TREATMENT ADHERENCE, HEALTH RELATED QUALITY OF LIFE AND AGING IN HIV-1 INFECTED PATIENTS

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Treatment Adherence, Health Related Quality of life and Aging in HIV-1 infected patients
Academic thesis, University of Amsterdam, The Netherlands
ISBN: 978-90-9030322-2

The work described in this thesis was conducted within the framework of the Research Institutes “Amsterdam Public Health” as well as “Infection and Immunity”.

Cover design and layout: Bregje Jaspers, Proefschriftontwerp.nl
Cover Photo: Jaap Verstraaten
Printing: Ipskamp Printing, Nijmegen

Printing of this thesis was financially supported by the Stichting Ondersteuning Wetenschap Verpleegkundig Specialisten and Rijnstate Vriendenfonds

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 8 juni 2017, te 14.00 uur

door

Nienke Langebeek
geboren te Utrecht

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Glossary

ART	Antiretroviral Therapy
cART	combination Antiretroviral Therapy
HAART	Highly Active Antiretroviral Therapy
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
STR	Single Tablet Regimen
EDM	Electronic Drug Monitoring
TDM	Therapeutic drug Monitoring
HRQL	Health Related Quality of Life

CHAPTER 1

General Introduction

Development of HIV/AIDS treatment

In 1984 researchers discovered that the Human Immunodeficiency Virus (HIV) was responsible for the development of the acquired immunodeficiency syndrome (AIDS). The virus primarily infects CD4+ cells resulting in impaired cellular immunity. As a result, patients who are infected become vulnerable to certain opportunistic infections and malignancies leading to AIDS. In the early days of the AIDS epidemic, there were no medicines to stop this process. After having been diagnosed with AIDS, people usually died within a few years. In 1987 zidovudine (AZT), the first nucleoside reverse transcriptase inhibitor (NRTI), was approved for use. Since than, more agents of the same class became available and dual NRTI-therapy was shown to be more durable than the AZT mono-therapy. In the early nineties a second class of antiretrovirals; the non-nucleoside reverse transcriptase inhibitors (NNRTI's) became available. The use of NNRTI's was limited due to rapid loss of effect caused by the development of viral resistance. (1). The introduction of a third class of antiretrovirals in 1996; the HIV protease inhibitors (PIs) , resulted in the use of a far more potent combination therapy consisting of three drugs of two separate classes and lead to a more lasting effect. These combinations became known as highly active antiretroviral therapy (HAART) and became the standard of treatment for HIV infection. This resulted in a dramatic decline in HIV- and AIDS-related morbidity and mortality (1-4). At the same time plasma HIV-RNA (viral load) measurements became available in daily practice, which enabled measuring the effectiveness of HAART. HAART resulted in sustained and durable suppression of HIV-RNA in the blood to levels below the detection limit of viral load assays, other than had been the case with mono- or dual NRTI therapy. Since then additional classes of antiretroviral agents have become available, i.e. entry-inhibitors and integrase-inhibitors. Standard combination antiretroviral therapy (cART) nowadays is largely composed of 2 NRTI's plus a third agent belonging to one of the other available classes of antiretrovirals. To date there is no cure for patients with HIV infection. Combination ART has markedly improved patients' life-expectancy and turned HIV infection from a lethal into a chronic and manageable disease (5). The introduction of novel agents also gives more options to treat patients with multi-drug-resistant HIV. Nonetheless, the risk of drug resistance resulting in treatment failure, always remains a concern. The most common underlying cause for drug resistance and virological failure is incomplete adherence to treatment (6, 7).

Adherence

Adherence to cART is essential in securing sustained treatment success. It can be described as the extent to which a patient follows a treatment plan that the patient and the medical professional have agreed upon to produce desired therapeutic results (8). Back in 1996 anti-HIV treatment consisted of a combination of many pills that had to be taken twice, or even three to four times a day, and often with food restrictions. Sufficiently high

levels of adherence to treatment were necessary to achieve and sustain viral suppression and prevent disease progression and death (9). Yet, many patients infected with HIV did not succeed in achieving or maintaining adequate levels of adherence (10). Suboptimal adherence may compromise treatment efficacy and result in selection of drug-resistant viral variants and viral rebound. Because of cross-resistance, it may also compromise future treatment options. In addition, suboptimal adherence is also a public health concern as it increases the risk of transmission of drug-resistant HIV (11-13).

