted the data significantly better than models with adherence as the only latent variable. It is, however, important to notice that the SEM technique does not allow us to rule out that other possible models (not tested in this thesis) might fit the data equally well.

In Model 1, the variables age, time on treatment, time on current treatment, trouble with drugs or alcohol and contacts with psychiatric health care were directly associated with adherence. These variables were in Paper II found to be associated with adherence.

Good patient-provider contacts (99, 143), social support (82, 97), belief in antiretroviral treatment (209), use of adherence aids (108) have all been shown to influence adherence directly, but the model where these variables were influencing adherence through readiness had a better fit to the data.

Due to this, it seems important to shift focus from adherence to measurement of, and interventions on, readiness in order to improve treatment outcomes since the concept of readiness seems central in improving adherence. Interventions that impact on the five components of the theory of trigger events need to be established. Patient-provider relationship can be improved by for instance having the same provider for longer periods of time. The treatment model at the HIV clinic at Karolinska University Hospital – Huddinge, has the aim that the patient should as far as possible have the same doctor, nurse and counsellor. Optimally, the atmosphere at a HIV clinic should also be open and non-judgemental so that the patient and providers feel comfortable about switching providers/patients if the relationship develops in a non-optimal way. To include several different health care professionals in the care of the HIV patient (as has been done in the treatment model at the HIV clinic) could improve the treatment support. To actively invite friends and family to the HIV clinic when the patient has an appointment, might further improve the social support. Involving friends and relatives might contribute to their understanding of the disease and treatment and increase their capability in supporting the patient. Belief in antiretroviral medication can be

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improved by arranging patient groups where treatment naïve patients are mixed with treatment experienced patients and the benefits and drawbacks of the treatment are discussed. The patient groups should, however, include at least one health care professional to ensure that the information given and received at the meetings are correct. Helping the patients to get control of their life can be done by offering them help by for instance nurses specialized in drug addiction, who knows how to get the patients into methadone treatment programs (and other similar programs) and offer them help in their contacts with the social services so they can get for instance a stable housing situation.

If the stage of readiness can be established for individual patients, there are also possibilities to make individualized treatment decisions for the patients. There have been attempts made to arrange strategies for achieving readiness into a logical order and adapting them to the patient's current stage, resulting in stage tailored treatments. Grimes et al (138) have developed nursing assessments and responses to the theory of stages in HIV disease (128). The researchers also proposed interventions, intended to help the patient deal with specific feelings present in each stage. The theoretical framework mainly used for matching interventions with stage of change or readiness has so far been TTM. The Harm Reduction Model has been fitted into the TTM in order to provide stage tailored interventions for HIV patients (139). A multistep progress towards developing treatment plans in HIV that correspond to the stage tailored interventions mentioned above has been proposed (131). Training sessions based on the general model Information-Motivation-Behavioral Skills Model (112, 210) have also been used both to achieve and assess adherence readiness in HIV patients (140). There is also a need to develop readiness measures based on TTE since no such measures are presently available.

The introduction of a satellite pharmacy

The interviewed doctors in Paper IV did not perceive the conventional pharmacy staff's role as anything other than dispensing and, hopefully, providing patients with information about their drugs. Other studies indicate that some doctors in USA and UK are positive about a more expanded role for the pharmacist, including reporting adverse reactions and answering drug related questions from doctors (150, 153). However, Swedish research in this area has not been reported.

Both nurses and doctors questioned the competence of the staff at conventional pharmacies and their way of working (Paper IV). One reason might be that nurses and doctors do not know the pharmacies way of working. Nurses

had a better understanding of policies and drug distribution procedures after satellite pharmacies were established on in-patient wards in the USA (156). Opportunities for face-to-face communication between nurses and pharmacists increased due to the satellite pharmacies and less time was spent communicating over the telephone (156).

The professions at the HIV clinic have defined different areas of competence and responsibilities in the local treatment model, leading to a better understanding of each other's roles. For instance, in Paper IV, the pharmacist's area of expertise was considered to be drug side effects and interactions, dietary restrictions, knowledge about herbal drugs and adherence related issues. In the USA, the role of the pharmacist was considered to be giving information about drug administration and doses, possible adverse drug reactions and food-drug interactions (150). Pharmacists are also expected to aid in issues related to patient adherence (211).

