Evaluation of the Adherence Improving Self-Management Strategy (AIMS) in HIV-Care: (Cost-)Effectiveness, Methodology, and Evidence Synthesis
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ENGLISH SUMMARY

Since 1996, HIV can be treated effectively with combination Antiretroviral Therapy (cART).

However, non-adherence to cART remains a problem for a substantial number of the patients.

Since non-adherence to cART does not only affect patients’ health and quality of life, but consequently also their health care consumption, productivity at work, and the risk of forward HIV transmission, it is important that effective and cost-effective adherence interventions are developed and implemented. Numerous adherence interventions have been examined in the past, but even the most intensive interventions had only modest effects on behavioral and clinical outcomes. There is also little evidence available regarding the cost-effectiveness of adherence interventions in general, and in HIV specifically. The methodological quality of earlier randomized controlled trials and the completeness of study reporting were often suboptimal, which can lead to inaccurate conclusions about the (cost-)effectiveness of adherence interventions. Moreover, there is still an ongoing debate about the application of quality of life as the preferred outcome measure in behavior change trials and in clinical care.

The primary objective of this thesis was to study the (cost-)effectiveness of the theory- and evidence-based Adherence Improving self-Management Strategy (AIMS), compared to treatment-as-usual. In this thesis we also synthesized the current literature of adherence interventions to examine the cost-effectiveness of interventions and methodological quality of studies. Furthermore, we examined the interrelationship between (health-related) quality of life and subjective well-being, and how these can be applied optimally in behavior change trials and clinical care. Finally, we examined how researchers can assess and report treatment-as-usual provided to control groups in adherence trials. The main findings from the individual studies will be summarized below.

Chapter 2 presents a systematic literature review in which the findings were synthesized of randomized controlled trials that evaluated the cost-effectiveness of adherence interventions in chronic diseases. In addition, the methodological quality of the studies was examined. MEDLINE, PsycInfo, EconLit, and the Centre for Reviews and Dissemination databases were searched for trial-based economic evaluations of adherence interventions. We collected information on study characteristics, cost-effectiveness of treatment alternatives, risk of bias, and the methodological quality of economic evaluations. Despite the large costs of non-adherence and the considerable quantity of examined adherence interventions, only 14 trial-based economic evaluations were available in the literature. Four of these trials were considered promising, since they showed cost-effectiveness ratios below their defined willingness-to-pay threshold. Yet, few interventions seemed to successfully improve behavioral or clinical endpoints. Varying methodological quality of studies was observed and only four studies were considered ‘high methodological quality’. Importantly, many studies did not
make allowance for uncertainty by presenting point estimates of incremental cost-effectiveness ratios without the conduct of cost-effectiveness acceptability curves. Thus, despite that some studies show favorable incremental cost-effectiveness ratios, and that authors were inclined to draw relatively positive conclusions, the general cost-effectiveness of adherence interventions was modest at best. To determine whether adherence interventions can be cost-effective, we recommend that proven-effective adherence interventions are studied in rigorously designed cost-effectiveness evaluations.

Chapter 3 presents the design of the multi-center randomized controlled trial that was conducted to evaluate the (cost-)effectiveness of the Adherence Improving self-Management Strategy (AIMS), among a heterogeneous sample of people living with HIV. The theory- and evidence-based AIMS-intervention is one of the few interventions that improved adherence and viral suppression rates in an earlier randomized controlled trial. However, evidence on the cost-effectiveness of AIMS is lacking. The AIMS-intervention will be compared to treatment-as-usual from a societal perspective, with a time horizon of one year. Fundamental to AIMS is electronic adherence monitoring using MEMS-caps (MWV Healthcare). MEMS-caps are electronic pill caps with a micro-processor that records the time of each bottle opening. The data obtained via the MEMS-caps can be downloaded online and the data show medication intake over the past period, which permits discussion of adherence barriers and potential solutions to deal with these for each individual patient. It was expected that, if proven cost-effective, AIMS can improve evidence-based counseling for HIV-nurses and clinicians.

