

Adherence to HIV treatment.

**Patient perceptions and physician communication
studied by observation, interviews, questionnaires, and patients' files**

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The thesis is based on the following papers (1-5), and on fieldwork notes only presented in the thesis.

- (1) Barfod TS, Rubow C, Gerstoft J. Patient perceptions of adherence to HAART. A qualitative interview study and a review of 26 similar studies. (Awaits submission) 2004.
- (2) Barfod TS, Rubow C, Hecht FM, Gerstoft J. "De-shaming" in Physicians' communication with patients about adherence to HAART in San Francisco and Copenhagen. A qualitative study. (Submitted) 2004.
- (3) Barfod T, Gerstoft J, Rodkjær L, Pedersen C, Nielsen H, Møller A et al. Patients' answers to simple questions about treatment satisfaction and adherence, and depression are associated with failure of HAART. A cross-sectional survey. *Aids Patient Care and STD's* (accepted for publication) 2004.
- (4) Barfod TS, Sørensen HT, Nielsen H, Rodkjær L, Obel N. "Simply forgot" is the most frequent reason for missed doses in patients with low adherence to HAART. A cross-sectional study. (Submitted) 2004.
- (5) Roeger BT, Barfod T, Kirk O, Katzenstein TL, Obel N, Nielsen H et al. Resistance profiles and adherence at primary viral failure in three different HAART regimens: Analysis of failures within two randomised studies. *HIV Med* 2004; 5(5):344-351.

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Preface

In 2000, when this study was started, half of patients treated with HAART had prevalent virological treatment failure (6). Poor adherence was viewed as an important reason for this (7), although pharmacokinetics and resistance mutations were also considered independent causes of treatment failure (8;9). It seemed necessary to take more than 95% of doses as prescribed to achieve sustainable treatment effect (7;10), and it was estimated that around 40-80% of patients took less than 90% as prescribed (11-14). This was clearly unsatisfactory, but the reason for these poor adherence rates was not clear. Demographic factors could not predict adherence (11;15-17), but suspected risk factors for poor adherence were depression (11;12;15-21) side effects (22), regimen complexity (11;16), and physician-patient interactions (12;21). However, the relative influence of these parameters on adherence was unknown (12;15). When the study was initiated, only few qualitative studies on patients' perceptions regarding adherence to HAART had been published (23-25), and none on the perceptions or behaviour of health care personnel.

There was thus a need exploring patient perceptions and experiences, and a need for a closer look at the role of the health care providers and the meeting between patients and medical culture. Creative, exploratory research methods were necessary. To study the role of adherence in treatment failure of different HAART regimes in relation to viral resistance, it was also necessary to combine creative ways of studying adherence with laboratory medical research. This is what the studies of this thesis have tried to do.

During the four years of the study, failure rates have gone down to less than one fifth of previous numbers (26). Recommended regimens have become more efficient and with fewer side effects, a reduced pill burden (3-9 tablets a day), and only twice-daily dosing (27). A wealth of qualitative studies on patient perceptions has also been published (28-51). HIV-research moves fast, but some things are unchanged. Adherence is still a main barrier to the effectiveness of HAART, and this thesis aims at providing current knowledge on the subject and putting our own work into context.

This thesis has four main sections:

- General introduction to the current literature on adherence to HAART.
- Original studies: abstracts of manuscripts, extended abstracts on other fieldwork.
- Discussion of methodologies.
- Discussion of main findings.

These four sections are followed by an epilogue and an appendix with manuscripts. The thesis supplements the manuscripts by presenting a few new data, mainly consisting of data generated through participant observation and autoethnography, and a fuller discussion of methodological strengths and weaknesses. The thesis then compares the sometimes conflicting results obtained from the various studies, and reflects on the phenomenon of non-adherence in relation to the medical culture. The manuscripts supplement the thesis with more description of methodology and results.

In medical qualitative research and anthropology it is advised to present and reflect on information about the researchers' background, contextual situation, preconceptions and personal experiences, so that readers can judge the viewpoint from which the study was done (52-54). This is placed in the epilogue.

A few abbreviations

CD4-cells	Cells with CD4-receptors (mainly T-helper-lymphocytes). The target of cells HIV. The CD4-count is the common marker of immune status in HIV. Often measured in mio/L.
VL	Viral load. A quantification of viral particles in blood. Often measured in cp/ml.
PI	Protease inhibitor. A main class of anti-HIV drugs.
NNRTI	Non-Nucleoside Analogue Reverse Transcriptase Inhibitor. A main class of anti-HIV drugs.
NRTI	Nucleoside Analogue Reverse Transcriptase Inhibitors. A main class of anti-HIV drugs.
HAART	Highly Active AntiRetroviral Treatment. A combination of three drugs, usually from two different drug classes.

Background: current status in the medical literature

HIV, HAART effects and failure

Human Immunodeficiency Virus (HIV) infects human cells that have CD4-receptors, mainly T-helper-cells. Clinical progression of HIV-infection and deterioration of the immune system is determined mainly by CD4 counts (27;55;56), and changes in CD4-counts very much depends on viral load (57). Highly Active Anti-Retroviral Treatment (HAART) is able to suppress viral replication to levels where the presence of the virus can no longer be detected in the blood (27), and thus usually reverses the progressive decline of CD4 cells. HAART has dramatically prolonged the prognosis of patients living with HIV, and offers increases in patients' quality of life in the physical as well as the mental domain.

Treatment failure can thus be defined clinically, according to CD4 counts and according to viral load. Viral load reacts to HAART within days, and in most studies of adherence, viral loads are used as reliable proxy measures of treatment effect and treatment failure.

Defining and measuring adherence

The term "compliance" was introduced in 1976 as a term for "the extent to which a person's behaviour (...) coincides with medical or health advice" (58), a definition that has been widely cited and criticized ever since (59), and has been used for adherence as well (60). Today, some still find compliance to be the most straightforward term (61), although most authors prefer the word "adherence", as "compliance" is felt to have negative, authoritative connotations (62). "Concordance" has recently been suggested as a better term, because it focuses attention on shared decision-making rather than on the medication intake behaviour (63;64). As a merge of these, adherence has been defined as "the extent to which a person's behaviour (...) corresponds with agreed recommendations from a health care provider". Generally, authors seem to perceive their own viewpoint on adherence as more understanding towards the patient, and they seem to perceive themselves to be in opposition to a "traditional" view of adherence, which is claimed to perceive non-adherence as a deficit in the patient. However, in this thesis "adherence" is used in accordance with the definition of compliance from 1976. Concordance is viewed as factor that is likely to enhance adherence.

There are two main quantitative measures of adherence. There is the percentage of tablets, taken as prescribed, and there is the proportion of patients in a population, which can be classified as adherent. These two measures are important to keep apart, when talking about adherence rates, as the first will usually be higher than the latter. For example one study found that 73% of the medicine was taken, corresponding to only 38% of patients taking more than 90% of the medication (14).

Adherence to HAART has been measured by many methods, but no gold standard exists. Pill-boxes with electronic memory in the caps ("MEMS-caps") (65-67), are perceived to be the most reliable way of measuring adherence, although they may underestimate (68) and perhaps enhance (69) adherence. Other valuable measures are self-report in questionnaires (67;70;71) or computers (72), as well as pill-counts (73), pharmacy records (74), and serum-concentrations of drugs (71;75;76). A blood test measuring the side effects of an often used antiretroviral (AZT) can provide some guidance (77-79). Physician estimates of patients' adherence are very inaccurate (80-85), although it may not be completely useless (86;87). Composite measures combining more than one method are considered the most reliable.

Self-report by questionnaire is the most widely used method in studies. Quite surprisingly, a systematic review has concluded that across a multitude of diseases, adherence is only overestimated very little or not at all by self-report (88). In contrast, several studies in HIV find that patients on average report only half of their non-adherence in questionnaires (e.g. (14)) and even less in interviews (68). But even though self-reported non-adherence to HAART may be an underestimation, it is still correlated with prevalence (67;89) and development (67;70) of treatment failure.

Prevalence and consequences of non-adherence

In non-HIV settings, two very much quoted reviews found that non-adherence in general caused one third of patients to receive no benefit of their treatment, one third receive some benefit, and one third of patients are adherent enough to receive the full benefit of treatments (58;90). A more recent review classifies 25% of patients as non-adherent (88). Across diseases, the costs wasted on drugs that were not taken appropriately has been estimated to be a quarter of the total drug expenditures, i.e. \$300.000.000 wasted per year in the US (88). The consequences of wrong medication intake across diseases in Denmark has recently been evaluated (91;92), and found.... Only part of these problems is due to patients' non-adherence, as the errors of health care providers are included in these analyses.

Several reviewers conclude, that HIV+ patients have higher average adherence rates than other patients (88;93), i.e. 88% of patients are classified as adherent (88). Adherence rates may, however be lower in unmonitored settings. Summarizing studies on adherence rates is difficult due to differences in definitions, populations and measuring methods. However, studies using relatively reliable measuring methods (i.e. combining MEMS-caps with self-report and pill counts) have found that the percentage of the prescribed tablets, which are actually taken, may differ from 95% (67) to 73% (14) and 71% (94).

Non-adherence seem to be the primary cause of virological HAART failure (10;76;95;96), although many factors interact. Non-adherence clearly predicts virological treatment failure (97;98), although pre-treatment CD4 and VL (98) also were important independent factors. Patients with higher viral loads when initiating treatment are more vulnerable to poor adherence or poor regimens (10;99;100). Besides, previous mono-therapy or drug resistance may also make patients more vulnerable to poor adherence (101). Findings on the importance of the timing of doses are ambiguous (102;103), but is generally not considered important as it used to be. Low potency of drugs may also have contributed in the past (95), but is less likely to be the cause of treatment failure in current regimens.

When all medication is taken as prescribed, less than two percent of patients may experience virological treatment failure per year (104). However, few other treatments are as unforgiving towards non-adherence as HAART. The risk of treatment failure associated with each level of adherence is hard to summarize, as it depends on the regimens and the prevalence of resistance mutations, and because studies use differing definitions on failure and poor adherence (105). However, there seems to be increased risk of virological treatment failure, even with small drops in adherence (10;106), and an increasing level of risk with every drop in adherence (10;106;107). For example, 84% of patients who had >95% of their prescribed medication dispensed had good viral response, whereas there was good response in only 54% of patients who had 90-<95% of their prescriptions dispensed (108). Another study found that 88% of patients who took >95% of their medicines had good virological treatment effect, whereas there was good virological response in only 45% of those, who

took 90-94,9% (10). Therefore, it seems reasonable to aim for 100% adherence (109) despite hypothetical threshold values of 80 or 95% (105).

It cannot be assumed, however, that patients with undetectable levels of virus all have good adherence. A study of mainly treatment-naïve patients, where the prevalence of resistance mutations may be expected to be low, found that those with prevalent viremia above 50 cp/ml, took on average 70% of doses, whereas those with undetectable levels of virus took 90% of their doses of Nelfinavir-based HAART (110). Another study also found that patients with viral loads below 400 on average took 87% of their doses (68).

The adherence needs of different regimens still need to be explored. One study suggests that the number of patients failing on regimens based on single PI's is higher than with the regimens based on NNRTI's irrespective of degree of adherence (111). It may not matter so much, however, that a slightly higher percentage have treatment failure with a certain regimen, if the rebounding virus has not developed resistance. And as described below, patients on a PI-based HAART may often have less resistance at treatment failure than patients on a NNRTI-based HAART.

Adherence and virological resistance.

When fully suppressive HAART is taken, no or very few resistance mutations develop. Virological resistance mutations are selected for when virus replicates in the presence of non-suppressive levels of antiretroviral drugs, and a bell-shaped curve is proposed as describing the relation between adherence (on the X-axis) and rate of resistance development (on the Y-axis).

The levels of adherence with the greatest risk of resistance development are still not determined. In a prospective study of patients treated with a mixture of HAART regimens and having viral loads below 500 cp/ml at enrollment, the greatest risk of virological failure with a resistant virus was in patients with 70-89% adherence (112). It is likely, that patients with ongoing viral replication despite treatment accumulates further resistance at a higher rate if they have very high levels of adherence (113;114). However, with very strong regimens and no prior virological resistance, resistance is likely to occur at higher rates with low levels of adherence, e.g. around 40-80% of tablets (113).

More of those who fail despite good adherence have resistance mutations, and fewer of those who fail with poor adherence have mutations (14;99;115). This is not surprising, as patients who fail despite good adherence on an otherwise strong regimen, would not have a rebounding virus if they had no resistance mutations. Furthermore, patients who stop their medication will often rebound with wild-type virus, because a simple treatment interruption seldom selects for resistance (except perhaps with NNRTI's due to their long $T_{1/2}$), and because the wild-type may overgrow the resistant virus in the absence of any medication in the serum. In treatment naïve patients receiving strong HAART regimens, it should not be interpreted as it is the highest levels of adherence that causes the mutations (116).

The relatively good effect seen in some studies of structured treatment interruptions (117) is surprising, and as other studies have shown that resistance development is a risk, the strategy is not advised in clinical practice.

There are differences in the prevalence of viral resistance at time of virological treatment failure among regimens. About half of patients may have resistance mutations at the time of failure after treatment with a weaker regimen like Nelfinavir-based HAART (99), or with strong but fragile reg-

imens containing Nevirapine (118-120), whereas resistance mutations are rare at primary failure of current PI-based regimens (99;121). Drug holidays may confer an extremely high risk of resistance development during NNRTI-based HAART (122), and mutations may even develop after a single dose of NNRTI (123).