Paterson et.al studied the level of adherence to unboosted PIs needed for virologic suppression and found that at least 95% adherence levels were required (6). More recent studies on more potent cART suggest that long-lasting viral suppression can be achieved even with lower levels of adherence (14-16). Viswanathan et.al found no difference in viral suppression for NNRTI-users whose level of adherence was between 85% and 89% compared to those whose adherence level was ≥95%. However, for users of unboosted PIs the viral suppression significantly differed when adherence levels were <95% compared to ≥95% (17). In comparison with other chronic conditions, this required level of adherence is high. In medical conditions other than HIV, it is usually assumed that adherence levels of 80% or more are sufficient to obtain benefit from treatment (18-20). The need to maintain high adherence rates makes HIV treatment more challenging than that of other chronic diseases.

Although current antiretroviral treatment regimens are easier to adhere to than those in the past, many patients still have difficulties to achieve and maintain the high levels of adherence needed to ensure sustained virological suppression (21, 22).

One of the challenges in daily practice and therefore in research is to find an accurate and usuable assessment of adherence. There are various adherence assessment methods, including self-reports, pharmacy refill, pill count, therapeutic drug monitoring (TDM), and electronic monitoring devices (EMD). Each method has its strengths and limitations and it is commonly accepted that there is no gold standard for measuring adherence. In research settings it is recommended to use more than one adherence assessment method as each method adds additional information.

Adherence is considered to be a complex behavior that is influenced by a wide range of factors, which can be categorized into: sociodemographic, condition-related, treatment-related, patient-related, and interpersonal factors (23, 24). Health care professionals need information about predictors and correlates of adherence, to prepare and support patients in achieveing and maintaining good adherence levels.

Health Related Quality of Life

Optimal adherence can contribute to the maintenance of one's health and can contribute to one's quality of life. Health related quality of life (HRQL) is multifaceted, incorporating physical, psychological and social well-being. It also refers to one's overall level of well-being or quality of life. (25, 26). Due to the advent of cART, life expectancy has increased significantly in HIV infected adults. Approximately one-half of the people living with HIV in the Netherlands are 45 years or older (27). As a consequence of the increased life expectancy, individuals with HIV are getting older although their life-expectancy remains lower than in the general population. Ageing HIV-infected persons have been found to be at increased risk of age-associated non-communicable co-morbidities (AANCC) compared to uninfected individuals (28). These co-morbidities might have a negative impact on patients' HRQL, because they are usually accompanied by declines in patients'physical and mental health. Miners et al. reported that the HRQL of persons with HIV infection is significantly lower than that of the general population, even when the former persons are virally suppressed (29).
Some of the research in this thesis was conducted in the early years of cART (chapters 3,4,5). At that time, integrase inhibitors and simpler regimens were not yet available. Nevertheless, the results of these studies are still relevant and the outcomes can be used in the care of patients with HIV.

The objectives of this thesis

1) To examine which factors predict or are associated with patients' adherence.

2) To compare different methods of assessing adherence and to identify the interventions that enhance and sustain high levels of adherence.

3) To examine how patients who are getting older with HIV infection and develop more co-morbidities associated with ageing, experience their quality of life.

The outline of the thesis

The first part – *Factors influencing adherence* – not only focuses on such factors, but also whether use of simpler ART regimens improves adherence, treatment satisfaction and quality of life.

In **Chapter 2** a meta-analysis is described that aims to review the evidence on predictors and correlates of adherence to cART, and to accumulate the findings into quantitative estimates of their impact on adherence. The literature was searched for original English-language papers published between 1996 and June 2014. Studies reporting on predictors and correlates of adherence of adults prescribed with cART for chronic HIV infection were included without restriction to adherence assessment methods, study design or geographical location.

In **Chapter 3** we describe the results of the FREE study: a randomized clinical trial in 207 antiretroviral therapy (ART) naive patients using standard triple-therapy - lopinavir/ritonavir (LPV/r) and a fixed dose of zidovudine and lamivudine (CBV) - as induction, followed by maintenance with the simplified regimen of fixed-dose zidovudine, lamivudine, abacavir (TZV) for those who reached an undetectable viral load (less than 50 copies/ml). Randomization of patients, continuing LPV/r and CBV or switch to TZV, took place between week 12 and 24. The interim results at 48 weeks after baseline were reported, addressing the question of maintening virologic efficacy with simplified single class cART.

In **Chapter 4** we investigated whether this simplified regimen of reducing pill burden, dietary requirements and reducing possible adverse events, enhanced adherence levels and resulted in more treatment satisfaction and an improved quality of life (QoL).

In the second part - *Assessment of and interventions on adherence* - we investigate assessment strategies of adherence and interventions to improve and maintain adherence levels.