In the UK doctors may delegate tasks they consider difficult and/or that have low status to other health care professionals, such as pharmacists (212). However, our results do not support this finding. The distribution of tasks in this clinic may have occurred because the doctors thought it would reinforce information they had already provided. Informing patients about their treatment has a central role in the local treatment model developed at the HIV clinic and, in Sweden, both doctors and pharmacists have a legal obligation to inform patients about how to use their drugs correctly.

Undermining doctor-patient relationships, providing contradictory information to the patients, lack of privacy, difficulty with collaboration and time-consuming waits at pharmacies were some of the disadvantages mentioned for conventional pharmacies (Paper IV). Similar results has been found regarding the fear held by doctors of pharmacists undermining the patient-doctor relationship (212). Australian doctors are also apprehensive that pharmacists might give less than optimal and/or conflicting advice since they did not know the clinical history of the patient (213). All concerned parties (patients, doctors and pharmacists) wanted common guidelines for medication information to remedy the situation (213). At our satellite pharmacy, the patient no longer had to act as the intermediary of information between the doctor and the pharmacist, because of the continuous direct contacts between the professionals at the HIV clinic.

In a Swedish problem detection-study (214), HIV patients reported problems regarding lack of privacy at conventional pharmacies. According to the health care personnel (Paper IV), one of the advantages of the satellite pharmacy was the preservation of the patients' privacy.

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This study suggests a relationship between the frequency of contacts between pharmacists and doctors and the latter's attitude toward pharmacists. A statistically significant positive correlation between doctors´ exposure to clinical pharmacists and their favourable opinions of clinical pharmacy has been found elsewhere (151) strengthening our finding. Doctors at the HIV clinic generally had more negative attitudes toward conventional pharmacies than the nurses, but they also had fewer contacts than the nurses. When contacts with pharmacy staff increased, because of the satellite pharmacy, one doctor said he even changed his opinion of conventional pharmacies too.

Community pharmacists working at health centres in the UK have more communication and collaboration with doctors than their colleagues in conventional pharmacies. The different professionals in health centres also consult each other more, resulting in a collaborative approach toward the provision of health care (211). This supports our suggestions that increased personal contact between health care professions leads to mutual trust and a developed collaboration. The same relationship seems to apply for the nurses, although they reported more contact with conventional pharmacies and hence were generally more satisfied with those pharmacies than the doctors. Nurse's satisfaction with pharmaceutical services has also been shown to improve after the opening of satellite pharmacies located in in-patient wards in the USA (157).

Team effectiveness depends on if goals and aims of the team are agreed upon and if the roles of the team members have been clearly defined (215), which was the case at the HIV clinic (Paper IV). Research also indicates that individual competence of the team members is important for success of the teamwork and also that doubts about teamwork may be eliminated if the members learn to know each other better (215). The pharmacists' specialist competence was acknowledged by the health professionals in this study. The pharmacists also formed an integral part of the HIV clinic's staff, including taking part in the clinic's social activities.

The general impression among the interviewed staff was that the adherence level of the patients had increased. This may have been influenced by knowledge of the results from ongoing adherence research at the clinic. In paper I, the proportion of patients who were considered adherent had increased from 28 % in 1998 to 57 % in 2002. However, it is impossible to say if this change was attributed to the opening of the satellite pharmacy alone. Other adherence-promoting activities had been introduced in the clinic over that time, such as the local treatment model. The drug treatment had also been simplified, with a switch from three times to twice daily, which also might have affected the level of adherence.

MAIN CONCLUSIONS

- In a cross-sectional study of a nationwide sample of 946 HIV-patients, 63% were categorised as being adherent according to the high demands on adherence believed to be needed for virologic control.
- Adherence to HAART at a HIV clinic changed over time. From 1998 to 2002, the proportion of adherent patients had increased from 28% to 57%.
- Adherence to HAART was affected by several factors. Good relationship between the health care provider and patient was associated with high adherence, while drug or alcohol problems, longer time on treatment and younger age were associated with low adherence.
- A model, where readiness and adherence were two separate latent concepts, fitted the data well and significantly better than two comparative models where adherence was the only latent variable. The model also indicated that readiness influences adherence positively.
- According to the health care personnel conventional pharmacies in Sweden seem to have some disadvantages when it comes to servicing the HIV infected population. A HIV satellite pharmacy was introduced at the clinic and formed a base for pharmaceutical care. The satellite pharmacy was found valuable by health care personnel, although there was room for improvements. The approach led to increased communication and trust between the health care professionals that, in turn, led to developed teamwork in medicines management. In this way the satellite pharmacy is an example of seamless care, since it bridges the gap between the HIV clinic and the community pharmacy.
- It might be more relevant for future adherence research to pin-point the patients at risk for non-adherence than classifying patients into either adherers or non-adherers. If patients at risk for non-adherence are identified (possibly with the help of readiness assessments) then stage tailored interventions can be launched prior to treatment initiation.