Factors affecting non-adherence

Many studies have been done on the associations between various factors and adherence, probably around 100 studies regarding HAART alone. Here only the findings of a few reviews on HAART (93;124-126) and guidelines (127;128) are mentioned along with a few larger surveys. Most of the reviewed studies are cross-sectional, and therefore cannot make conclusions about causality. Most original studies used multivariable analysis, others did not, so there may be a risk of some associations being caused by confounding.

Patient factors

In reviews across diseases, demographic factors like low education and income were only slightly correlated with non-adherence, but adolescents were clearly less adherent than other age groups (88), and psychiatric patients may have lower adherence too (129). Demographic factors have also shown little correlation in HIV (93;126;127), although African Americans (130) and other ethnic minorities (124) may have lower adherence. There seem to be correlation between high adherence and the patient's perceived importance of taking all doses as prescribed (128;130), the patient's belief in own ability to take all doses as prescribed (126;130), perceived social support (124;126;128), relation to the physician (93;124;128), stable living conditions (130;131), being happy to receive treatment (130), and trust in treatment effect (93;124). Low adherence seems associated with fear of toxicity (93;124;126;128;130), alcohol abuse (93;124;128;130), depression (93;124;125;128;130), and drug abuse (93;124;125;128;130). Previous low adherence may also be a relatively strong predictor (132).

Medication factors

A review across diseases found a clear correlation between number of doses per day and the percentage of the prescribed tablets which was taken: 1ds: 79%, 2 ds: 69%, 3 ds: 65%, 4 ds: 50% (133). Overall, there is not agreement about the role of regimen complexity in HAART. Some find inconsistent results (124), others find it correlated (126). The number of doses per day may be correlated with adherence (130), as may the number of tablets, although the association is weak (134). With modern twice-daily regimens with low pill burdens, only few patients (e.g. with alcoholism) are likely to benefit from once-daily regimens.

Health care services and communication

In HIV, good institutional services were almost uniformly associated with adherence (124). All reviewers (93;124-126) and guidelines (127;128) find an association between adherence and the patient-physician relationship.

Regarding communication, a recent, comprehensive review concluded that adherence across diseases is influenced by the communication with the physician, but that detailed discussions leading to concordance are unlikely to take place in most clinical practice (63).

Other studies have, however, been more skeptical regarding the effects of communication on behavior. A Cochrane review concludes, that physicians do get "better" at communicating with patients after having received appropriate training, as measured by a changed way of communicating (135).

Another review concludes on two trials that there is also evidence for an effect on patient's experience of stress and distress (136). However, a large study of patients with various diseases found that training in shared decision making had no effects on health, although longer time for the consultations made patients expect themselves to be more adherent (137). A review also finds, that physicians' communication style only has little correlation to patients' actual adherence (138). Steele finds, that information-intensive direct questioning gives a lot more information on patients' adherence, than indirect or simple questioning (139). This may not be surprising.

Patient experiences

Several studies on patients' experiences of HAART has been done, and 26 of these meet standard quality criteria for qualitative research (23;25;28-51). These studies are mentioned in abstract (1) and reviewed more extensively in manuscript (1).

Physician experiences

In HIV, the majority of physicians report that they counsel patients on adherence at most or all follow-up visits (24;140-142). Most physicians feel it is their responsibility to counsel on adherence, although some of them are not convinced that it has any large effect on adherence (141). Physicians' communication with patients about adherence to HAART has its problems. In questionnaire and interview studies, physicians have identified lack of time, resources, and education as important barriers to their communication with HIV-positive patients about adherence (140-142).

Enhancing adherence

A systematic review of randomised trials in non-HIV settings found that interventions aimed at enhancing adherence had to be multidimensional to have any effect, and even so the effects were generally very modest (143). In HAART, a review found that only preliminary, yet promising data exist (144). A recent, large study found very little effect of counselling and no effect of beepers (145), although various tools may have shown some effects in other diseases (127). Even interventions costing \$100 and reducing HAART failure rates with only 10% has been found cost-effective (146).

Thinking about non-adherence – theoretical models

To understand adherence and non-adherence, some theoretical models have been proposed. Adherence has been analyzed as the result of the patients knowledge, motivation and behavioral skills (147), a model that has been widely cited, e.g. (60;148). A grounded theory places the patients' state of mind as the central determinant of adherence (40). Another model emphasizes the roles of Purposeful action, Patterned Behaviour and Feedback, and distinguishes between intentional and unintentional adherence (149). However, most authors simply view adherence as depending on factors related to the patient, the regimen, the health provider (127) and often also the social setting (93;124;128). The health belief model is also widely used (150).

Some things are missing in the literature

Research in many aspects of adherence to HAART is needed. However, certain gaps in the literature justify our studies:

- No review of qualitative studies on patients' perceptions of adhering to HAART has been published to date. The strategies patients use for adhering, and how they fit with the physicians' counseling strategies may need further study in light of the poor intervention effects.
- Physicians' communication with patients about adherence to HAART has only been studied through interviews, not by direct observation. A theoretical model of physicians' communication with patients about adherence to HAART has not been developed.

- It is not known, whether answers to simple questions about psychosocial issues are associated with treatment failure.
- Studies of patients' stated reasons for poor adherence have not distinguished between patients with poorer or better adherence, and thus the high prevalence of "forgetting" as a reason for missing may be occurring mainly in patients who have relatively good adherence.
- The role of adherence in treatment failure in different HAART regimens is still not clear.
- An exploration of the relationships between adherence and the medical culture is warranted.

Aim

The aims of the present analysis of adherence to HAART therefore is to:

- Review the existing knowledge on patient's perspectives on adherence to HAART and explore Danish patients' perspectives on adhering to HAART in relation to the existing knowledge. (Manuscript 1).
- Explore and explain physicians' work and communication strategies with patients' adherence to HAART. (Manuscript 2).
- Study psychosocial patient factors associated with non-adherence to HAART. (Manuscript 3).
- Compare the reasons for missed doses in patients with lower versus higher adherence. (Manuscript 4).
- Describe the role of adherence in treatment failure of different regimens and its relation to virological resistance. (Manuscript 5).
- Describe aspects of the behaviour of the different social actors in this field, supplementing the actor's own verbal understanding with participant observation, and describing the first hand experience of living these roles. (Other field notes).
- Stimulate a broader understanding of adherence by comparing various themes as viewed through different methodologies and from different social actors on the scene, and by exploring and discussing their relation to the cultural setting in which medication prescription takes place (Discussion section).

Overview of methods and timeline for data collection

In the present study, several approaches were used to describe and understand adherence and non-adherence. Interviews were used to explore patients' experiences, and formal observation and subsequent interviewing was done to explore physician's strategies for working with patients' adherence. Questionnaires and patients' files were used to quantify the reasons for poor adherence. However, we also wanted a "closer look" at the behaviour and emotions of two main participants on the social scene regarding adherence, and used participant observation of physicians and autoethnography for studying the experience of adhering to a regimen. Data were thus collected from six different sources over a four-year period. Data from the first four sources are presented in manuscripts (1-5). Data from the last two sources are collected from fieldwork notes has not been written into manuscripts, and are only presented here as an extended abstract.

Manuscripts are based upon data collected through:

- Interviews with patients
- Observations and interviews with physicians
- Questionnaires to patients
- Retrospective study of patients' files

Time of data collection

March 2000 - Febr. 2002

Dec. 2001 - Aug. 2003

July 2002 - June 2003

Febr. 2002 - Febr. 2003

Fieldwork notes (gray shadow) collects data from:

- Participant observation of clinical work
- Autoethnography: Intake of placebo pills

Time of data collection

July 2001 - Dec. 2004

Jan. 2002 - Dec. 2003

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Abstracts of original studies

For details of study 1-5 please see the attached manuscripts.

(1) Interviews with patients - own study and a review of 26 published studies

Aim: To achieve a broad picture of patients' perceptions of the factors influencing adherence.

Methods: Qualitative interviews with a mixed sample of HIV+ patients were performed from March 2000 to February 2002. Patients were asked to tell what made it easier or more difficult to take medications. Interviews lasted for 1-2 hours, were taped and transcribed. A content analysis was done on paper shortly after the interviews had been done. Subsequently, all available qualitative studies of patient perceptions of adherence were collected through comprehensive literature searches. Study results were summarized and fitted together in a content-based coding tree. Finally the interview data were related to findings from the interview study. Grounded theory was used for conceptualizing new discoveries.

Results: Twenty patients were included in the interview study, and twenty-six qualitative studies were found in the literature. In the literature review, a myriad of factors were found to influence adherence - pointing to the importance of the patients' life-style and commitment, the role of side effects, the relation to the physician, and the role of social factors. These factors often interacted with adherence in unpredictable ways that may point to necessity of knowing the patient's individual situation. Our own interviews confirmed the main findings from the literature. We discovered that some patients used "suppression of thoughts about HIV" as a strategy for adherence.

Conclusion: Many factors interact in unpredictable ways that often make sense only when the individual patient's background is known. Suppression of thoughts about HIV is used by some patients as a strategy for adherence, which may clash with physicians' attempts at enhancing adherence by motivating through information.

(2) Observations and interviews of physicians: "de-shaming" communication.

Aim: to explore, conceptualise and explain the patterns and difficulties in physicians' communication with patients about adherence to Highly Active Antiretroviral Therapy (HAART) in an American and a European setting.

Methods: physicians at three large HIV clinics in San Francisco and at two in Copenhagen were observed for one day during their clinical work and were subsequently interviewed. Transcribed interviews and notes from observations of providers' communications about adherence were analysed using Grounded Theory methodology. Primarily, descriptive concepts were used. Subsequently, analytical concepts were developed.

Results: In San Francisco, 16 of 23 eligible physicians participated, in Copenhagen 18 of 19. Adherence was mentioned in 94 of 144 observed consultations with patients on HAART. Physicians' communication with patients about adherence often seemed difficult and awkward.

ward, and a central strategy was identified and labelled as “de-shaming”. The main patterns were similar in both settings, and we developed a model of physicians’ adherence communication, consisting of four steps: deciding whether to ask about adherence or not, introductory “de-shaming” strategies, phrasing the question, and responding to the patient’s answer. We found physicians’ adherence communication strategies in these four steps to be mainly determined by physicians’ perceptions of three factors: Adherence, awkwardness and believability.

Conclusion: physicians’ communication with patients about adherence was largely determined by the physicians’ perceptions of adherence, awkwardness and believability, and it often involved “de-shaming” strategies. We present a conceptualisation and a model of adherence communication, potentially aiding reflective thinking on the subject for use in clinical practice as well as future research.

Other aspects of observations and interviews with physicians (not in manuscript)

Physicians’ explanations for patients’ problems has been identified and coded in all the interviews. A preliminary conclusion may be, that these explanations do not differ substantially from the explanations presented in reviews and qualitative interviews with patients.

What physicians told patients about the sideeffects of their treatments became a special focus of interest during the study. A preliminary conclusion may be that physicians systematically understate side effects, in order “not to worry the patient” and support them in wanting to take the medications.

Physicians’ talk with patients about sex also became a focus of interest during the study, as it appeared to be sparse. Observations of the first 14 physicians in San Francisco have been systematically coded on this subject. Out of approx. 45 consultations, sex was mentioned in five. In three of these, the patient claimed to have no sex. In the other two, one claimed to do only “petting”, the other had a venereal disease and claimed that the condom broke. In all these discussions it was the physicians who asked the patient a series of questions, reminding more of a rehearsal than a dialogue. In none of these cases the discussion was elaborate. This may be interpreted as pointing to a more general difficulty physicians may have in discussing awkward matters with patients. However, these dialogues may have been more flowing more easily if the observer had not been present, and many patients actually declined to be observed because they had sexual issues to discuss.

Six nurses were also observed and interviewed, two in SF and four in Cph. A preliminary conclusion may be, that some nurses do focus more on actual handling of medications in daily life, than physicians do. However, to which extent they work with adherence is very diverse, depending on the individual nurse as well as the time and circumstances.

(3) Questionnaire study: psychosocial issues, treatment failure and adherence

Aim: To ask all the patients of a large population-based cohort receiving HAART a few short, explicit and direct questions about these factors, and to examine the associations between their answers and prevalent treatment failure (and adherence).

Methods: All patients receiving HAART in Western Denmark and central Copenhagen were offered participation. Participants answered a short, self-administered, anonymous questionnaire assessing psychosocial and behavioural factors and treatment adherence. Findings were linked with data on demographics, disease history, and treatment effect. Treatment failure was defined as two consecutive measurements of HIV-RNA above 400 copies per ml taken at least 14 days apart. Prevalence odds ratios were estimated by logistic regression.

Results: A total of 887 out of 1126 patients returned a completed questionnaire (response rate 79%). The overall rate of treatment failure in participants was 20%. Adjusted odds ratio estimates for treatment failure were 2.3 (CI 1.3–4.3) for patients who stated poor treatment satisfaction, 2.1 (CI 1.2–3.7) for patients not fully disagreeing that they were depressed, and 2.8 (CI 1.5–5.4) for patients who stated to have been non-adherent within the preceding four days. These were also the only three factors significantly associated with treatment failure in a crude analysis. Due to the cross-sectional nature of the study, causality could not be determined. These questions, however, may be relevant screening tools in clinical practice and in follow-up studies.

Conclusion: Self-reported depression, satisfaction with treatment and adherence were independently associated with treatment failure. In unadjusted analysis, most psychosocial parameters were associated with adherence, but treatment satisfaction was not.

(4) Questionnaire study: the most frequent reasons for missed doses.

Aim: to study patients' stated reasons for having missed taking some of their HAART, and to compare the reasons stated by patients with lower adherence to the reasons stated by patients with higher adherence.

Method: all patients visiting the clinics during a one-year period were eligible if they had been started on HAART at least six months before this period. Consenting patients were given an anonymous self-administered questionnaire. Lower adherence was defined as reporting to have missed a dose within the preceding four days.