In **Chapter 5** we compare and combine various methods to assess adherence to an unboosted PI-containing regimen. The combination of measurements included: electronic monitoring devices (EMD), pill count, pharmacy refill data, self-reports, diaries for registration of food patterns and special events related to the use of EMD, adherence assessment by the physician and clinical nurse specialist, and in-depth interviews with the patients. Twenty-eight patients divided into two groups were included in this study: group 1 were naive patients to cART and group 2 were patients already using a PI containing regimen for more than 48 weeks. Patients were monitored for 24 weeks during which three (non-naive patients) or four (naive patients) visits were planned. During these visits all combinations of adherence measurements were conducted, except the indepth interviews. These interviews were conducted at the end of the follow-up period (week 24) in a subgroup of patients.

Since the advent of cART, numerous interventions aimed to enhance adherence to cART and virological treatment outcomes have been developed and evaluated. Several systematic reviews have synthesized the effectiveness of such interventions (30-33). In **Chapter 6** we conduct a meta-analysis to review available evidence about the effectiveness of EMD-

informed counselling amongst patients prescribed with cART for a chronic HIV infection, and to accumulate quantitative estimates of the effect of such interventions on medication adherence and virologic treatment outcomes. Moreover we aim to identify study design features that are associated with stronger intervention effects.

The third and last part is devoted to *Health Related Quality of Life and aging*.

In view of the longer life expectancy of people living with HIV, the care should increasingly be aimed at improving HRQL.
In **chapter 7** we investigate HRQL in HIV infected individuals and a highly comparable uninfected control group. Participants are 45 years or older, participating in the Age$_h$IV cohort study. The objectives of this analysis are to investigate the independent impact of the number of co-morbidities, ageing and HIV-infection on HRQL and depression.
For this study we used relevant available data from 541/598 (90%) of the HIV-infected participants and 524/550 (95%) of the HIV-uninfected participants. They all completed questionnaires on HRQL and depressive symptoms at enrolement. Participants were also asked to complete an extensive questionnaire concerning socio-demographics, medical history, and medication use.

Chapter 8, the discussion and future perspectives, is an overview of 30 years of my carreer as a clinical nurse specialist in HIV care, and discusses the influence of adherence and HRQL research in daily nursing practice. It also discusses the implications of this thesis for future HIV-nursing care and the possibilities for further research.

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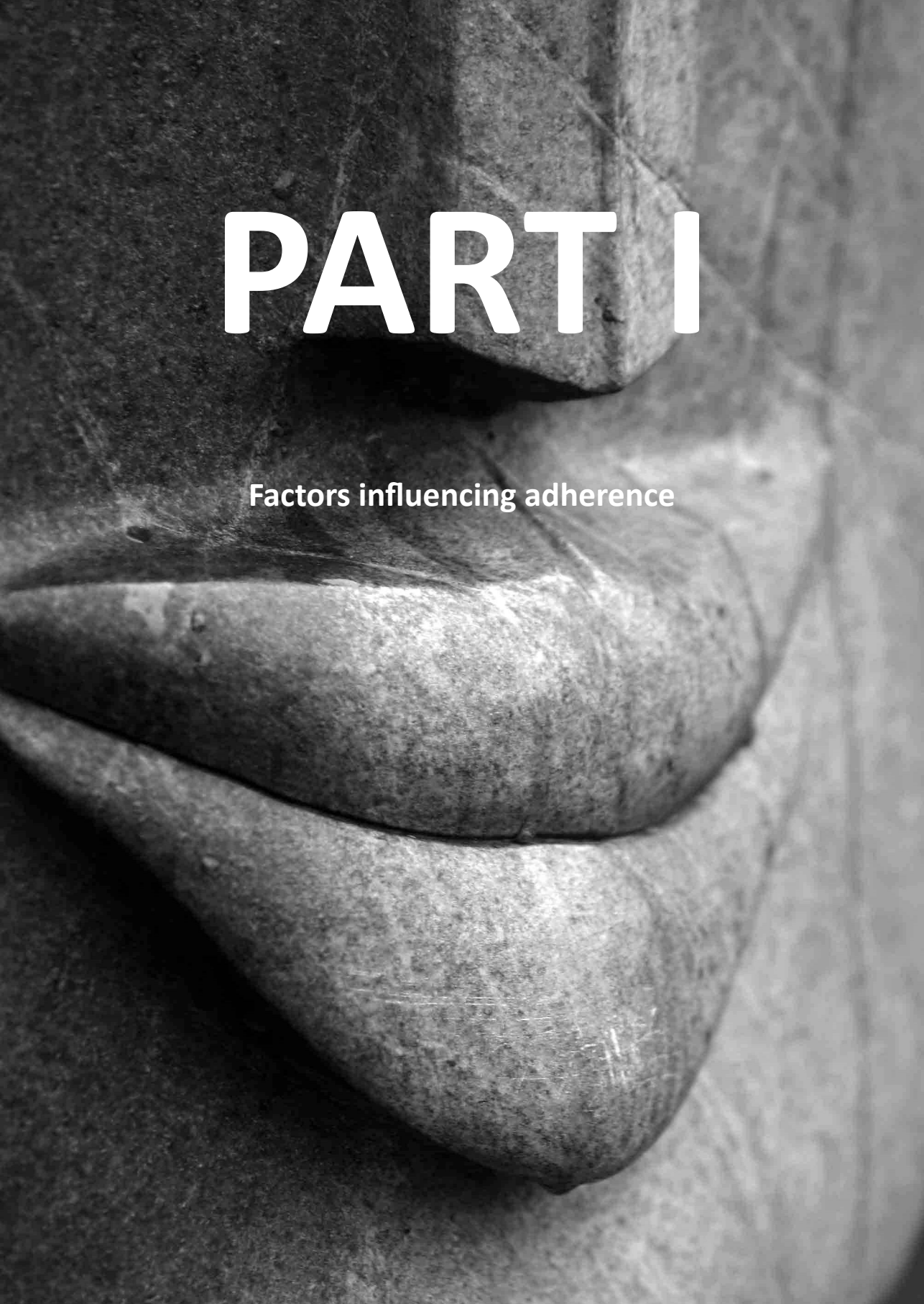