Chapter 4 describes how health-related quality of life and other quality of life domains relate to subjective well-being among people living with HIV. Health care interventions are increasingly expected to aim beyond health-related quality of life, and also focus on promoting people’s subjective well-being. However, little is known about which (health-related) quality of life domains predict subjective well-being, and whether indeed health-related quality of life (the main outcome in cost-utility analyses) is its main predictor. To explore the relationships between these concepts, participants from the AIMS-study completed a cross-sectional survey shortly after their randomization visit (N = 191). The survey comprised assessments of subjective well-being (life satisfaction), physical health, mental health, social well-being, financial well-being, environmental well-being, and sexual well-being. The main direct predictors of subjective well-being were mental health and environmental well-being, while physical health was only weakly associated with subjective well-being. Financial and social well-being explained subjective well-being indirectly. These findings suggest that whereas promoting physical health is the main focus of current HIV care, environmental and mental well-being might be more relevant for improving subjective well-being.
Chapter 5 explores the use of an open-ended questionnaire (TAU open-ended questionnaire) to assess treatment-as-usual in adherence trials. Treatment-as-usual is usually insufficiently described in trial reports. Yet, the active content of treatment-as-usual provided to control groups varies considerably between trials and influences trial effect sizes. Reporting guidelines (e.g., WIDER, CONSORT, and TIDieR) call for control group descriptions in equal detail as intervention content. However, how to assess the active content (i.e., behavior change techniques) of treatment-as-usual remains unclear. The TAU open-ended questionnaire was therefore developed and examined on its feasibility and reliability. The HIV-nurses from the AIMS-study completed the semi-structured TAU open-ended questionnaire, with free text for nurse responses. The questions reflected the broad categories in which adherence support is normally delivered: informing patients, motivating patients, goal setting, problem solving, and it made a distinction between activities that are typically done during the start-up of a treatment and follow-up sessions. Two study authors independently coded behavior change techniques from the nurse responses (using an adherence-adapted taxonomy). The analyses showed that the clarity and completeness of nurse responses were generally adequate. Twenty-six unique behavior change techniques were coded, of which 23 reliably. The total number of behavior change techniques coded for each nurse ranged between 7 and 19. The study suggested that the TAU open-ended questionnaire is a feasible and reliable tool to capture active content of support provided to control participants. Since we observed considerable variability in the number of behavior change techniques provided to control participants, this study illustrates the importance of reliably collecting and accurately reporting control group support.

Chapter 6 presents the results of the effectiveness evaluation of the AIMS-RCT described in chapter 3. The total sample (N = 223) consisted of 110 treatment-experienced with suboptimal adherence levels and at least one unsuppressed viral load during the previous three years, and 113 treatment-initiating patients. Of these, 110 were randomized to the AIMS-intervention and 113 to treatment-as-usual. The patients were recruited by 21 HIV-nurses in seven HIV-clinics in the Netherlands (the Academic Medical Center, Amsterdam; the Slotervaart Hospital, Amsterdam; the St. Lucas-Andreas Hospital, Amsterdam; the Leiden University Medical Center, Leiden; the HAGA Hospital, The Hague; the Erasmus Medical Center, Rotterdam; Isala Clinic, Zwolle). The primary outcome measure was log-transformed viral load. The secondary outcome measures were detectable versus undetectable viral load, and treatment failure (defined as two consecutive detectable viral loads). Intention-to-treat analyses showed that the intervention was effective across all time points (F(1,199) = 7.23, p = .008), that patients in the intervention group had a 2.03 times higher odds of having an undetectable viral load across the three time points (95% CI 1.06 to 3.89), and that patients in the control group had a 3.08 times higher odds of failing on treatment (95% CI 1.18 to 7.94). This trial showed thus significant and clinically meaningful effects of the AIMS-intervention. In addition,
AIMS was delivered by minimally-trained nurses (a short three-day training program and one booster session) and seemed to fit within routine clinical care.

Chapter 7 presents the trial-based economic evaluation of the AIMS-intervention from a societal perspective, compared to treatment-as-usual. The differences in societal costs were examined against log viral load and treatment failure (for the cost-effectiveness analyses), and utilities (for the cost-utility analyses). For the analysis from the societal perspective using utilities as the outcome parameter, the base case cost-effectiveness probability was between 55% and 53% when ranging the ceiling ratio from €0 to €70,000 per quality-adjusted life year. The primary sensitivity analyses that addressed some of the major concerns with the data used for the base case analyses (i.e., considerably lower percentages of missing data and standardized recall periods), however, showed a probability of 80% to 68% of AIMS being cost-effective (for the same range of ceiling ratios). The probability that AIMS is cost-effective using viral loads as outcome measure was 55% to 95% when ranging the ceiling ratio from €0 to €5,000 (and higher) for one log decrease in viral load and 53% to 95% when ranging the ceiling ratio from €0 to €14,000 (and higher) for one prevented treatment failure. Also taking into account the relatively low intervention costs (approximately €83 per patient per year), these results suggest that the AIMS-intervention is cost-effective even within a one-year trial follow-up period. A planned model-based economic evaluation, also taking into account viral resistance and reduced forward HIV transmission, should reveal how cost-effective AIMS is on the long run.

To conclude, non-adherence to cART is a widely recognized health care problem, with worrying clinical and economic consequences. It is therefore important to improve adherence and to study the effectiveness and cost-effectiveness of adherence interventions in rigorously designed and comprehensively reported randomized controlled trials. Many adherence interventions have been examined in the past, but the effects on adherence and clinical outcomes were generally modest, and there is little high-quality evidence about the cost-effectiveness of HIV-treatment adherence interventions. This thesis examined the (cost-)effectiveness of the AIMS-intervention in Dutch HIV-care, compared to moderately- to high-quality treatment-as-usual. The results did not only proof effectiveness of the AIMS-intervention, but there are also indications that the AIMS-intervention can be cost-effective. The (cost-)effectiveness was studied in a rigorously designed and carefully reported multi-center trial, resulting in methodologically sound evidence. Although the AIMS-intervention did not improve health-related quality of life within the one-year study period, we anticipate that sustained effects of AIMS will lead to fewer occurrence of viral resistance, lower HIV transmission risks, and thereby improved quality of life on the long run. We therefore believe that incorporation of AIMS in routine clinical care would lead to improved treatment success rates and enhanced patient well-being, with acceptable value for money.