Results: we received correctly answered questionnaires from 840 (75 %) of the 1126 eligible patients. Patients with lower adherence reported the same reasons for missed doses as patients with higher adherence (*Spearman's* $\rho = 0.9492$, $p < 0.0001$). In patients with lower as well as patients with higher adherence, the most common reasons for missed doses were "simply forgot", "were away from home" and "had a change in daily routines".

Conclusion: Reasons for missed doses were identical in patients with lower or higher adherence, and the most common reasons were related to "forgetting".

Other data from the questionnaires

The questionnaires have been used for a simple description of the psychosocial status of the Danish HIV-population (unpublished report), and for validating the results of other studies (151).

The questionnaire contains other measures, which await detailed analysis. Regarding other measure of adherence, these data suggest that 43% stated to have taken all their medicine within the preceding month, 48% stated to have taken 90-99%, and 9% had taken less than 90% percent of their medication. The questionnaires also have data on the patients' experiences of side effects, which awaits detailed analysis.

(5) Patient file study: virological resistance and adherence at treatment failure.

Aim: the objective of this study was to describe the interplay between resistance and adherence in virological failure of three fundamentally different HAART regimens.

Methods: we retrospectively identified 56 verified primary virological failures (HIV-RNA > 400 cp/ml) among 293 patients randomised to either two NRTI's + ritonavir/saquinavir (RS-arm)(n = 115), two NRTI's + nevirapine + nelfinavir (NN-arm)(n = 118), or abacavir + stavudine + didanosine (ASD-arm)(n = 60) followed for a median of 90 weeks. Data on adherence were collected from patient files, and genotyping was done on plasma samples collected at time of failure.

Results: we found that treatment interruption or poor adherence was mainly caused by side effects and accounted for 74% of failures. In addition it was associated with absence of resistance mutations. In the 30 failing patients not switched from randomised treatment we found resistance in two out of 12 in the RS-arm (184V only), four out of six in the NN-arm (all four had NNRTI-mutations), and seven out of 12 in the ASD-arm (NRTI-mutations only). Two adherent patients on randomised treatment failed in the RS-arm, none in the NN-arm, and six in the ASD-arm.

Conclusion: primary virological failure was mainly caused by treatment interruption. No primary PI-mutations were found in patients failing on boosted saquinavir, whereas resistance to NNRTI's and NRTI's was prevalent in several patients failing on regimens based on these medications.

Fieldwork notes on participant observation and autoethnography (extended abstract)

Aim

The aim of the fieldwork notes is to describe aspect of the phenomenon of adherence and non-adherence, that are "closer" to the behaviour and emotions of physicians, than what can be achieved through the mental and verbal filter of questionnaires and interviews. We also wanted to describe the phenomenon of adherence and non-adherence in relation to two main actors on the social scene: the patient and the physician.

Anthropology

One of the strengths of the anthropological method is its ability to describe people's actions in relation to their culturally embedded social roles (Jenkins), and questioning the power relations between these social roles (e.g. the patient-role and the physician-role) (152). Another strength is its use of fieldwork to get a "closer" look at behaviour and emotions, than what can be achieved through for example interviews and questionnaires.

And this is what was wanted. By observing the physicians in their daily practice, by experiencing the demands that are put on physicians and by taking placebo tablets myself, it was hoped to get insight into the mutual dependencies among these social actors, and to get a closer look on actions and emotions.

This was wanted mainly to get a fuller description of the phenomenon of adherence. But also, secondarily, to provide the basis for an assessment of the role of the researcher in the creation of knowledge in the other, more distanced methodologies used in this thesis. The use of the participant observation and autoethnography is further mentioned in the discussion section.

Methodology of fieldwork notes

In this study, a fieldwork notebook was kept. Notes were written on the experiences with doing the study, the experiences and observations during my clinical work as a physician, on the interactions with colleagues and other health personnel, and any other aspect of my life that could bear some relevance for the study of adherence.

Notes were written approximately every second day, starting from the outset of the study, and more systematically during the last three years of the study. From October 2001 and onwards, the notes were written on computer, and in line with the recommendations (153), each note were from December 2002 and onwards categorized as pertaining to one of six pre-defined types of notes: 1) Planned actions; 2) Actions – how the time was spent; 3) Descriptive observations; 4) Analytical notes; 5) Methodological considerations; 6) Personal experiences and emotions. The date of writing was noted, and each note was to be assigned one or more "themes" or "categories" about its content (e.g. "forgetting" or "interview methodology"). "Jottings" was also to be made on pieces of paper whenever a relevant thought occurred, and subsequently to be written into the fieldwork notebook.

The field notes on participant observation and autoethnography, including analytical speculations and descriptions of the methodology, but excluding the transcribed interviews, was 1.424.000 characters long, including the automated writing of the six major categories of types of field notes. For practical handling of the large amounts of text, the NVivo software was used (version 2.0, by QSR International Pty). This means, that all notes pertaining to a specific theme or category could easily be retrieved across dates.

The act of writing and coding notes may in itself stimulate analysis (154). For the analysis of the notes, specific topics were retrieved and re-read, but due to time constraints and the large quantity of text, not all writings were systematically re-read. No specific anthropological theory was used in the analysis, although the concept of social identities has been borrowed from Jenkins (155).

The aim of the present analysis is to describe aspects of the phenomenon of adherence and non-adherence, which transcends the spoken word of informants while talking to a tape-recorder.

Notes on participant observation of physician behaviour are presented from two different data sources: 1) notes on my own work as a physician working with patients, and 2) notes in observations and interactions with colleagues. The “closer” look at the act of taking pills was studied through autoethnography. Autoethnography may not be a usual part of fieldwork, and visiting patients in their homes, having them show the researcher how they take the medicine, could have been an alternative strategy. Autoethnography has, however, been proposed as a valid method for knowledge about experiencing phenomena, as one gains first hand experience with emotions, which is a thing completely different from hearing about them (156).

Relations between these findings and findings from the other data sources are further mentioned in the discussion section, along with further discussions on the methodology.

1) Notes on participant observation: working as a physician.

Participant observation methodology was used for my work as a physician. Data from the participant observations are here divided in two categories: a) seeing patients; b) interactions with colleagues and other health care providers.

a) Seeing patients

Actions: to get some experience with the field, it is not unusual that infectious disease PhD-students studying clinical aspects of HIV at Rigshospitalet get introduced to out-patient clinical work by working clinically for a half day every week, especially during the first one or two years of the study. So did I for a period of 18 months (May 2001 - Nov. 2002). These were my patients. Not my study objects. But field notes were taken, especially on the experience of working with patients' adherence. For an extended period of time (March 2002 – August 2004), physicians and nurses at the ward could refer patients with adherence problems to me, for an extended consultation. In total, I had 12 extended conversations with referred patients.

Observations: with my routine patients, I found that I often forgot to ask about adherence, because there were so many pressing issues. When I remembered to talk about it, it seemed beneficial to have patients tell in detail about how they actually handled taking the medicine, and it was emotionally gratifying to sense, what I interpreted as peoples' gratitude for my thorough care and interest. During the conversations with referred patients, I found that it took more than an hour, to get around all relevant issues, and that it could be quite difficult to assist patients in exploring the background for their poor adherence. Quite often, patients had their adherence impeded by a false notion that there had to be at least 10 hours between two doses, if they were on a twice daily regimen, so if one dose was delayed, they either skipped it, or ran into very complicated changes in the intake routines. There would often be aspects of the medication intake, which they had not thought of, but which impeded their adherence, e.g. that they did not like taking the medicine in front of their partner. This took time to elicit, and it was necessary to ask specifically for these problems (e.g. how patients handle taking the medication, if they are very busy or are afraid of stigma). I usually concentrated on maintaining a good atmosphere, and sometimes forgot to cover several key topics regarding adher-

ence. Over time, I developed the enclosed guide for relevant topics, and learned how to consult it during the conversation. This was helpful for being able to cover a broader spectrum of topics. Admittedly, it may be quite seldom that I was able to change a patient from non-adherent to adherent, neither among my routine patients or the patients especially referred to me. When patients remained non-adherent despite what I experienced as our good, close conversation, I got angry, disappointed, and felt ridiculed.

Interpretations: the collection of these data started before the collection of interviews with physicians, but also went on afterwards. This may have created an atmosphere of colleagues talking together, rather than merely a lecture, and may have facilitated a more open dialogue. The emotional experiences of gratifying contact and disappointed frustration made me more aware of the importance of the emotional responses of the physician, which inspired the focus of analysis of the interviews. The time-consuming difficulties I had with eliciting patient's adherence problems would probably not have been so evident, if I had only interviewed physicians, who have had to adjust their ambitions to the existing time-schedules of a clinic. The aid I experienced from the checklist also inspired me to propose similar tools for colleagues, although they had only sparsely expressed a need for one.

b) Observing and interacting with colleagues

Actions: I participated in weekly conferences, where difficult HIV-cases were brought up by physicians to be discussed with colleagues. Conferences often lasted for one hour or a little longer, and usually about three to eight patients were discussed, often with side effects, virological treatment failure, virological mutations or adherence problems.

Observations: when patients with adherence problems were mentioned, there was often a mixed sense of despair: "what can we do?" and the sense that this was the responsibility of the patient, not our problem. To some extent, physicians seemed to feel responsible for the patients' adherence – hence the frustrated reaction. We often got lost in speculations about explanations like psychological repression, careless life-style etc., and ended up with the conclusion that the problems were either already explained (e.g. alcohol abuse), or they were bound to remain enigmatic and unsolvable. Some also proposed that HIV-medicine may have a special status in some patients' mind, as it was at times observed that patients were able to adhere to their HAART regimen, although they were unable to adhere to other medications, or oppositely, that patients refused HAART but accepted treatment for opportunistic infections. Some also proposed a link between emotional difficulties with the diagnosis and adherence, e.g. because patients who claimed very improbable routes of infection also tended to have problems with adherence. At times, non-adherent patients were judged to be crazy or not very bright, described by various euphemisms. During the years I slowly developed the routine and courage to question the treating physician about specificities of the patients' motivation and handling of medication intake. For being able to ask these questions with some certainty, it was also necessary to have a list of important topics to cover, not to get confused during the stress of wanting to perform well at the conferences. Specific information about these topics was often not known by physicians (i.e. what time of the day, the patient took the medicines, whether long-term side effects were feared, etc.) Physicians sometimes told about patients who kept saying that they took all their medications, even though we could see they did not. One was referred to a psychiatrist, but was quickly returned because no mental illness was present.

Interpretations: these observations provided data that was not elicited during interviews. The observations suggested, that physicians might feel insecure about what they should do to support the patient sufficiently. On the one hand, physicians' intermittent focus on the patients' symbolic perception of the treatment, and the evaluations of the patients as borderline psychiatric may be quite relevant. On the other hand, they can also be viewed as ways of "exotizing" and "crazying" people with mental processes and behaviour that could not be otherwise explained. This behaviour, and the sometimes lacking focus on the details of patient's knowledge, motivation and behavioral strategies, may suggests the need for an increased focus on the necessary routines or guidelines for handling of poor adherence. Such a guide might be able to assist physicians in their efforts to cover all relevant topics, so that patients are maximally supported, and so that physicians with more certainty can state, that all reasonable support is continually being offered, and then the final responsibility must belong to the patient.

2) Notes on the autoethnographic experience of adhering to a placebo-HAART regimen

Aim: the aim was to get a first-hand experience of adhering to a medical regimen, to describe the first hand experience of the process of trying to adhere to a regimen, and thus get a "closer look" than what can be achieved through the investigation of patient's verbal accounts in the interviews.

Actions: I planned to take two placebo dummies, one of each kind, two times a day for two years. Starting January 2002 I counted up equal amounts of two kinds of vitamin-pills in two containers for HIV-medication (approx 100 pills), divided this number by two and counted this number of days ahead. If I missed a dose, I noted it my diary and the reason why. When the pills were supposed to be over due to the calendar, I counted the pills that were left, and calculated my adherence rate. I then counted up pills for the next period.

Observations:

I found that I managed to keep track of my adherence approx. 80% of the time. The remaining 20% of the time were lapses, after I had completed a container of medication, and until I counted up tablets for a new refill. In the meantime, I took tablets without counting the amount in advance. During the times, where I managed to keep track of my adherence, I was able to take approx. 85% of doses. From the start, I linked medication intake to tooth-brushing morning and night. About half of the missed doses, I did not notice I had missed, until I could tell from the remaining tablets at the end of each period. Those doses, I was aware of missing, was missed because I forgot. The reasons for forgetting could be roughly divided into two: 1) because I had interruptions in the daily schedule. Some doses were missed because I forgot to bring them along, e.g. on weekend vacations, others because of changes in the routines. 2) Because I had difficulty with short-term memory. It was astonishing to experience how I could be in the process of brushing my teeth, and thinking about taking the medication, and then forgetting it after the tooth brushing was done. There was a slow learning process during the enhancement of adherence. The interruptions in daily routines were counteracted by having extra pills at work and at our weekend hut at the countryside, and by always packing the tablets as the first thing when traveling. The short-term memory problems were counteracted after the first year of tablet intake, where I developed the habit of taking the pill-container in

my hand, as soon as I remembered it, and not letting go of the container before the tablet had been taken. I was very ashamed of my performance.

Interpretations: the experience of taking tablets myself shed new insights into the difficulties of remembering the medication during slight irregularities of the daily habits, and the problems with short-term memory. The process of “forgetting that it was forgotten” is a phenomenon, which was not elicited through interviews and questionnaires. The process of learning also had not been very evident in the interviews. The personal experience of the difficulties provided me with a sense of urgency and shame, which has made me more understanding of the difficulties patients face. This experience may also have colored my questioning in interviews and the analysis of interview and participant observation data, as I did not have to struggle with side effects and difficult emotions regarding the diagnosis, which may then have received a diminished attention.