PART I

Factors influencing adherence

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BMC Medicine 2014, 12:142

http://www.biomedcentral.com/1741-7015/12/142

CHAPTER 2

Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis

Abstract

Background: Adherence to combination antiretroviral therapy (ART) is a key predictor of HIV treatment success and potentially amenable to intervention. Insight into predictors or correlates of non-adherence to ART may help to guide targets for the development of adherence enhancing interventions. Our objective was to review evidence on predictors/correlates of adherence to ART and to aggregate findings into quantitative estimates of their impact on adherence.

Methods: We searched PubMed for original English-language papers, published between 1996 and June 2014 and the reference lists of relevant articles. Studies reporting on predictors/correlates of adherence among adults prescribed ART for chronic HIV-infection were included without restriction to adherence assessment method, study design or geographical location. Two researchers extracted data in duplicate. Random-effect models with inverse variance weights were used to aggregate findings into pooled effect estimates with 95% confidence limits. The standardized mean difference (SMD) was used as common effect size. The impact of study design features (adherence assessment method, study design, countries' United Nations Human Development Index (HDI)) was investigated using categorical mixed-effect meta-regression.

Results: A total of 207 studies were included. The following predictors/correlates were most strongly associated with adherence: adherence self-efficacy (SMD=0.603, p=0.001), current substance use (SMD=-0.395, p=0.001) concerns about ART (SMD=-0.388, p=0.001), beliefs about the necessity/utility of ART (SMD=0.357, p=0.001), trust/satisfaction with the HIV care provider (SMD=0.377, p=0.001), depressive symptoms (SMD=-0.305, p=0.001), HIV stigma (SMD=-0.282, p=0.001), and social support (SMD=0.237, p=0.001). Smaller but significant associations were observed for: being prescribed a protease inhibitor containing regimen (SMD=-0.196, p=0.001), daily dosing frequency (SMD=-0.193, p=0.001), financial constraints (SMD-0.187, p=0.001) and pill burden (SMD=-0.124, p=0.001). Higher trust/satisfaction with the HIV care provider, a lower daily dosing frequency, and less depressive symptoms were more strongly related with higher adherence in low and medium HDI than in high HDI countries.

Conclusions: These findings suggest that adherence enhancing interventions should particularly target psychological factors such as self-efficacy, and concerns/beliefs about efficacy and safety of cART. Moreover, these findings suggest that simplification of regimens may have smaller, albeit significant effects.

Key word: adherence, compliance, HIV infection, antiretroviral therapy, meta-analysis.

Background

Adherence to combination antiretroviral therapy (ART) is a key predictor of antiretroviral treatment success that is potentially amenable to intervention (1). Sufficiently high levels of adherence to ART are necessary to achieve and sustain viral suppression and to prevent disease progression and death (2). Yet, many HIV infected patients do not succeed in achieving or maintaining adequate levels of adherence to ART (3).