FUTURE PERSPECTIVES

Integration of the pharmacist in to the multidisciplinary team might be achieved through clinical pharmacy. The area of clinical pharmacy has been developed during the last 20 years, especially in the US and UK. Specialised clinical pharmacists might be of importance for patient groups with complicated treatment regiments. Unfortunately, clinical pharmacy is still in its infancy in for example Sweden, as well as in many other countries, so this is still an area ripe for further development. Close collaboration with other health care professionals is a precondition for such a developement.

I believe the most important implication for future research is that it will be necessary to shift focus from adherence to readiness, especially in conditions where treatment can be postponed such as antiretroviral treatment. The benefits of readiness compared to adherence are that readiness might be measured prior to treatment initiation and hence predict if a patient is ready to become adherent and hence predict future treatment outcome.

Since the health care professionals have been shown to have difficulty predicting adherence it is necessary to find new approaches to this dilemma. If the health care professionals are underestimating a patient's ability (or readiness) to adhere, the patient's treatment initiation might be postponed and hence a patient who is ready to adhere well (and would benefit from the treatment) might not be given this opportunity. On the other hand, if the health care professionals overestimate the ability of a patient to adhere then treatment is initiated but not adhered to, which in turn would possibly lead to treatment failure. Due to this, further research is needed in the area of prediction and measurement of readiness for antiretroviral treatment.

Several factors amendable to change have been found to be associated with adherence. This implies that although the initiation of HAART is extremely important to ensure good treatment results, it is also important to follow up and motivate the patients continuously throughout the treatment. Continuous measurement of the patients' readiness to maintain treatment adherence, by identifying when interventions are required, seems to be an approach worth further investigation.

The phenomenon of readiness itself needs further investigation and in order to find the most suitable way of measuring readiness, prior to treatment initiation, head to head comparisons of the available readiness measures needs to be done. There is also a need to evaluate which of the available readiness measures that can be altered in order to successfully measure changes in readiness for patients on treatment. Several studies aiming at answering these questions are being conducted, or are in the planning phase, at the moment. Further, many of the newly infected HIV patients in Sweden today are of non-Swedish origin and a readiness instrument that would be useful in clinical practice must be feasible for many different ethnic groups. Ethnicity must hence be considered during the construction of the instrument.

It is also interesting to study readiness for antiretroviral treatment in other ethnic groups and in developing countries. For instance, the relationship between provider and patient might be affected by ethnicity and hence it might also influence the degree of readiness.

In the developing countries the distribution of medication has been one of the problem areas for the access to antiretroviral drugs, in addition to the limited resources. However, readiness might also be of importance in this context since it might enable a more cost-effective treatment by identifying patients that are ready for the treatment. In a developing country, the proportion of patients in earlier stages of change, indicating lower readiness, may be higher. The living conditions and health care services may be less favourable in these areas of the world and might hence influencing readiness negatively. The ability to identify low readiness, and act up on it, might therefore be even more important in that context.

Self-efficacy is a concept not measured in this thesis but it might influence the degree of readiness. It has been proposed that positive provider interactions not directly influence medication adherence but rather influence medication adherence by the intermediary of adherence self-efficacy (216). Whether this positive influence actually is due to self-efficacy alone or due to readiness (of which self-efficacy might be a part) needs further attention.

There might also be useful to investigate whether different types of antiretroviral treatments require higher levels of readiness than others. Antiretroviral combinations with higher levels of side-effects might be more demanding for the patients, and hence there might be a need for a higher level of readiness before initiating treatment.