Discussion of methods

Interviews with patients

In the literature review a myriad of factors influencing adherence was found, and in the interview study, suppression of thoughts was discovered as a strategy for adherence.

In medical qualitative research, it is a rarely seen advantage of the study that it summarizes other studies in the field. Very few of the other 26 included studies did this. And the straightforward, descriptive procedure makes it likely that the myriad of factors is a valid result. It may, however, be argued that the review was too descriptive to qualify as a “Descriptive metasummary” (157), and should rather be called “a conventional narrative review” (158). A more analytical approach might have been more in line with current recommendations, although still debate on the right method to summarize qualitative studies (157;159;160).

In the interview study, a descriptive approach was also used for the initial coding (161;162). This is very common in medical research, although it is also very common to falsely claim that more analytical methods have been used (163). We did a primary analysis after the interviews were done, then did the literature review, and finally focused on the aspects of our study not mentioned by the literature. If we had done more ongoing analysis of interviews and literature during the collection of interview data, we might have been more able to do purposive data sampling (162;164), and could have focused on the emerging fields of interest, and evolved them into greater clarity (e.g. suppression of thoughts as an adherence strategy). It may be speculated, why we found suppression of thoughts to be a strategy for adherence, when others did not? Perhaps because the interviewer unconsciously had a presumption that “seeking and giving information on the importance of adherence” would be a relevant strategy for strengthening adherence, and was surprised to find that the opposite could also be the case. Grounded Theory (154;164), a more analytical approach, was only used as inspiration for the conceptualisation of newly discovered categories.

The fact that I presented myself as a physician is likely to have influenced the data. I tried to keep an informal atmosphere, but most likely patients would probably have told stories that could provide health care professionals with new insights, that differed from what they hear every day in the clinic, e.g. if I had been patient advocate visiting people in their homes. The strategy of suppressing thoughts about HIV, could in theory be an excuse that patients gave to me as a health care person, because they felt they knew so little about HIV and resistance.

Observations and interviews with physicians

A model of physicians communication with patients about adherence was developed: The physician decides to ask about adherence, may prepare the patient for the question, asks, and reacts to the patient’s answer. These actions are highly influenced by the physicians’ perceptions of adherence, awkwardness and believability, and often included an element of “de-shaming”.

Data sampling

Inviting all physicians within certain institutions is not fully in line with “purposive sampling”, but is quite common due to practical reasons (165), and may be defended because of the comparative aspect of the study, although this turned out to be of lesser interest. The double use of observation and confronting informants with the observed behaviour has the potential to make informants reflect on aspects of their behaviour, of which they were not previously aware (166). However, the observational methods were highly unstructured, and this is known to have little inter-observer reliability (52). This calls for immediate validation by presenting informants with interpretations (52;162), which was used during the interviews, and for reflexivity (52;54), which is presented in this thesis. The model is thus based on data that were sampled in a reasonable way.

The changing analytical approach

At first the study was intended to use a more descriptive method for data analysis. However, after attending a Grounded Theory seminar in September 2003, the analysis moved in a more analytical direction after the data had been collected. Thus, the study intends to develop new concepts for the discovered basic social processes, and articulates hypotheses about interaction factors. However, since the data had been collected before most of the analysis took place, the pure Grounded Theory methodology was not followed. Furthermore, no definite “core category” was chosen. Also, the paper was written in “past time” descriptive style rather than “present time” as a pure theory, in order to underscore the “data-grounded” nature of the study.

Grounded Theory: more theory – less description.

Grounded Theory is a systematic method for generating concepts from data and formulating relevant hypothesis about the “Basic Social Processes” by which the people under study handle their main concerns (154;164). According to Glaser, Grounded Theories should be evaluated by their product, i.e. whether the theory “works”, “fit” is “relevant” for explaining the substantive area (154), and whether it is “modifiable”. The here presented model may fulfill these criteria when used for explaining important parts of what goes on in physicians’ communication, but other aspects of the communication may not be accounted for. Other criteria regarding the research process and the grounding of data (164) are hard to fulfill due to their complexity and the space limits of the paper and this thesis.

Grounded Theory methodology is under debate. Glaser focuses on generating theories (154), whereas Strauss and Corbin focuses more on advising on practical procedures, and allows one to stop a conceptualized, descriptive stage of the analysis (164). This study did not choose one of these above the other. The study aimed for theory building, though the analysis was stopped when a “model” had been developed. This study combined the practical analytical advice given by Strauss and Corbin (164), and I have gained the courage to “theorize” from Glaser’s writings and his personal help with the analysis of this study.

Heisenberg principle

Physicians do change behaviour when observed (167), a phenomenon related to the “Hawthorne effect” (168) and the “Heisenberg uncertainty principle” (169). Physicians were asked about this. Many had a general concern: “It probably always changes your behaviour a little bit when someone is in”. Some felt it had raised their awareness of adherence during the consultation, especially during the first consultation, but usually stated something like: “We did a

pretty good job, the patients and I, in terms of just kind of trying to ignore you there”. Several also explained something like this physician: ”I’m very used to having people observe ... I mean it’s probably half the time over the last umpteen years I’ve had somebody observing around.”

However, in two Danish cases the nurses, who had subsequently spoken to patients as part of the clinical routine, on their own initiative spoke to the researcher. One said, that *all* the patients of one physician had given uninvited statements to the nurses that the physician had talked and chatted a lot more than usual. Another nurse said that several patients of another physician had complained that he was more “stiff” and formal than usual.

Despite the reassuring statements from physicians, it cannot be excluded that physicians because of the observation talked more about adherence, than they would usually do, and perhaps with less natural ease. The main findings are, however, likely to be valid, since physicians stated so themselves, and also referred to other consultations during the interviews. Finally, concepts transcend description, and the model is modifiable.

Method mixing or method slurring?

It is not uncommon in medical qualitative research (54) to incorporate aspects from multiple methodologies including Grounded Theory (154;164), anthropology (170;171) and general interview research (162). The manuscript is also written in grammatical past time rather than present time in order to seem less theoretical to reach a medical audience. The strength of this study is that the methods were adapted to the needs of the research question. However, it is a weakness that the mixing of methodologies means that we are left with a simple model rather than an fully developed grounded theory, and that the possibilities of anthropological methods have not been fully used (i.e. a detailed, comparative analysis of the two cultures, a “thick” description and analysis with the aid of established theories).

Using a computer

Glaser with his strong focus on analysis and conceptualisation, is in favour of written notes, and an opponent of taping and transcribing interviews, as it slows down the process, and he sees no use for computers in the analysis (154). Others view them as potentially helpful in handling transcripts (162;164). This study has probably been slowed by the use of the software NVivo, but may also have gained in validity.

Questionnaire studies

The questionnaire was based upon the ACTG adherence questionnaires (172), which has been widely used, e.g. (173;174). There are two ACTG adherence questionnaires, each five pages long. These two were simplified and merged into one. Taking inspiration from the “Yale scale” for measuring depression (175), we only asked one single question for each psychosocial factor, though to be associated with adherence. To make participants feel free to give socially undesirable answers, we emphasized confidentiality, made permissive introductory remarks, and asked explicitly for honesty (176). To further facilitate answers that deviated from the socially desirable, we used a four-point Lickert scale instead of a yes/no strategy. In the analysis we then dichotomized answers, summarizing the three least desirable answers in one category.

We found that depression, adherence and treatment satisfaction were associated with prevalent treatment failure, and that forgetting was the most common reason for having missed a dose in patients with poorer as well as better adherence.

The lack of association with support from family, relationship with physician, regular daily habits and alcohol intake, may be interpreted as a real lack of association or as lack of sensitivity of the questions to detect an association. It may also be that the cause and the effect were reversed and neutralized each other, (i.e. lack of family support leads to non-adherence, which leads to treatment failure, which leads to increased support from family), or that the effects were present only in non-participants.

The questions were validated through a pilot study and through cognitive interviewing (177), and *construct validity* was established by finding very good correlation between self-reported adherence and perceived importance and ability to take the medicine every day (question B1 and 2). Others have perceived the association between self-reported adherence and viral load as a validation of the adherence measurement (70), and according to this criteria, ours was valid as well. However, measurement validity could have been further strengthened too. We attempted to establish validity by using it together with the full-length ACTG adherence questionnaires and some validated measures of coping strategies and the relation to the physician. In this way we hoped to test *concurrent criterion validity* and *content validity* (176). However, this was done in a prospective study of incident failure that failed to include a sufficient number of patients, and was closed after nearly two years of inclusion time (May 2002 - March 2004). Only twenty patients filled out these questionnaires, and it is unlikely that can provide any estimate of the validity of our psychosocial screening questions. *Face validity* was aimed for by presenting the questionnaires to a handful of colleagues, but this could have been done more systematically with a wider panel of scientists (176). With this lack of systematic validation, there is also some ambiguity left in the interpretation of the associations found, e.g. we do not know if the “depression” question identifies clinical depression. On a similar line, the high prevalence of “simply forgot” may also in part be explained by the phrasing of the questionnaire, e.g. the “simply” may make participants particularly prone to give this reason.

The non-responders to the entire study or to some questions lessens the power of the study, and may also have introduced bias (178). A response rate of 79% may be considered reasonable, but since most items consisted of just one question and not of subscales, it was not possible to use the mean of a subscale, and those questionnaires were excluded in the multivariate analyses. Approx 20% of included patients were not analyzed in the multivariate analysis because they had a missing item. A remark on the questionnaire urging participants to mark every item might have been helpful.

All questionnaires were manually checked by the author, and other inconsistencies were not common. The open-ended questions gave a range of details, but did not cover a special theme or suggest any weaknesses in the questionnaire.

The aim of the multiple regression analysis was to explore possible correlations with psychosocial factors, removing the possible effects of “nuisance” variables regarding demographic data and disease history. In the selection of variables for the logistic regression we reduced the number by including only variables from the database with known association with treat-

ment failure, and by excluding one of the psychosocial questionnaire variables from the analysis, if two such variables were suspected to be associated because they covered the same parameter (179). It is defensible to largely select variables for regression analysis based on prior information (180;181), and this was done in our case. Subsequently, some exploratory stepwise regressions were done. We also found little difference between crude and adjusted odds ratios, suggesting lack of confounding. Multiple regression computing was done by data manager Niels Obel with SPSS version 10.0 statistical software.

The use of Spearman's rank correlation test for testing the differences between the reasons for missed doses may be questioned. The test proves that the ranks of reasons are correlated. Whether or not the test is able to test, if one or two variables are significantly differently ranked among the two groups of patients, may be a slightly different question.

Answers to the question about stigma were left out from the manuscript about psychosocial variables and their relation to treatment failure (abstract #3), because we did not have confidence in the results due to the phrasing of the question. The question was phrased as a negation, which is generally advised against (176). Furthermore, it was a "negative" question, where the socially desirable answer was "fully disagree" after a series of questions where the socially desirable answer was "fully agree". We therefore did not have confidence in the results. It could have been included in the paper, but would have confused the picture and the methodological issues would have taken too much space to discuss.

Retrospective study of patients' files

Poor adherence and treatment interruptions were found to be present in the majority of patients with treatment failure, and were associated with the emerging virus to be of wild-type. Side effects were the most common reason for poor adherence or treatment interruption.

However, the method of collecting adherence data – retrospectively from patients' files – meant that the degree of adherence and the "reasons" for missed doses were created through a series of steps:

- the patient's perception
- the patient's willingness to share this perception with the physician
- the physician's perception of the patient's statements
- the physician's choice of topics to be written in the file
- the researcher's detection of the writing in the files
- the researcher's analysis, summary and presentation of findings

Each of these steps lowers the validity of this retrospective method for assessing the *degree* of adherence. First of all, patients with HIV rarely tell physicians about their non-adherence (36-38). Second, physicians are usually not very good at estimating adherence (182), and do not always document their evaluation in the patient's files (183). Third, the categorization of adherence into "good" "poor" and "stopped", although we had originally aimed for more detailed categorisation.

Each of the steps also affects the *explanations* for poor adherence and treatment interruption, although document analysis is not an unusual source of qualitative data (165). Specifically the high number of patients mentioning side effects as a reason, not only for stopping treatment, but also as a reason for poor adherence, is surprising. Thirteen patients had poor adherence,

and side effects were the most commonly mentioned reason, mentioned in seven files, followed by alcohol, which was mentioned only four times (data not shown in manuscript). The regimens given during the study are not likely to have much more side effects than current treatments. However, others have found that patients mainly tell physicians about their non-adherence, if it is caused by side-effects (37). It may be that patients exaggerate this explanation, as they feel this is more acceptable and relevant for the physician to know, than more personal factors related to their life-style. It may also be that physicians for the same reasons are particularly prone to note side effects in the patients' file.

However, the demonstrated relationship between the blinded assessment of degree of adherence and prevalence of resistance has been observed by others (14;115;184), and strengthens the validity of the data, as does the association with viral load at the time of failure also observed by others (185;186).

Fieldwork notes on participant observation and autoethnography

Why this method? Did it have any effect?

It has already been discussed in the results section, how this method was used as a way of getting beyond verbal accounts, and supplementing the formal observation of physicians during the interview study. Here it is discussed, how it worked in reality, and some broader reflections on the methodology are presented. Using one's own experiences with adherence, from the role of the physician as well as the role of medication-taker, definitively also provided the entire study with more sense of urgency, commitment and stamina. It may also have provided the entire study process with a sense of legitimacy – that it was not only the studied objects – the patients and the physicians - who had to submit themselves to interrogation. I may have felt more in my good right to persistently ask provoking questions, when I was not only trying to explore *their* problem, but was trying to solve *our* problem.