Insight into predictors or correlates of non-adherence to ART offers the potential to identify patients at risk for low levels of adherence. This would enable health care providers to target patients in most need and to tailor their care appropriately. Moreover, knowledge of predictors/correlates of non-adherence to ART may help to guide targets for the development of interventions to enhance or maintain adherence to ART.
Medication adherence is considered to be a complex behaviour that is influenced by a wide range of factors that have previously been categorized into socio-demographic, condition-related, treatment-related, patient-related and interpersonal factors (4, 5). In recent years, a number of systematic reviews and meta-analyses have investigated predictors/correlates of adherence among patients prescribed ART for chronic HIV infection. One systematic review provided a comprehensive assessment of predictors/correlates of adherence to ART, but did not aggregate findings into quantitative estimates of their effect on adherence (5). A number of other reviews did aggregate findings into quantitative estimates, but focussed only on patient-reported barriers and facilitators (1), socio-demographic factors (3), clinical, comorbid, and treatment-related factors (6) and depression (7), or investigated a particular patient population, i.e., drug users (8).

The objective of the present study is to comprehensively review current research evidence on socio-demographic, treatment-related, condition-related, patient-related and interpersonal predictors and correlates of adherence to ART, and to aggregate findings into quantitative estimates of their impact on adherence. Thereby, we aim to assess the relative importance of each predictor/correlate of adherence. Studies on adherence to ART have been conducted in a variety of countries and settings and have used a variety of research designs and adherence measurement methods. For these reasons, another aim was to assess the impact of such study design features on predictors/correlates of adherence.

Methods

Our meta-analysis was conducted in accordance with PRISMA statement guidelines (9). Two of the authors (NL and PN) searched PubMed for papers published from August 1996 to June 2014 using the following strategy: Search: (((((“adult”[MeSH Terms] AND hasabstract[text] AND (“1996/01/01”[PDat] : “2014/06/10”[PDat]))) AND ((“patient compliance”[MeSH Terms] OR “medication adherence”[MeSH Terms] AND hiv) AND hasabstract[text] AND (“1996/01/01”[PDat] : “2014/06/10”[PDat]))) AND hasabstract[text] AND (“1996/01/01”[PDat] : “2014/06/10”[PDat]))) NOT children[MeSH Terms] Filters: Abstract available, From 1996/01/01 to 2014/06/10. Additionally, the reference lists of the papers retrieved were reviewed for additional publications. Eligible studies met the following criteria 1) consisting of an original research study 2) written in English 3) reporting on adult (older than 16 years of age) HIV infected patients 4) being prescribed self-administered ART for chronic HIV infection 4) using a quantitative method to assess adherence to ART and 5) reporting a statistical association between a potential predictor/correlate and adherence. No geographical restrictions were applied. We excluded studies that exclusively focussed on the following specific populations: drug users, prison inmates, homeless persons, and psychiatric diseases patients.

We considered the following sociodemographic predictors/correlates of adherence: age, gender and financial constraints. Financial constraints were defined as being unemployed or having an income level in the lowest category as defined within a particular study. Treatment-related predictors/correlates were: duration of ART, number of prescribed antiretroviral pills per day (i.e. pill burden), daily dosing frequency and whether or not the regimen contained a protease inhibitor (PI). Disease-related predictors/correlates included CD4 cell count and time since HIV diagnosis. We also investigated inter-personal predictors/correlates: social support, HIV stigma and trust or satisfaction with the HIV care provider. Finally, patient-related predictors/correlates were current substance use (alcohol and drugs), depressive symptoms, adherence self-efficacy (the extent to which patients’ belief that they will be able to adhere), motivation to adhere, locus of control (the extent to which individuals believe that they can control events that affect them), concerns about adverse effects of ART, and beliefs in the necessity or utility of ART.

Two authors (NL and PN) independently extracted data from each study that fulfilled inclusion criteria using a scoring sheet. We extracted the following information: name of the first author, year of publication, sample size, country in which the study was conducted, year study was started, adherence assessment method (self-report, electronic monitoring device (EMD), pharmacy refill, pill count), and whether patients were initiating, restarting or switching an ART regimen or were already on ART, and the potential predictors or correlates of adherence. Factors that were assessed at the same time as the adherence measurement

were considered to be correlates and factors assessed prior to the adherence measurement to be predictors. Because we included studies conducted in any country around the world, we categorized countries according to the United Nations Human Development Index (HDI) (10) during the year the study was started into low- (HDI ≤ .50), medium- (HDI between .50 and .79), and high development (HDI ≥ .80) countries.

When data from the same study were reported in multiple publications, we selected the publication with the largest sample size and/or reporting on the largest number of predictors/correlates. If the study evaluated adherence at multiple timepoints, the value of the first measurement was used to avoid dependence. When relationships between predictors/correlates and adherence were reported for discrete subgroups within one study, groups were included as independent samples.