Another future challenge is to incorporate readiness assessments in routine clinical practice if they will prove to be successful. When implementing patient based assessments in clinical practice, a number of obstacles should

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be considered and overcome. The cost (both in time and money), is one of these obstacles, as well as the need for staff education to be able to interpret the results. The data should be fed back to all health care professionals involved in the care of the patient, in a way that makes sense and can be integrated with clinical information. To minimize these obstacles, the optimal assessment needs to be easy for the patient to understand, easy for the health care-providers to interpret, take a minimal amount of time to perform and have an assured predictive validity and high internal reliability.

Readiness might, of course, not only be useful for HIV treatment but also for many other conditions where high levels of adherence is crucial (e.g. immunosupressed patients) and other chronic diseases where treatment initiation can be postponed. The level of cost-effectiveness would also possibly increase if the patients that are ready for treatment could be singled out from the ones that need more support prior to initiation of treatment.

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APPENDIX

Appendix 1 - Questionnaire used in Paper I

(Only originally available in Swedish, the questionnaire was translated to English for inclusion on the thesis by B. Södergård. The questionnaire below was used in the 2002 assessment)

For patients on HIV treatment (Antiretroviral treatment)

We want to know if we can do more to help you to take your medication. If you need more information, practical aids such as a Dosette box or similar things. Below you will find some questions that we would like you to complete.

If you have any questions regarding the questionnaire please contact the people responsible listed at the end.

The questionnaires are returned to the box for the questionnaires in the reception. You are of course anonymous!

How did you become infected?
Sexually ☐
Intravenous drug use ☐
Blood transfusion ☐
Unknown ☐

How long have you known about your HIV infection? ………………………………

What year were you born? …………………………….

Are you: Man ☐ Woman ☐

Can you understand and speak Swedish?

Yes ☐ No ☐

If you do not speak Swedish – What language do you speak at the HIV clinic?

English □
French □
Spanish □
Interpreter □ What language? ……………………………………………………

Do you have a permanent place to live?

Yes □
No □

If you have answered no. Where do you live now?

Relatives □
Friends □
Treatment home □
Other…………………. □

Do you have any relation/friend you can discuss your medication with?

Yes □   No □

If the answer is yes, who is it you can talk to? Please write down the relationship you have.

……………………………………………………………………………………………

When did you start taking HIV medicine for the first time?

Month and year: …………………………………………….

What HIV treatment do you have now? …………………………………………………...

What are the drugs called that you use? …………………………………………………

When did you start taking the HIV medicines you are using now?
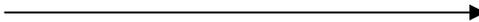
Month and year: …………………………………………….

Do you think that your present treatment will prevent you becoming ill as a result of HIV?

Yes, absolutely □
Yes, probably □
Perhaps □
No, probably not □
No, absolutely not □

How motivated were you to start your treatment? (Mark an X on the line)

Not at   ⟶   Highly
all motivated   motivated

How motivated are you to continue with your treatment today? (Mark an X on the line)

Not at   ⟶   Highly
all motivated   motivated

Have you previously had any side-effects from your treatment?
Yes ☐   No ☐

If you have answered yes, what were these side-effects? Tick several boxes if you have had several side-effects.
Nausea   ☐
Vomiting   ☐
Headache   ☐
Diarrhoea   ☐
Tingling sensation or numbness;
         Arms   ☐
         Legs   ☐
Rash;
         On face   ☐
         Other place   ☐ …………………………………………………
Other side-effects   ☐
………………………………………………………………………………..……….
…………………………………………………………………………………………

Do you have any side effects to your current treatment?
Yes ☐   No ☐

If you have answered yes, what were these side-effects? Tick several boxes if you have had several side-effects.
Nausea   ☐
Vomiting   ☐
Headache   ☐
Diarrhoea   ☐
Tingling sensation or numbness;
         Arms   ☐
         Legs   ☐
Rash;
         On face   ☐
         Other place   ☐ …………………………………………………
Other side-effects   ☐
………………………………………………………………………………..……….

Have you had any treatment interruption due to side-effects?
Yes ☐   No ☐

If yes, how many times? ………………………………………………………….

For how long was your longest treatment interruption?
…………………………………………………………………………………………

What was the reason for the treatment interruption?

………………………………………………….……………………………………

Who gave you information when you started on your first treatment?
You can tick several boxes.

Doctor ☐
Nurse ☐
Pharmacy ☐
Research nurse ☐
Patient organization ☐
Mass media ☐
Other patient ☐
Partner ☐
Other ☐   Who …………………………

Would you liked someone else to have given you additional information?
Yes ☐   No ☐

If yes; Who was it and what additional information would you have wanted?