Generally about the fieldwork notes

Reliability of fieldwork notes is enhanced by systematic categorization of events (153), as it was done in this study, although it was often difficult to separate actions from observations and analysis. However, the reliability is diminished by the unstructured choice of topics and timing of the writing, i.e. it was mainly when something was perceived to be interesting that anything was written at all. This may have diminished the exploratory power of the fieldwork and strengthened the influence from personal interests. The fieldwork notes covered two main data sources: participant observation working as a physician, and an autoethnography.

Participant observation

The participant observation methodology in general has advantages to sticking only to interviews and questionnaires, as everyday observations and informal discussions may get closer to the every day life.

In my work as a physician caring for patients, there might have been an ethical problem, if I had used my patients as research objects without telling them. I did tell some of my patients, that I was doing research in adherence, and that my work as a physician was part of my research, but I did not tell all of them systematically. This is ethically defensible, as I was supposed to be their physician anyway, and focused only on doing the clinical work as well as

possible. They were not my research subjects, they were my patients. However, I was observing my own work with patients as part of the study.

In the study of my interaction with colleagues, there is also an ethical problem of using the everyday work as data, without explicitly telling my colleagues, that I did so. The fieldwork data here presented therefore focuses on my own experiences, and is not a study of my colleagues. Another problem with using the interaction with colleagues as fieldwork, is the general problem of doing fieldwork in one's own culture, as described below. Discussing physicians' relations to the pharmaceutical industry may also be a topic that I will have to handle with care not to harm my relation to my colleagues.

Own intake of placebo pills - autoethnography

A piece of autoethnography is included in this thesis for several reasons. In the first place, because autoethnography can be one of the most rewarding genres of text to read (e.g. the papers of Carolyn Ellis (187;188)). Secondly because it is advised in qualitative research to reflect on the effect the researcher has on the research process and findings, a process called enhancing the reflexivity (52;54), and a description of personal experiences may be a tool for this. Thirdly the placebo pills were taken to get some sense of solidarity with the study subjects.

So where does the "exposure of the subjectivity" stop and the "findings" start? I found the hassles of daily unstable living to be a main barrier for adherence, I found that I often did not know that I had forgotten the medicine, and I was shameful. This may be seen as a finding in itself – that trying to adhere can be like that. But it can also be seen as a way of exposing my personal bias.

General remarks on methodology

Doing fieldwork in one's own culture.

Doing fieldwork in one's own culture has the advantages of an easier understanding of the viewpoints of the studied people, and of a more easy access to data. The disadvantages of doing fieldwork including interviews and participant observation in one's own culture (as opposed to studying foreign cultures) are that the researcher is at an increased risk of going mute and blind or biased because of the personal involvement. Blind or biased, because it can be hard to analyze matters without distance (189). Mute, because one does not want to create problems for one's future career by being too critical of future colleagues and employers (152). In my case, the disadvantage of using fieldwork as research method, is also the increased risk of being dumb, because I do not have any formal methodological or analytical training.

Traditionally it has been advised that anthropology, which studies all aspects of medical institutions and questions its power-relations (corresponding to sociology *of* medicine) is best carried out by researchers operating from independent positions outside the formal medical setting, whereas the applied side of medical anthropology (corresponding to sociology *in* medicine) is best carried out in collaboration with the health personnel (152). However, recent theorists claim that these two aspects of medical anthropology is artificial, and that both aspects are present in most studies (152).

In this study I have tried to avoid getting mute by trusting the good intentions of myself as well as my colleagues. I have tried to counteract the blindness and my bias by keeping fieldwork notes and a personal diary and consulting analytical texts. I have felt an involuntary detachment from the society at the ward. But it is likely that I am still unable to analyze aspects of the medical culture, which I along with my colleagues take for granted.

In the study observing physicians' interactions with patients, I suspect that some patients and physicians have felt more comfortable (than others?) with having me in the room during consultations, and certainly the participant observation would not have been possible, had I not been a physician. I suspect also, that I have been more able to understand the difficulties my colleagues have when talking to patients about adherence. And I suspect that I have been able to present my findings in ways that are more easily understood by physicians.

It may be difficult to discuss the communication habits of physicians

A researcher studied physicians' communication with patients (personal communication). His studies will never be completed or published. He informally told me that he found it difficult to talk with physicians about their communication habits, because he felt that it was the physicians' personalities, which were often the problem. And they did not like to have their personalities criticized. However, one may also look at this problem differently. If the physicians' personalities are a problem, it may be because they lack formal training in communication. Sufficient formal communication training will probably make physicians able to transcend their personality. If physicians are not formally trained, they will have to rely on their common sense, their personalities and their experience.

Qualitative research in medicine

Prestigious medical journals have equally appreciated the value of qualitative research, although some are more radically qualitative, e.g. emphasizing reflexivity (54;190), whereas others are more concerned with rigorous methodology checklists (165;191), and yet others emphasize the existence of diverging norms for quality in qualitative research (53;192-194). The vast majority of qualitative studies in HIV and other medical areas uses interviews as their method for data collection, and they almost always take a descriptive approach, although they often claim to use more analytical methods (163). This may perhaps be viewed as a way of "playing safe", as transparent methods for data collection and analysis may seem more reliable. However, more complex methods for data collection, where the researcher is in closer contact with the researched, and more use of theories, have been called for in medicine (171;195).

Anthropology and qualitative methods in medicine

Differences are in the purpose and the methods. The purpose of anthropology is to shed light on cultural phenomena, whereas the purpose of qualitative methods in medicine is more focused on utility, - i.e. to enhance health care. The methods used in anthropology involves fieldwork and participant observation (153;171;195;196), and studies often use more than one data sampling method, and anthropologists use theories to analyze their data. Medical qualitative studies usually use only one method of data collection, which is usually interviews (Sandelowsky) although participant observation is in theory considered a valid data source (165;195). Theories are rarely discussed, but there is a focus on achieving credibility through descriptions of the methodology.

Medical anthropology is “formal anthropological activities concerned with health and disease”, and the methodologies are not principally different from the ones used in other branches of anthropology (152;197).

This thesis tries to borrow methodology from (medical) anthropology, and use it for medical purposes – i.e. ultimately to increase people’s health. The primary expected audience of this work is medical professionals.

The multitude of methodologies

Using more than one method, more than one theory, more than one data source, or more than one researcher, is often advised in qualitative research to give a fuller picture of the field under study – a procedure called “triangulation” (53;54;162;165;194). This goal has been achieved regarding the data sources and the methodologies.

Discussion of results

This discussion section does not give a full overview of the factors influencing adherence, but focuses on the factors studied in the here presented original studies.

A myriad of reasons

The review of qualitative studies showed that many factors might influence adherence. The patients in the questionnaire study also reported missing for a wealth of reasons. Data from the physician interviews also suggests that physicians share this view. However, in the questionnaire we only found that 3 out of 7 expected variables were significantly associated with prevalent treatment failure, which may be due to methodological issues, but may also be attributed to the fact that patients respond differently to different life circumstances, and although one factor may be important for adherence in the individual, it may not be the case in a large group of patients. The monotone mentioning of side effects in patients' files is somewhat odd, but are probably best explained by aspects of patient-physician interaction, the unusual regimens, and the fact that these patients probably had extremely poor adherence. The very high prevalence of reasons relating to forgetfulness in patients' stated reasons in the questionnaire might point to the fact that "simply forgot" may cover other underlying explanations. The field notes showed that physicians also often have difficulties when trying to understand the reasons for patients' adherence, but also that they try hard to come up with meaningful explanations. The field notes on working as a physician showed that it may take more than an hour to go over all the necessary potential reasons for poor adherence, if the health care person does not have routine in using a guideline.

Forgetting

Forgetting was the most frequently mentioned reason for missed doses by patients, and was the greatest barrier in the autoethnography. In the review of qualitative interviews, several background explanations for forgetting doses were mentioned.

However, the only large study on the effect of reminder devices on adherence to HAART have shown no effect (198). Reminder devices should not be trusted as a solution to forgetfulness, but they may still be part of the standard armamentarium in clinics, for the few patients who may benefit from them, and their effect is also likely to depend on an optimal combination of functions and design. It may even be suggested that clinics should be able to offer a range of reminder devices and pill boxes, so that patients could choose a type and design they felt good about and which supported their sense of identity rather than annoying them with ugly sounds and reminding them of hospitals.

Intentional and unintentional non-adherence should be conceptually separated. For example, intentional non-adherence is more associated with the individual's reasons for and against taking medications, whereas unintentional is more related to demographics (199). Forgetting is non-intentional, but other non-intentional kinds of non-adherence exists, e.g. "ran out of medicine".

Knowledge

Some patients in the review of qualitative interviews said they were adherent, but later described medication intake behaviour, which was non-adherence according to medical stand-

ards. This was interpreted as lack of knowledge by the primary investigators. Several physicians were also observed to ask patients, what regimen they were taking because physicians had often experienced misunderstandings to cause non-adherence. This is in accordance with studies suggesting a link between adherence and knowledge of one's regimen (200) or general HIV knowledge (201;202).

Motivation

In the review of interviews, a firm commitment was often mentioned as necessary for adherence, and patients felt motivated by observing the effects of treatment. In the physician study, physicians were also observed to use information, praise and shaming of patients to motivate for adherence.

Perceived efficacy of HAART has also been found to be associated with adherence (203). However, motivation may not be the main factor in adherence. It has been suggested that motivation mainly influences intentional non-adherence (199), and that non-intentional adherence is the most common (202). Furthermore, across other diseases, risk behaviour was predictable by perceived behavioral control in multivariate analyses, but not by intention (204). Still, there is a strong focus on motivation in many explanatory models and interventions for adherence, e.g. (205-207), which does seem reasonable. In theory, motivation may be viewed as balance between benefits and drawbacks, which may both be influenced by theoretical knowledge, personal experiences, second-hand stories and fantasies. It may be beneficial to address these during adherence counseling, supplementing with support and behavioral advice.

Treatment effect, satisfaction and adherence perceptions

Perceived treatment effect was a strong motivator for adherence in the review of interviews. In the questionnaire study, we also found satisfaction with treatment to be independently associated with treatment effect as a proxy measure for adherence, although the line of causation is not clear. Another questionnaire study also finds this link (208), but has the same problem with causality. A follow-up study, however confirmed the relation between confidence in HAART and subsequent adherence (209)

Even though perception of the treatment as effective is correlated with adherence (210;211), the correlation may not be strong, and studies have also suggest, that many are able to take the medicines without believing strongly in its effects (212)

In our questionnaire study, very few did not perceive adherence to be important, and we could show no correlation with adherence. Knowledge about the importance of adherence has, however been shown to be correlated with adherence in other studies (130;201;213).

Side effects

In the interviews, side effects were mentioned as a strong barrier to adherence. Also in the retrospective look at patient files, side effects were given as the most common reason for poor adherence as well as interruption of treatment, although the validity of this finding may be discussed. Compared to this it is quite surprising that side effects were not even among the ten most common reasons in the questionnaire study, not even in patients who had missed a dose within the preceding four days.

These contradictions can hardly be solely explained by stronger side effects of the treatments in the file study, since patients failing the three-NA arm also had side effects as their most common reason for treatment failure (data not shown). However, it may be, that some of those patients with very severe side-effects, did not answer the questionnaire.

A more likely explanation may be, that patients report side effects to their physicians, as two qualitative study indicate (34;37). It may be suggested that side effects are perceived by patients as something the physicians can do something about, whereas the physicians are not perceived as able to help with remembering. It is well known, that different data collection methods give different results. This may not necessarily be interpreted as bias, but simply pointing to the fact that human knowledge is shaped by context. Interviews done by a human being may give more data on difficult emotions, whereas self-report to a computer may give more data on stigmatizing behaviour (214). This supports the hypothesis that “simply forgetting” the medication is perceived to be a stigmatizing behavior, whereas “side effects” are seen as a socially acceptable cause. Contrary to this hypothesis, one other study found, that side effects were more commonly mentioned as a reason for poor adherence in a questionnaire than in interviews (215). However, in this study the interviews were confidential and not done by health care providers, and only half of those who were interviewed did also answer the questionnaire.

Psychological resistance

In the interviews and the fieldwork, a few patients said they could not swallow pills because of prior side effects, as a kind of conditioned reflex (data not shown). However, in the questionnaire, “reminding of disease” was an uncommon reason for missing doses.

The review of interview studies found that the emotional trauma of the diagnosis was a major factor in non-adherence. In the fieldwork, physicians were also observed to speculate on the relation between claiming a “very unlikely” route of infection, and poor adherence, and interpreting it as a sign of some unresolved emotional or social conflict. A quantitative study has also found that in-depth processing of the emotional trauma of HIV may be correlated with good adherence (216).

According to “reactance theory”, people may value freedom in daily activities highly (217), and when adhering to a regimen is perceived as a threat to that freedom, non-adherence is likely to occur. A psychological “resistance habitus” may also be part of some gay men’s identity (218), and most likely in heterosexuals as well, which may make submission to healthy behaviour difficult.

Stigma

In the review of interviews, this was a major barrier to adherence, and it was also among the ten most common reasons in the questionnaire study. However, in the physicians study, physicians were not observed to discuss this very much with patients (data not shown), as they generally did not do much discussion of handling of specific barriers to adherence.

Behaviour

In the qualitative interviews, busy lives, substance abuse, traveling and other factors interfering with a stable daily routinized life also interfered with adherence. In the questionnaire study of associations with psychosocial factors, we did not find any correlation between prev-

alence of treatment failure and abuse, and only a modest association with regular life-style. This may be interpreted as lack of sensitivity of the questionnaire to accurately detect these factors, or a hypothetical confounding from a “boy-scout-factor” which makes the same kind of people admit that they have been abusing and also makes them take the medicine. Many other studies have found a correlation with abuse (93;124;125;128;130).