The quality of the reporting of included studies was assessed using the twenty-two items recommended by the STROBE statement (11). Items fulfilling the STROBE statement were assigned as √ and items not fulfilling the statement were assigned as -.

Statistical analysis

We used the standardized mean difference (SMD) as the common effect size to express the magnitude of the association between predictors/correlates and adherence. If studies did not provide the SMD, we calculated the SMD from r, means and standard deviations, odds ratios, t-, x^2-, or F-statistics, contingency table data or exact P values (12). When studies reported an insignificant association without data we assigned a value to the SMD of 0.001. We adjusted the SMD using the small sample size bias correction prior to analysis. Values of the SMD of 0.2, 0.5 and 0.8 can be interpreted as small, medium and large effects, respectively (13).

Predictors/correlates were selected for quantitative pooling if ten or more independent effect sizes could be calculated. Random effect models with inverse variance weights were used to aggregate individual effect sizes into pooled effect estimates with 95% confidence limits (CI) using the SPSS macro MeanES from Lipsey and Wilson (12, 14).

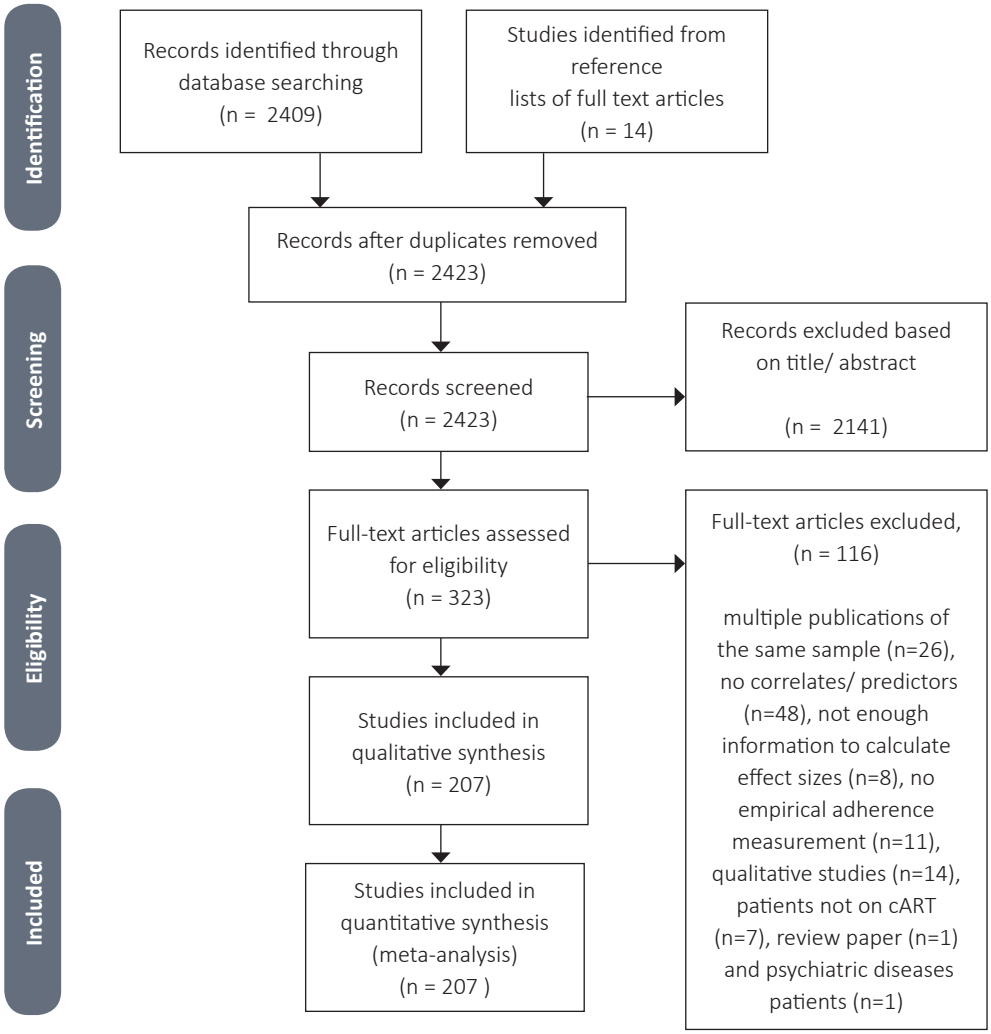
We examined whether the effect sizes differed significantly across levels of potential moderators of the predictor-adherence relationship, if there was heterogeneity across studies (I^2 >50%) and sufficient data (k>4 in each subgroup) to support these analyses (15). The following study design features were investigated as potential moderator: whether the factor was a predictor or correlate, whether the adherence assessment method was self-report (versus all other methods) or EMD (versus all others), whether the study was conducted in a high HDI country (versus medium and low HDI country), and whether patients were already on ART (versus initiating, restarting or switching ART). For the moderator analyses,