………………………………………………………………………………………

Do you use any aids or special system to remember to take the tablets?
Yes ☐   No ☐

If you have answered yes, what aids/system do you use?
Dosett   ☐
Alarm clock   ☐
Other   ☐   Please specify ………………………………………

How often do you forget to take your tablets?
Every day ☐
Once a week ☐
Several times a week ☐
Once a month ☐
Never ☐

Which dose is it that you usually forget?
Morning ☐
Midday ☐
Evening ☐
Night ☐

Have you forgotten any dose during the last 24 hours?
Yes ☐   No ☐   Do not remember ☐

If yes, which dose?
Morning ☐
Midday ☐
Evening ☐
Night ☐

Do you know the reason for forgetting to take your medication? What do you think is the reason?

………………………………………………………………………………………

Do you have any relation/friend who reminds you to take your medicines?
Yes ☐   No ☐

If yes, please specify who reminds
you……………………………………………………

If you want additional information.. When and how do you want to receive it (you can tick several boxes)
At a regular clinic visit ☐
At a extra visit when this is the main reason ☐
Other option ☐
……………………………………
Alone ☐
Together with your partner ☐
Together with other person close to you ☐
In a smaller group with other patients ☐
At a lecture ☐
Other ☐
……………………………………

Who do you think is most capable of giving you such information about your treatment so it becomes most convenient for you to be able to manage the treatment (you may choose several options)
Your doctor ☐
Some other doctor ☐
Your nurse ☐
Research nurse ☐
Your counsellor ☐
Other counsellor ☐
Pharmacy personnel ☐
Someone that has taken the medication themselves ☐
Other HIV infected patients ☐
Patient organization ☐
Other, please specify …………………………………… ☐

What time a day would be best for you to get additional information? (You may choose several options)

Morning 7-9 ☐
During day 9-11 ☐
Lunch 11-13 ☐
After lunch 13-15 ☐
15-17 ☐
Evening 17-19 ☐
Other option ☐

………………………………………………………

Do you sometimes forget to take your medication/pills?

       Yes ☐
       No ☐

People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?

       Yes ☐
       No ☐

Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?

       Yes ☐
       No ☐

When you travel or leave home, do you sometimes forget to bring along your medication?

       Yes ☐
       No ☐

Did you take your medicine yesterday?

       Yes ☐
       No ☐

Do you have a special routine or reminder system to help you take your medications?

       Yes ☐
       No ☐

When you feel like your HIV infection is under control, do you sometimes stop taking your medicine?

       Yes ☐
       No ☐

Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?

       Yes ☐
       No ☐

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How often do you have difficulty remembering to take all your medication?

Never/rarely	☐
Once in a while	☐
Sometimes	☐
Usually	☐
All the time	☐

Thank you for taking the time to answer these questions. We hope that we will be able to offer a more personalized information regarding the treatment by the help of the answers and requests that you and other patients have provided to us.

Margit Halvarsson	Björn Södergård	PehrOlov Pehrson
Forskningssköterska	Apotekare	Överläkare

Appendix 2 - Questionnaire used in Paper II-III

Patient information

In treating HIV it is important to follow the prescribed dosage otherwise there is a risk that the medicines will be less effective. Earlier studies show that it is difficult to achieve good compliance. Using a dosett is a way of making medication easier.

The clinic for infectious diseases at the Huddinge University Hospital has developed a medication dosett that should be easy to use and discreet. We intend to distribute this new dosett without charge to all HIV patients in Sweden who are being treated with HIV medicines. In connection with this we intend to distribute a questionnaire concerning compliance with HIV treatment. As all HIV patients in Sweden will be included in this study it will give us the opportunity of studying a large number of patients. The results may help us to find reasons for lack of compliance. Such new knowledge may improve and facilitate medication.

You are now being asked if you are interested and if you are willing to fill out a questionnaire concerning your HIV medication. If you agree to participate you will be anonymous and no questions will reveal your identity. It is, however, possible to receive the dosett even if you do not wish to fill out the questionnaire.

Refusing to participate in the questionnaire study will not affect your continued care at the clinic.