Self control

Risk behaviour has been shown to be predictable by perceived behavioral control in a multi-variable analysis, but not by intention (204). This may run contrary to an “understanding” interpretation of risk behaviour – including non-adherence – interpreting it mainly as a question of choice or priorities. To the extent that behavioral control is a main predictor of non-adherence, it may also explain some of the helplessness, which physicians seemed to feel, when trying to make people “pull themselves together”. Changing a personality characteristic like behavioral control may prove exceedingly difficult in clinical routine.

Daily handling

The review of qualitative studies emphasized the support gained from “tricks” like “routinising” ones lifestyle and coupling intake to regular activities, and storage of extra containers at convenient places. In the physician study, daily handling of the medication also seemed easier and less shameful to discuss than the number of missed doses, although the topic was relatively seldom touched upon. The field notes on the author’s own work as a physician was in line with this, and the autoethnographic experience strongly supported the importance of good handling routines, and pointed to the learning time that may be necessary.

Suppression of thoughts as an adherence strategy

In the patient interview study, three patients handled adherence by suppression of thoughts about HIV and medication, and the strategies of “worry-avoiding non-adherence”, “worried non-adherence” and “worried adherence” seemed to be an enlightening categorization of behaviour.

That avoidance of knowledge may be a prevalent strategy in handling one’s ill health, may be supported by a study which found that after the diagnosis, no patients with leukemia sought extra information about the disease, although especially younger patients felt that they ought to (219).

This may perhaps conflict with physicians’ felt obligation to inform patients. It may also be speculated, whether physicians are at risk of over-emphasizing the information-giving aspect of health care – not only because they feel obliged to provide patients with an informed choice, but also because this what they have been trained in – having a lot of knowledge. It has, however, been shown that physicians across settings are aware that too much info can be counterproductive when counseling about adherence (220).

Assessing adherence – and forgetting to have forgot

In the review of qualitative interviews, patients became aware of having missed doses, either by remembering about the medicine, when it was too late, - or when circumstances or their own priorities hindered them in taking it on time. Discovering that too much medicine was left in the container was also mentioned (i.e. they had not noticed that they had forgot), although only in one or very few studies. It is, however, a disadvantage of the interview meth-

odology that forgetting to have forgot is often not discovered, as the information relies on the consciousness of the interviewed person. This is also demonstrated in the adherence-model “reconciling incompatibilities” (40), which is based on interview-data, and which focuses on conscious lapses in adherence. In the physician study, physicians assessed adherence by treatment effect, refill claims, general evaluation of the patient’s stability, and by the patient’s self-report, - and an evaluation of the believability of the self-report. In the questionnaires we used the measure of having missed a dose within the preceding four days. Such a short span is recommended to enhance recall, although it has the disadvantage of covering only few days, and therefore risk classifying moderately adherent patients as fully adherent. The preceding four days may also deviate from the general adherence, e.g. if it does not include a weekend. For use in the face-to-face contact with the patient in the clinical encounter, it may also be speculated whether the proximity in time would make it more shameful to admit having missed doses, than if for example an entire month was asked about. As mentioned in the background section of this thesis, a large review of studies have found that across a multitude of diseases, adherence is only overestimated very little or not at all by self-report (88), although studies in HAART has shown that only about half of missed doses are identified by interviews.

The autoethnography showed that “Forgetting to have forgot” can be common. This points to the possible advantage of pill-counting and other control-measures to check on adherence. It may seem as incredibly obvious, that people may forget that they forgot. But it is a theme, which is only sparsely mentioned in the study of patient interviews, and physicians were very seldom – if ever, observed to discuss with patients, if they were able to check their own adherence, e.g. by marking in the calendar, when a new container of tablets were started. The background for this has not been explored, but it could be that physicians want to show patients respect, and therefore do not want to question their words or experiences.

Guidelines for clinical practice generally advice health care persons to keep some track of reported missed doses (93;128).

Support

In the review of interviews, many patients stated that they received substantial support from friends and family. However, many patients also got discouraged from the medicine by their peers, and “doing it for one’s own sake” seemed to strengthen adherence. In the questionnaire study, we found support from partner for medication intake to be the only factor correlated with self-reported adherence in crude as well as adjusted analysis (data not shown). The field work with patients also suggested, that “social support “ may have many kinds of influence on patients’ adherence (data not shown in manuscript). Some patients feel they get great support from their partner helping them to remember, others feel that the presence of their partner or other supportive persons makes adherence difficult. The difficulties may arise when patients have not told their supportive persons about the diagnosis. However, in some cases patients had disclosed the diagnosis, but they just preferred not to take it “right in the face” of their partner or supportive person. The pills and the diagnosis may be something, they do not want to constantly expose. In literature reviews, perceived social support is found to be associated with good adherence (124;126;126;128), although a large study found that it was associated with poor adherence (130).

Contextual factors: the role of the setting... and the culture

Findings from interview studies were mainly noting that people of ethnic minority status may have problems with language, and associated problems with understanding the importance of adherence.

The physician study also had a comparative aspect. This did not become focus, but some communication differences were noted. Average consultations were longer in San Francisco than in Copenhagen (26 vs 16 min). The atmosphere was often observed to be less formal in San Francisco than in Copenhagen, e.g. some physicians gave patients a hug and told them about the physician's own private life. In San Francisco physicians did not wear white coats, which the majority did in Denmark. On the other hand - several male physicians in San Francisco wore a tie, which was never observed in Copenhagen. Consultations with patients on treatment tended to include adherence slightly more often in San Francisco than in Copenhagen. Discussions about adherence seemed a little more thorough in San Francisco than in Copenhagen, and a question-style implying that some doses might have been missed was mainly observed in San Francisco, whereas a question-style implying good adherence was mainly observed in Copenhagen.

The comparative aspect of the study also made us aware of factors that may contribute to the observed differences in communication. For example, differences may be tentatively explained by differences in culture, such as a more reserved Danish modesty (221) vs an American tendency to open sharing of feelings (222). In San Francisco there is also a traditionally very strong gay grass-root HIV movement, probably linking HIV-specialist physicians closer to their patients. In San Francisco, physicians came from different specialties and may have more actively chosen to work with HIV, whereas in Denmark, virtually all infectious disease specialists also care for HIV patients, most of them as only one part of their job. The communication differences may also be explained by the longer consultations and the lack of follow-up by nurses in San Francisco as well as by the more burdened patient population.

Several studies have found an increased adjusted prevalence of poor adherence (106;130;223) in ethnic minority groups, especially African Americans. Some of the differences may be due social and psychological differences, as differences in harder demographic factors had been controlled for. In a Danish cohort, it has been observed that whites and non-whites have the same rates of treatment success (224). However, immigrants from Asia had treatment failure rates below average, whereas immigrants from Africa have treatment failure rates above average (personal communication, Søren Fangel-Jensen).

Communication

The review of qualitative studies found that patient often do not tell physicians about their non-adherence even though they find the relation with the physician to be good. In the physician study, physicians' communication with patients about adherence often seemed difficult and awkward, and a central strategy was identified and labelled as "de-shaming". A model of physicians' adherence communication was developed, consisting of four steps: deciding whether to ask about adherence or not, introductory "de-shaming" strategies, phrasing the question, and responding to the patient's answer. Physicians' adherence communication strategies in these four steps were found to be mainly determined by physicians' perceptions of three factors: Adherence, awkwardness and believability. In the questionnaire study, hav-

ing misunderstood the information about medicines or dosing was mentioned by less than five percent of patients as a reason for having missed a dose.

The difficulty of communicating about non-adherence may point to the general difficulty of discussing this topic, but may also be interpreted as a consequence of physicians' probably to sparse training in adherence and in communication. The large proportion of immigrant patients in Denmark (225) and the US (36), who has views on HIV that diverges very much from the medical perspective, may suggest that at least in this population, there is a large gap in physicians' communication with patients, - although good communication may not necessarily result in shared worldviews.

Physicians communicate with patients about adherence to HAART across a large amount of significant barriers. Physicians have a specialized knowledge and jargon, and they seldom belong to the same social subgroups as their patients. Patients may have a traumatic relation to their disease status, and they may be ashamed of not being able to take all doses as prescribed. The frustration, that physicians were observed to express, may in part be a frustration of not being able to overcome these barriers.

When physicians get detailed and specific in their discussion with patients about their adherence behaviour, it might also get patients to see the point in being open about adherence problems. This helpful strategy of "getting specific" is also in line with Bendix's simple advice for communicating with "nervous patients", which in 1977 were sent out by the Danish Medical Association to all Danish physicians (226). Bendix first two pieces of advice are to make the patient talk about "situations, not symptoms" and to make the patient keep talking by repeating the patient's last words ("the parrot method").

A meticulous observational study of communication about prescription medicine in general practice showed that physicians perform the communication tasks, which they rate as important – except regarding "the risks of the treatment" and "the patients' ability to follow the treatment plan" (227).

The role of the relationship with the physician in adherence

In the review of patient interviews, a supportive physician was mentioned as very important regarding adherence, and in the Danish study, several patients with adherence problems complained of a physician, who was perceived as not understanding of their problems (data not shown in manuscript). In the study of physicians, there were large differences between physicians in their degree of support for patients' adherence. In the questionnaire, relationship with physician was not associated with treatment failure, and only 10% of patients did not fully agree having a good relationship with their physician. "Had a poor relationship with my physician" was even the very least common reason for missing doses. In patient's files, there was only one note, where the poor adherence was interpreted as caused by a poor relation between physician and patient (data not shown in manuscript). The fieldwork suggested that physicians feel responsible for patients' adherence, and get frustrated when the patients do not adhere.

A note on trust may be warranted. Trust in the provider has been shown to correlate with adherence, and is mentioned by patients in the review of qualitative interviews as important. In the physician study, it was found that physicians try to create trust by being informal. This

probably means that physicians think that patients believe more in them as human beings than as part of a trustworthy establishment – the health care system. A study found, that to patients with serious illnesses, the three physician factors that were important in creating trust, were: good interpersonal competences (aspects that could be learned), technical competences, and being the patient's ally (228). Another study found similar factors to be what patients in general are looking for in a physician: Technical expertise, a personal relation, and respect (229).

Other health care providers

This thesis has focused on physicians. Nurses obviously also play a great role – in some settings a greater one than the physician. In the physician study, some physicians in Denmark said they mainly expect the nurse to talk about practical handling of medicine, as they saw themselves as more responsible for discussing indication and choice of regimen (data not shown in manuscript). As mentioned in this thesis below the abstract, a few nurses were also observed and interviewed. In the US, Nurse Practitioners worked very much in the same way as the physicians, whereas the nurses in Denmark talk with patients after the patients has talked to the physician. Danish nurses were observed to vary a lot in their discussion of adherence with patients. Some asked very much about motivation and handling of the medication – others did not at all. A clinical pharmacist was also interviewed in San Francisco, who said he worked very systematically with many aspects of adherence, not very differently from the way physicians are suggested to do in the end of this thesis.

Differences between nurses' work and the work of physicians are not a main topic of this study. It is likely, that the power physicians have, e.g. in deciding about the indication for treatment, makes adherence discussions different from the discussions patients can have with nurses, although many of the here sketched aspects of adherence communication may have relevance for nurses as well.

Shame, de-shaming and awkwardness – identity and low believability

In the review of patient interviews, shame was mentioned in the form of patients not wanting the physician to be judging them. In the physician study, many physicians said they tried to de-shame the patient, and it was also observed to facilitate communication. The autoethnography also demonstrated, that shame of non-adherence can be devastating.

Physicians expect and manage awkwardness and low believability in other areas of clinical work, e.g. regarding sexual risk-taking, use of tobacco and alcohol, and in victims of domestic violence (230;231). But regarding non-adherence to treatment, physicians may expect cooperation and may tend to get more upset by low believability because they may feel more responsible for treatment than for prevention, and because individualized implementation of treatment recommendations may depend on believable information from patients.

Awkwardness and believability seem to be powerful impediments that need to be taken into account in theories and guidelines about communication and support for health behaviour change and adherence. If left unattended, these issues may force physicians to resort to silence or simple advice. Patients' shame may be a generally underestimated factor in the medical encounter (232), and has been proposed to be like "The elephant in the room": so big and disturbing that we don't even see it even though we keep bumping into it (233). Similarly, physicians may be so used to discussing sensitive subjects with patients that they hardly notice the awkwardness anymore.

Power-relations in the medical culture

Non-adherence causes frustration

Patients as well as physicians may have culturally embedded traditional expectations to the ideal patient-physician encounter, implying that patients present their problems to physicians who then provide a “quick fix” or give their expert advice. The patient is then either cured or finds ways of carrying out the advice. These expectations are not met when the patient has difficulties identifying and presenting the problems, when physicians cannot fix them, and when patients are unable to follow the given advice. The following frustration and confusion may create the awkwardness.

Power?

According to Foucault humans often create much of their identity through their permanent struggle for freedom and their revolt against authorities. Non-adherence and low believability can be viewed as the patient’s revolt against the power of the physician, as a lack of trust and as fear of punishment. And physicians do hold multiple powers over patients: the power of knowledge, the prescribing power, and the power to morally condemn patient behaviour or turn off their compassion (234). When the patient does not adhere, and especially when the non-adherence is not told about, it may be a way of reversing this power-relation. Anthropologists have also proposed interpreting low believability regarding non-adherence as the patient’s reactions to the authoritative powers of physicians (235).

In the field work as a physician, it was also found that patients may get more intensely “present”, more happy, when then talk about their own tricks for handling medication intake, but also when they talked about the “scheduled deviations” that they allowed themselves (data not shown in field notes). This aspect was not clear in any of the other original studies. But is it not common knowledge, that it may be more fun to things “my way”, than to do things “the right way”?