subgroup analysis were performed by grouping effect sizes by study design feature and assessing heterogeneity between groups using the between-group Q statistic (Q-between) within a mixed effects model using the method of moments estimation. If Q-between is significantly greater than Q-within (heterogeneity within groups due to error), this indicates that a moderator variable explains a significant proportion of the total heterogeneity in effect sizes. The moderator analyses were conducted using the SPSS macro MetaF from Lipsey and Wilson (12, 14).

Results

Figure 1 shows the study selection process. A total of 207 studies were included in our analysis, reporting on a total of 103,836 patients (16-223). A total of 200 studies consisted of one independent sample for calculating effect sizes, five studies of two samples and two studies of three samples, resulting in a total of 216 independent samples (k=216). A total of 67% (k=145) of the samples reported on correlates of adherence and 33% (k=71) on predictors. A total of 54% (k=117) of the samples included patients already on ART and 46% (k=99) included patients who were (re)starting or switching. The following adherence assessment methods were used: 77% self-report (k=166), 11% EMD (k=23), 8% (k=18) a pharmacy refill-based measure and 4% (k=9) a pill count-based measure. A total of 67% (k=145) of the samples were from countries with a high HDI, 19% (k=40) from countries with a medium HDI and 14% (k=31) from countries with a low HDI. For characteristics of the included studies, see Additional file 1. (https://static-content.springer.com/esm/art%3A10.1186%2Fs12916-014-0142-1/MediaObjects/12916_2014_142_MOESM1_ESM.pdf)

Figure 1: Flow diagram



Locus of control and motivation to adhere were excluded from our analysis because less than ten independent effect sizes could be calculated for these two predictors/correlates.

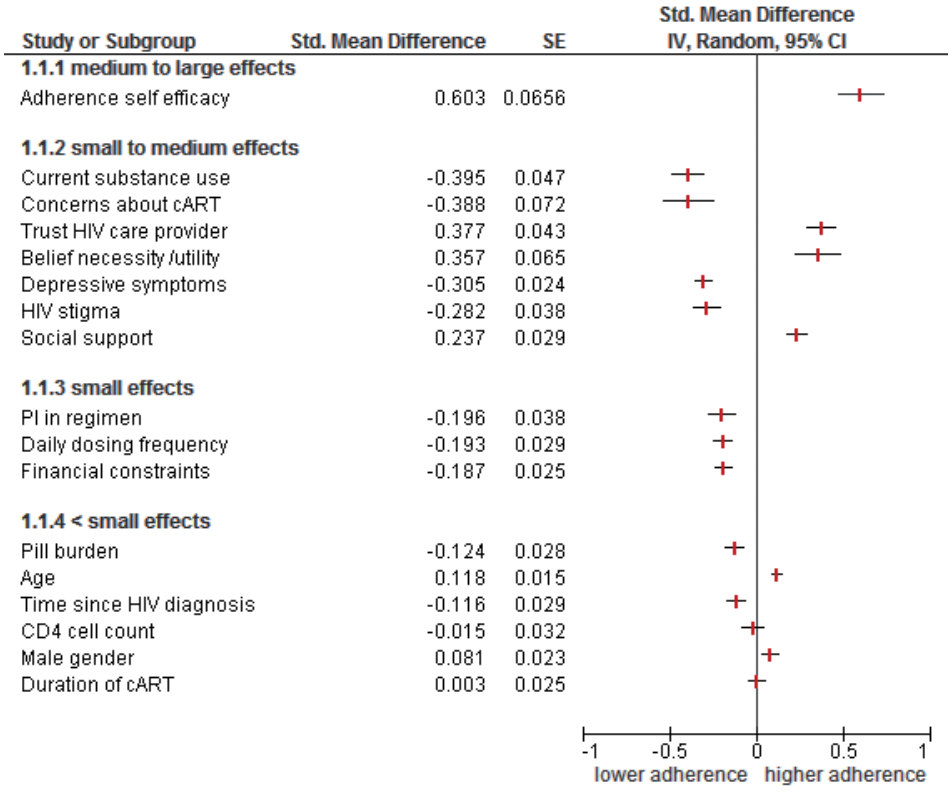
The strongest association with adherence was found for the predictor/correlate adherence self-efficacy, with the pooled effect size being medium to large (SMD=0.603, 95% CI 0.47 to 0.73, k=39, p=0.001; Figure 2 (1.1.1)).