If you have any questions please contact one of those responsible for the study:

Björn Södergård	Margit Halvarsson	Stefan Lindbäck
Pharmacist	Research nurse	Chief physician/
		Head of section,
		HIV unit

Address:
HIV-verksamheten
Infektionskliniken
Huddinge Universitetssjukhus
141 86 Stockholm
Phone 08-585 82269
e-mail: researchteamhiv@hs.se

QUESTIONNAIRE ON COMPLIANCE

Please reply to the questions as truthfully as possible. No one will be able to connect the questionnaire with you.

What is your year of birth?   ……………

Are you:
        Male ☐
        Female ☐

Are you from?
        Europe ☐
        Outside Europe ☐

Do you have a permanent place to live?
        Yes ☐
        No ☐

How were you infected with HIV?
        Sexually ☐
        Intravenous drug abuse ☐
        Blood transfusion ☐
        Unknown ☐

Amount of virus in blood:
        Under measurable level ☐
        Over measurable level ☐

When did you start taking HIV medicine for the first time?
        Year: ……………

When did you start taking the HIV medicines you are using now?
        Year: ……………

How many times per day do you take your HIV medicines?
        Once per day ☐
        Twice per day ☐
        Three times per day ☐

Do you think that your present treatment will prevent you becoming ill as a result of HIV?
        Yes, absolutely ☐
        Yes, probably ☐
        Perhaps ☐
        No, probably not ☐
        No, absolutely not ☐

How motivated are you to take your medicines? (Mark an X on the line)

Not at   ———————————————————▶   Highly
all motivated   motivated

Do you have any relation/friend you can discuss your medication with?
        Yes   ☐
        No   ☐

Do you have any relation/friend who reminds you to take your medicines?
        Yes   ☐
        No   ☐

Do you sometimes forget to take your medication/pills?
        Yes   ☐
        No   ☐

People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?
        Yes   ☐
        No   ☐

Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
        Yes   ☐
        No   ☐

When you travel or leave home, do you sometimes forget to bring along your medication?
        Yes   ☐
        No   ☐

Did you take your medicine yesterday?
        Yes   ☐
        No   ☐

Do you have a special routine or reminder system to help you take your medications?
        Yes   ☐
        No   ☐

When you feel like your HIV infection is under control, do you sometimes stop taking your medicine?
        Yes   ☐
        No   ☐

Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?

        Yes   ☐
        No   ☐

How often do you have difficulty remembering to take all your medication?

        Never/rarely   ☐
        Once in a while   ☐
        Sometimes   ☐
        Usually   ☐
        All the time   ☐

What do you think is the most troublesome part of your treatment?
(Grade on a scale of 1-5 in the boxes, where 1 is the most troublesome)

        Number of tablets   ☐
        Side effects   ☐
        Fear that the medicines will not work   ☐
        Number of times per day you have to take the tablets   ☐
        Hiding from those around you that you are on medication   ☐
        Other, state what……………………………………….

How do you experience contacts with medical staff?

        Very good   ☐
        Good   ☐
        Neutral   ☐
        Bad   ☐
        Very bad   ☐

Do you think you have or have had problems with drugs or alcohol?

        Yes   ☐
        No   ☐

Are you in contact with or have you been in contact with
the psychiatric care services?

        Yes   ☐
        No   ☐

Thank you for your help!

Appendix 3 - Interview guide used in Paper IV

(Originally available in Swedish, the interview guide was translated to English for inclusion in the thesis by B. Södergård)

Collaboration with the pharmacy	Adherence (HIV)	The role and importance of the pharmacy staff
How do you perceive the pharmacy?	What do you believe is the role of the pharmacy in the treatment of HIV?	How do you perceive the pharmacy staff?
How do you perceive the contact / collaboration?	What do you believe is the pharmacy's role regarding increasing adherence to therapy?	What is your impression regarding the pharmacy staff's competence regarding the HIV treatment?
In which areas do you believe this collaboration is of special importance? Why do you feel this way?	Has the opening of the satellite pharmacy led to any changes in the level of adherence?	On what occasions have you felt that you have wanted to consult a pharmacist regarding HIV treatment? Why at that moment?
What changes in the level of adherence has the satellite pharmacy lead to, according to you?		How do you believe your attitude towards the pharmacy staff can influence your patients?
How do you perceive these changes?		How do you believe the other health care staff can help the pharmacy staff to gain trust among the patients?
How could the collaboration be improved?		What is the value of the pharmacy staff and their contributions, from your perspective?

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