How should physicians handle patients who get part of their identity through opposing the authority of the physician? It may be a helpful to ask patients about their strategies. In the physician interviews, many Danish physicians also said they tried to make it clear to the non-adherent patients that they should do it for their *own* sake, not to satisfy the physician (data not shown). Why was this necessary? Because physicians had the feeling that patients felt an obligation to present themselves as “good patients”? The physician study also found that a de-shaming dialogue might be beneficial.

However, a re-phrasing of the power-terminology may also be warranted, focusing on mutual dependency. Physicians may be viewed as being dependent on patients, as patients are need to “fulfil their part of the contract” by adhering to the prescribed regimen. So physicians may get desperate, or feel helpless, and not able to help the patient as needed, when treatment fails because of non-adherence. Similarly, patients are, of course dependent on the information and advice they get from physicians. The shame, and the low believability may also be interpreted in the light of the dependency. If patients were not dependent on the advice from the physician, they would not need to expose their weaknesses. And at the same time, their status as “good patients” is also dependent on the physician’s approval of their behaviour.

HIV treatment may cause changes in the role of the Infectious Disease specialist

Communication about adherence seemed a main obstacle to physicians' work with adherence. We identified awkwardness, question-styles and handling of non-believability to be core concepts in understanding the difficulties physicians face when discussing adherence with patients.

Part of the explanation for this finding may be historical. Classical virtues of the physician were to comfort, alleviate, and heal. During the last 50 years, however, physician values may have been more focused on diagnosing, treating and preventing. More recently, the medical world in general has experienced a transition from acutely to chronically diseased patients, a transition to which the medical education has not yet adapted (236). In acute treatments, the role of patient perceptions may be relatively limited. However, in chronic treatment, patient perceptions come into focus again – in part because of compliance issues. In countries like Denmark, where HIV is treated by infectious disease specialists, the discovery of HAART may thus be causing changes in the demands of physicians. Infectious disease specialists in countries like Denmark may be in a transition phase, enhancing their focus on patient perceptions, because long-term treatment with HAART becomes a larger part of their work.

Lack of training?

In the physician study and the participant observation, physicians were at times observed to call the patient “crazy” or euphemisms hereof, when they felt unable to get non-adherent patients adherent. This may be interpreted as an expression of the physician's helplessness. The awkwardness and the under-use of de-shaming also suggest shortcomings in physician training regarding adherence and communication.

Physicians' strategies for handling of awkwardness and low believability seemed to depend more on their common sense and personality than on professionally learned skills. This may also be interpreted as a consequence of a traditionally not very strong focus on communication skills in the medical education.

Regarding communication about adherence, more specific knowledge and curiosity about barriers to adherence that would enable physicians to engage in detailed discussions with patients on the subject. Discussions with patients about how they handle the barriers to adherence can assist patients in remembering about missed doses (237) and in adjusting their adherence strategies (238). Detailed discussions about the barriers to adherence can also de-shame patients by assuring them that the difficulties of adherence are appreciated. Physicians may also need additional training in communicating with patients about shameful topics (233) and partnership building (63;236).

The patient's view, understanding – and anthropology

Anthropologists have stressed that non-compliance is the result of ideas and values, that differ from those of the doctor's (239), and have viewed this viewpoint of “understanding the patient” as being opposed to a traditional “patient-deficit model” (33). For anthropologists, there may be an interest in cultural factors, as a basic field of interest for its own sake. In medical use of qualitative methodologies and anthropology, the focus is on achieving health. Thus, rather than setting up the anthropological point of view as opposed to a traditional (i.e. medical) viewpoint, it may in medicine be more fruitful to focus on the goal: “What should physi-

cians and patients do regarding adherence to HAART?” For answering this question as good as possible, anthropological methods are needed along with other methodologies.

Who is responsible? Premature contentment and ongoing doubt in physicians.

Physicians are responsible for providing reasonable amounts of counseling and support. Capable and sane patients are responsible for their own choices. The implementation of these simple principles are, however, not always straightforward. What is “reasonable amounts of counseling and support”? Sometimes physicians may “prematurely content” themselves and feel they have done enough, when they have told the patient about the dangers of non-adherence. At other times, physicians will “keep doubting”, asking themselves whether all reasonable aspects of support and information really have been provided. Premature contentment and ongoing doubt may be more likely in fields like these, where appropriate behaviour is not yet defined and worked into the medical culture.

A practical approach

As an alternative to the dichotomy between on the one hand the perception of adherence as a deficit in the patient, and on the other hand the perception that aims at understanding the patient's point of view, one may focus on how patients and physicians can best be supported.

In clinical practice, physicians and patients need to discuss, whether treatment is indicated, weighing benefits and drawbacks – including the risk of resistance development with the current adherence level. When patients and physicians agree that treatment is indicated, the patient should be offered a reasonable amount of ongoing support for adherence. With the achieved level of adherence, the indication for treatment should then be continuously revised.

From this practical point of view, the main question is, what constitutes “reasonable amount of support”. A tentative suggestion is written in the next section: “recommendations”. The recommendations for patients and physicians are the same – it is the same factors, that patients should consider, and that physicians should assist patients in considering.

Adherence and indication

Guidelines stress that the indication for HAART is influenced by the patient's ability to adhere (27), or the patient's motivation for treatment (240). It has been discussed in the literature, to what extent treatment should be delayed in a non-adherent patient (241), though specific numbers were not mentioned. Suppose a patient with maximal support and preparation is only able to take 85% of the HAART doses. If the patient is expected to be able to reach higher levels of adherence at later stage, should treatment then be deferred, until the CD4 count is for example 100? And what if the patient is never expected to be able to adhere, is there then any reason so defer treatment at all? These are unanswered questions that would need to be discussed, if physicians are to get more confident in their handling of adherence issues.

Adherence and virological resistance in specific drug classes.

In the retrospective study it was found that in all three regimens, patients who had virological treatment failure, more often had resistance mutations, if they failed despite good adherence, whereas patients who had poor adherence more often failed with wild-type virus. Other studies have found similar results (14;99;115). It was also found that in approximately half of the patients, treatment failure occurred in patients who had a treatment interruption, whereas the

other half was almost equally divided between patients with good or poor adherence. In accordance with the literature, it was also found that triple-nucleoside analogue treatment is inferior, and that protease-inhibitor-based HAART seldom has resistance mutations at failure, but a general discussion of resistance at treatment failure in different regimes is beyond the scope of this thesis.

“Reasons” for missed doses – philosophy about causality

What do we mean, when we say, that one thing causes the other? It has been proposed, that a causal relation is present, when one event generates the other by ways of some sort of mechanism (242). However, causes run in unending chains of events causing each other, and each can be described on a multitude of levels. Any knowledge is a social product, although the things we know things about are not (242). It may thus be impossible to definitively answer, whether patients “forget” their medication because they are busy or because they feel ambivalence towards the medication. However, what may appear as metaphysical discussions about causality can be viewed as discussions about what actions to choose in a specific time and place (243). We need to discuss what actions to take, even though “causality” may be debatable. Again: perhaps the most fruitful discussions about adherence in this medical context start (and end) with asking the question: “How should physicians behave?”

Implications for practice and research

Recommendations for clinical practice

One problem of the adherence encounter is that usually only a minority of relevant topics are covered by physicians during a consultation regarding HAART (244) or other medications (63). Here is a simple list of headlines that may be helpful, when there is a need and sufficient time for a comprehensive adherence discussion with a patient. It is here written as designed for a follow-up consultation with patients already on treatment, but the headlines may also be useful for a discussion prior to initiation of treatment. All patients in long-term treatment have a right to be checked regularly. This is unlikely to make all patients adherent, but may enhance their chances, and as a physician it is nice knowing that all measures of importance have been taken. Adherence is often poorly documented in patients files (183). These topics may also serve as a guide for a note in the file. They are also described in letter (245) and pamphlet (246).

Contact

- open the subject by “de-shaming” the patient regarding non-adherence, e.g. by saying:
 - “many find it hard to take all their medicine every day”
 - “many find it hard to talk about that they have been missing doses”

Information

- check that the patient knows the medications, doses and timing of the regimen

Motivation

- ask the patient about perceptions of benefits as well as drawbacks for
 - treatment – as well as adherence
 - ask about knowledge, first hand experiences, second hand stories as well as fantasies
- advice to think positively: “it keeps you living”

Behaviour

- ask about:
 - daily medication intake routines (timing of doses, cues for intake, pill-boxes etc.)
 - handling of risk situations for missing doses
 - e.g. being busy, side effects, travel, parties, reminding of disease, stigma, etc.
 - advice to routinize so it is not a constant mental burden and reminder of disease

Support

- check that all support has been offered and discussed:
 - people: family, friends, nurse, peer support, pharmacist
 - things: pill boxes, beepers, medication charts.

Number of missed doses

- ask the patient, how many doses have been missed in the preceding month.
- does the patient have a system for checking this? (a mark in calendar when new pill-bottle)

Recommendations for patients

Also described in pamphlet (247).

1: Knowledge - try to obtain exact knowledge about your treatment

- Which tablets to take, how many and when.
- How accurately you have to follow this.
- What to do if you:
 - Have forgotten the tablets? (Normally, take them immediately).
 - Are sick or throw up? (Normally, take them anyway).
 - Have unacceptable adverse effects (call a health care person).
- Let your health care person explain you the importance of taking all your medicine every day.
- Call The Outpatient Clinic, if you have any questions.

2: Motivation - hold on to your wish about receiving treatment

Taking medicine every day requires a firm and well-considered decision.

- Hold on to your wish to live.
- Be fully aware that the treatment works – can you feel it?
- Side effects: Do you have any?
- Accept a certain risk of long-term side effects.
- Does the treatment fit into your life-style and habits?
- Is this the right time for treatment?
 - Depending on symptoms and risk of illness.
 - And whether you are ready to take all the medicine every day!
- Think positively.
 - The treatment keeps you well.
 - The treatment itself is not a sign that you are ill.
 - The medicine does not rule your life – you rule the treatment.

3: Convenience – plan how to handle your medicine

- In the beginning it takes great effort to build a routine.
- Later it will work almost automatically.
- Use various tricks:
 - Make it a routine to take your medicine, e.g. when you brush your teeth or eat (taking it punctually is often harder).
 - Then you will remember it – without worrying about it.
 - Have extra tablets in your pocket, at work and the weekend hut.
 - Be prepared that it is difficult to remember the medicine in certain situations, e.g. when:
 - Travelling, being busy, partying and using alcohol or drugs.
 - Side effects, forgetfulness, depression.

- When you feel healthier or more ill than usual.
- When you want to hide your medicine intake for others.

4: Check – do you actually take all your medicine?

- Make it easy for yourself to see if you have taken the last dose (put it out in advance; use blister-packs or pill-boxes).
- Make it easy for yourself to see if you have taken all the tablets lately (mark your calendar when opening a new pill bottle).

5: Support – get all the help you can

- Consider things which may help you:
 - Pill-boxes, dosage boxes, reminder schedules, alarms (watch or cell phone).
- To ensure your intake of medicine, ask for support from:
 - Partner, family and friends.
 - Support groups/patient associations.
 - Nurse and doctor.

6: Openness – make full use of your providers

- All nurses and doctors want to help you taking medicine every day.
- Do not feel ashamed about having problems with the medicine. Many find it difficult – and many also find it difficult to talk about.
- Find some providers with whom you can speak honestly about these things.
- One of the most important issues when visiting the clinic is to talk about problems concerning taking the medicine.

Suggestions for future research

More analyses on existing data

The questionnaire data can be used further for

- What parameters predict subsequent viral failure in a prospective analysis?
- Regarding different adherence measures – the 1-month VAS and the treatment interruptions – which are most correlated to prevalent or subsequent treatment failure? - especially interesting if looking at different treatments.
- The reasons for missed doses in different groups of patients could also be rewarding – are the reasons the same in patients with and without side effects, with and without depression?

Physician interviews have provided a wealth of data that can be further explored, e.g.:

- Physicians' perceptions of the factors affecting adherence.
- The ways physicians assess adherence.

Interviews with patients can be used

- For a comparison with physician interviews regarding the perceptions about the factors affecting adherence
- An exploration of patients perceptions of shame, communication and the role of the physician

Field notes can be used for a comprehensive, descriptive and analytic narrative of the experience of working with patients' adherence and doing fieldwork in one's own culture.

The pamphlets should be evaluated after some months of use, e.g. by interviews (248).

Ideas for the production of future data

A future questionnaire should contain the date, where the patient filled in the questionnaire. It should contain a simple question about whether the patient had ever received HAART. The question about stigma should be phrased without a negation. If questionnaires are to be more comprehensive than the current version, more incentives and support for participation should be available. If details about patient's sex-life are wanted, there is probably no reason to be able to link findings with disease history data, and a questionnaire without a running number may be considered to enhance honesty.

In general, there seems to be no need for more interview studies about the factors influencing adherence in general. However, many of the identified factors need further exploration, and the selection of subgroups of patients is also very relevant. Randomized intervention studies could explore the effect of intensive support and counseling, especially if the intervention is physically located at another place than the routine care. Quality assurance programs seem to be a very feasible next step. We have a wealth of knowledge on factors that may enhance patients' adherence, and some indicators that these factors could be used more than they are today. A systematic implementation of the proposed guidelines for physicians and patients may be warranted, along with follow-up studies on their uptake and use.

Summary

The purpose is to study patients' adherence to HAART, focusing on reasons for poor adherence, patient perceptions, the communication strategies of physicians, and the role of adherence in treatment failure of various HAART regimens. The study consists of five manuscripts, discussed together in the thesis.

The first study is a review of 26 qualitative studies of patients' perceptions of adherence to HAART, and results from interviews with 20 patients in Denmark. It was concluded, that many factors associated with the patient, the treatment, the health care provider and the social context interacts in complex patterns.

The second study consists of observations and qualitative interviews with 16 physicians from San Francisco and 18 from Denmark. It was concluded, that physicians "de-shame" patients to enhance believability, but that conversations on adherence were still awkward.

The third study used questionnaires to identify psychosocial factors associated with adherence and treatment failure. Most psychosocial factors were associated with self-reported adherence, e.g. drinking alcohol, being busy and not having social support. However, treatment satisfaction was not associated with self-reported adherence.

The fourth study also used questionnaires. Among patients with poorer as well as better adherence, "forgetting" was found to be the most frequently mentioned reason for having missed a dose.

The fifth study retrospectively reviewed patients' files. Most patients with treatment failure had stopped treatment or had poor adherence, usually because of side effects. Resistance mutations were more prevalent in patients failing despite good adherence.

The notes on fieldwork stepped closer to the behaviour and experience of the physician's and the patient's roles in adherence issues, by using participant observation and autoethnography as data sampling techniques. Participant observation concluded that physicians may benefit from a more professional handling of adherence issues, and the autoethnography drew attention to the process of "forgetting to have forgot", and the issue of shame.

In the thesis it is concluded, that it is hard to point out the main reasons for poor adherence, as many factors interact, and that communication on the subject is often insufficient and awkward. It is thus recommended that health care personnel consciously de-shame patients and handle low believability of patient statements with skilled care, and that all the relevant factors for adherence are regularly checked in every patient: knowledge, motivation, behaviour, degree of adherence, and support.

Resumé på dansk (Summary in Danish)

Komplians ved HIV. Patienters opfattelser og lægers kommunikation

Formålet med studiet er at belyse hiv-positive patienters adherens (komplians) overfor antiretroviral behandling (ARV), med fokus på årsager, patienters opfattelser, lægers kommunikation og disse faktoreres betydning for behandlingseffekt ved forskellige behandlingsregimer. Studiet består af fem arbejder og en samlende afhandling.

Det første arbejde belyser ved litteraturgennemgang og interviews patienters opfattelser af, hvad der gør det let eller vanskeligt at tage medicinen. Litteraturen viser et komplekst samspil af motivation, bivirkninger, livsstil og håndgreb til håndtering af medicinindtag. Interviews pegede herudover på, at bevidst suppression af påmindelse af hiv ved tabletindtag for nogle var en virksom strategi.

Det andet arbejde belyser ved observation og interviews lægens kommunikation med patienten om adherens i San Francisco og København. Man fandt, at lægernes kommunikation med patienterne om adherens i begge byer i vid udstrækning var farvet af, hvordan lægerne håndterede, at emnet kunne være ”pinligt”, og af lægernes vurdering og håndtering af troværdigheden af patienternes udtalelser om medicinindtag.

Det tredje arbejde belyser ved spørgeskemaer korrelation mellem behandlingssvigt og patienters besvarelser af simple, psykosociale spørgsmål. Patientens angivelse af depression, utilfredshed med behandlingen og dårlig adherens var associeret med behandlingssvigt.

Det fjerde arbejde belyser ved spørgeskemaer patienters begrundelser for ikke at have taget en dosis medicin, og sammenligner begrundelserne hos patienter med hhv bedre og dårligere adherens. Man fandt, at begrundelserne i de to grupper var ens: ”Glemte en dosis”, ”havde et brud i rutinerne” og ”var væk fra hjemmet” var de tre hyppigst anførte.

Det femte arbejde belyser ved retrospektiv gennemgang af journaldata baggrunden for behandlingssvigt i et randomiseret studie. Man fandt, at halvdelen af tilfældene skyldtes ophør af behandling, og en fjerdedel skyldtes dårlig adherens, begge dele oftest pga bivirkninger.

Noterne fra feltarbejde belyser ved hjælp af deltagerobservation rollen som behandler og belyser ved hjælp af autoetnografisk metode oplevelsen af at skulle tage tabletter hver dag. Feltarbejdet går et skridt tættere på observeret adfærd og emotionelle fænomener end de øvrige metoder. Det konkluderes, at behandlere kan have brug for en afklaring af, hvordan non-komplians professionelt bør håndteres. Feltarbejdet bragte det fænomen, at man kan ”glemme at man har glemt” i fokus og oplevelsen af skam over at glemme.

Afhandlingen gennemgår litteraturen, og resultaterne fra de fem arbejder sammenlignes og diskuteres. Det konkluderes, at mange faktorer har betydning for patienters adherens, men at det på grund af faktorerens interaktion er vanskeligt at udpege de primære ”årsager”. Det konkluderes endvidere, at kommunikationen mellem læge og patient om adherens ofte er vanskelig. Det anbefales behandlere at søge at reducere non-adherente patients skamfuldhed, og at udvikle frugtbare strategier til at håndtere lav troværdighed i patienters angivelser af deres komplians. Det anbefales behandlere og patienterne jævnligt at tage nogle væsentlige faktorer af betydning for adherens op til overvejelse: Viden om regimet, motivation for behandling og adherens, adfærd med hensyn til tabletindtagelse, graden af adherens, og støtte.

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The support from family and friends has been truly great and invaluable. Probably the hardest thing about doing a study like this – apart from the intermittently overwhelming feeling of incompetence and of being too slow at work, and the lack of time for other things in life – is

the alienation from other people. However, my wife Camilla has worked at least as hard as I have during these years, keeping the family floating. This thesis is as much her work as it is mine, and I am very grateful for that. The support from our parents and other relatives has been truly great as well, especially the help from aunt Ingil. My sons, Villiam and Felix, have provided me with the most invaluable joy along the way. Warm thanks also to members of the extended family - Lene, Frej, Xander and Ronco - for their extremely important support. The friends, who has accepted the meagerness of my contributions to our life together, and still supported me with their friendship, shall be warmly thanked as well.

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Thanks a lot.

- Toke

Epilogue

The researcher's background, context and preconceptions.

In medical qualitative research and anthropology it is advised to present information about the researchers' background, contextual situation and preconceptions, so that readers can judge the viewpoint, from which the study was done (52-54). The researcher is also expected to reflect on the role of these factors on the findings – a process called reflexivity (52-54).

Background – and its impact on the study

The author's professional background at the onset of the study was three years of clinical experience since graduation as a physician. Of these, one year had been at the department of infectious diseases, where this study was also done. This clearly makes it easier for me to understand the problems physicians face, but also makes it more difficult to penetrate the implicit assumptions of the profession.

The author's contextual background was a wish to make a career in the field of infectious diseases, and I still wish to do so. This has probably eased my access to data, but also makes it more difficult to present unpopular and critical observations and interpretations.

The author's research background was experience from an interview study at the Institute of General Practice with physicians and alternative therapists on placebo. This routine has been an advantage in doing the study.

The author's theoretical background regarding adherence was limited to the "general knowledge" described in the preface, thus situating me from the start quite like most other younger physicians.

I did, however, have a specific interest in patient-physician interactions and the symbolic meanings of medications due to my prior work on placebo treatments and placebo effects. My conclusions regarding how to behave in clinical practice has some resemblance to the suggestions for clinical practice – i.e. the need for exploring patient perceptions and for careful communication regarding the benefits of treatment.

As a patient, my own experiences with taking medicine are sparse. I only have to take asthma medications “as needed”, and I do not have a problem with adhering to that. However, I have experienced the extreme sensitivity to communication, which one develops during times, when personal losses are experienced, and this may have sharpened my focus on how physicians handle patients’ emotions. Through my upbringing I was exposed to a moderately critical attitude towards taking medicine, this probably making it easy for me to understand some patients’ reluctance to take medicine.

Theoretical perspective

Medical anthropology and sociology can be done from a medical perspective satisfying the perceived needs of the health care system, and it can be done from a more critical perspective, questioning the power-relations in the culture of health care (150;152). Often, both aspects are present in the same study (152), and we also wanted to analyze the phenomenon of non-adherence from both perspectives. However, due to the background and contextual situation of this author, the critical approach may be limited. Furthermore, only one supervisor was an anthropologist, whereas the other three supervisors were physicians as well. Finally, the target audience of this study is physicians, and the papers have been or will be submitted to medical journals, and this thesis is submitted to the medical faculty. The perspective may therefore be more in the service of physicians and less critical.

Preconceptions:

Prior to the study, I was only able to explicate roughly the following preconceptions about patients and physicians: 1) patients become non-adherent because they value other things in life higher than adherence, and because they are critical towards medical science and the medical industry; 2) physicians treating HIV in Denmark are very intelligent and dedicated, but do not have much professional training in adherence and communication, and physicians recommend treatments mainly dictated by guidelines and do not take patient values sufficiently into account.

It is difficult to analyse, how these verbalized preconceptions shaped the findings. It seems that the preconceptions were largely confirmed, but quickly lost their relevance. The first preconceptions about the roles of patients’ values and critical attitudes towards medicine and the medical industry has been re-framed, so emotional ambiguity and simple behavioural habits for handling of medication plays larger roles in non-adherence. The preconceptions regarding the intelligence and dedication and lack of communication training of physicians have also been largely confirmed, but again the focus on values has diminished. Now the lack of honest dialogue is perceived to be a larger barrier to physicians’ work with adherence than the lack of focus on patient values and the lack of flexibility regarding the indication.

Experiences with methodologies

I was starting to see patients, “just to get some clinical experience in the field”. My primary physician supervisor and I mentioned this to my anthropology advisor, as we felt slightly worried that it would take too much time and energy away from the research, which we only perceived to be the interviews and the questionnaires. My physician supervisor and I both got astonished when my anthropologist supervisor calmly said: “oh yes, of course you must do some fieldwork as a participant observer. Do some field notes along the way.” We both got a minor chock, as it had not occurred to us to look at it this way. This was the start of the fieldwork notes.

In the writing of this thesis, the fieldwork notes has taken most of my time an energy. Trying to learn a completely different look at what constitutes knowledge, and trying to produce it, has been a large challenge.

However, working with the other methodologies has also felt like stumbling around in darkness. Retrieving adherence information from patients’ files is not a very valid methodology – and questionnaire and interview methodology is not a familiar methodology in the infectious diseases community in Denmark. Balancing the role of being a member (or trying to become a member) of the community and analyzing it at the same time, has also proven difficult and time-consuming.

The multitude of methodologies and viewpoints, done with little prior experience in a society with little prior experience, may have been a little bit too much to handle, if any of the methods were to be meticulously carried out with optimal accuracy, and to fully integrate the diverging results into a finished and polished entity of knowledge. This multitude, however, has also given a fuller picture, even though the text may seem slightly scattered and fragmented. A thesis for the faculty of medicine is not supposed be more than 30 pages long. This is probably not enough for an analysis involving multiple methodologies including fieldwork, if not all data has been presented in manuscripts.

I have learned a lot about research methodology. Qualitative research involving interviews, documents and observations, Grounded Theory, participant observation, autoethnography and questionnaire methodology. I am very grateful for that. And I am eager to do more. After a small break.

The form of the thesis

This study was initiated to give a comprehensive overview of the behavioural and cultural aspects of adherence, and a strategy of multiple methodologies was chosen. The literature review also initially aimed at comprehensiveness, although this proved impossible due to the enormous amount of studies in the field. There still are a lot of references, 99% of which are held in hard-copy by the author.

The background section has more emphasis on the “harder science”, whereas the discussion section is more about behavioral and cultural issues. This is done to show the breath of the topic of adherence, but also to illustrate the characteristic tension between the background of this study, its methods and its results.

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- (245) Barfod T, Gerstoft J. Adherence counselling: Contact, Knowledge, Motivation, Behaviour, Support and Number. Letter To be submitted 2004.

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List of attachments:

Manuscripts 1-5

- 1) Barfod TS, Rubow C, Gerstoft J. Patient perceptions of adherence to HAART. A qualitative interview study and a review of 26 similar studies. (Awaits submission) 2004.
- 2) Barfod TS, Rubow C, Hecht FM, Gerstoft J. "De-shaming" in Physicians' communication with patients about adherence to HAART in San Francisco and Copenhagen. A qualitative study. (Submitted) 2004.
- 3) Barfod T, Gerstoft J, Rodkjær L, Pedersen C, Nielsen H, Møller A et al. Patients' answers to simple questions about treatment satisfaction and adherence, and depression are associated with failure of HAART. A cross-sectional survey. Aids Patient Care and STD's (accepted for publication) 2004.
- 4) Barfod TS, Sørensen HT, Nielsen H, Rodkjær L, Obel N. "Simply forgot" is the most frequent reason for missed doses in patients with low adherence to HAART. A cross-sectional study. (Submitted) 2004.
- 5) Roegge BT, Barfod T, Kirk O, Katzenstein TL, Obel N, Nielsen H et al. Resistance profiles and adherence at primary viral failure in three different HAART regimens: Analysis of failures within two randomised studies. HIV Med 2004; 5(5):344-351.

Contact letter for interview with patient (DK)

Patient information and signature sheet for interview with patients (DK)

Guide for interview with patients (DK)

Contact letter for physicians (DK)

Information sheet about observation for patients (DK)

Guide for observation of consultations (DK)

Guide for interview with physicians (DK)

Contact letter for physicians (US)

Information sheet for patients (US)

Guide for interview with physicians (US)

Scheme for collection of adherence data from patients' files (DK)

Questionnaire (UK)

List of available items not included as attachments

Note. A few other manuscripts have been written from this study. They are not attached and are not part of the thesis, since they are letters to the editor (245;249), a case story (250), or are only partly about adherence (251), or because my contribution to the writing was only around 10-15 % (252). Two pamphlets intended for national use has also been produced (246;247).

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