The following predictors/correlates were significantly associated with adherence with their effect sizes being small to medium: current substance use (SMD=-0.395, 95% CI -0.49 to -0.30, k=80, p=0.001), concerns about ART (SMD=-0.389, 95% CI -0.53 to -0.25, k=14, p=0.001), trust/satisfaction with the HIV health care provider (SMD=0.377, 95% CI 0.29 to 0.46, k=30, p=0.001), beliefs about the necessity/utility of ART (SMD=0.357, 95% CI 0.23 to 0.49, k=25, p=0.001), depressive symptoms (SMD=-0.305, 95% CI -0.35 to -0.26, k=90, p=0.001), HIV stigma (SMD=-0.282, 95% CI -0.36 to -0.21, k=47, p=0.001) and social support (SMD=0.237, 95% CI 0.18 to 0.29, k=67, p=0.001). The predictors/correlates yielding small to medium effects are shown in Figure 2 (1.1.2)

The following predictors/correlates were significantly associated with adherence with their effect sizes being small: being prescribed a PI containing regimen (SMD=-0.196, 95% CI -0.27 to -0.12, k=26, p=0.001), daily dosing frequency (SMD=-0.193, 95% CI -0.25 to -0.14, k=29, p=0.001) and financial constraints (SMD=-0.187, 95% CI -0.24 to -0.14, k=110, p=0.001). The predictors/ correlates with small effect sizes are shown in Figure2 (1.1.3)

The following predictors/correlates were significantly associated with adherence but their effect sizes were very small: pill burden (SMD=-0.124, 95% CI -0.18 to -0.07, k=57, p=0.001), age (SMD=0.118, 95% CI 0.089 to 0.147, k=158, p=0.001), time since HIV diagnosis (SMD=-0.116, 95% CI -0.17 to -0.06, k=57, p=0.001) and male gender (SMD=0.081, 95% CI 0.037 to 0.12, k=142, p=0.001). Two predictors/correlates were not significantly associated with adherence: CD4 cell count (SMD=-0.015, 95% CI -0.079 to 0.048, k=67, p=0.64) and duration of ART (SMD=0.003, 95% CI -0.047 to 0.052, k=51, p=0.92). The predictors/ correlates with very small effect sizes are shown in Figure 2(1.1.4).

Figure 2: Predictors/correlates of adherence to ART

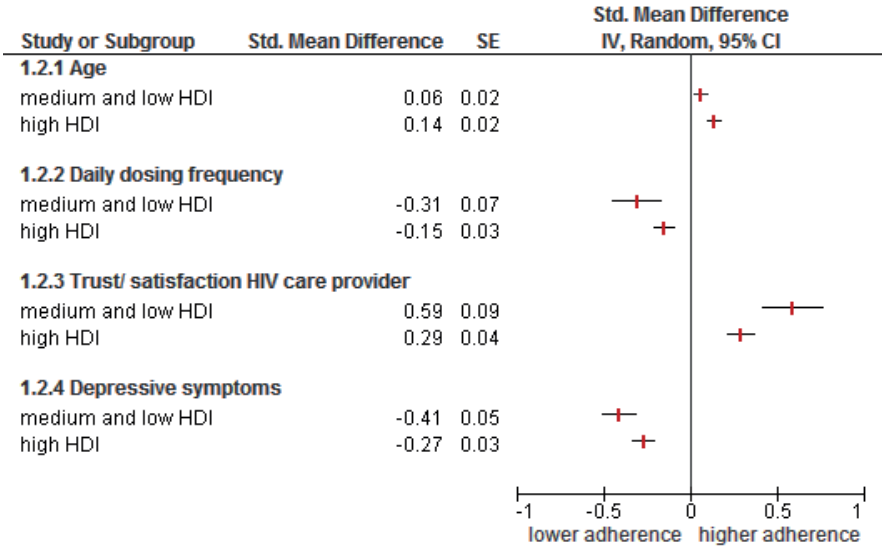


For forest plots of the individual studies examining predictors/correlates, see Additional file 2. (https://static-content.springer.com/esm/art%3A10.1186%2Fs12916-014-0142-1/MediaObjects/12916_2014_142_MOESM2_ESM.pdf) For the scoring of included studies according to the items of the STROBE statement, see Additional file 3. (https://static-content.springer.com/esm/art%3A10.1186%2Fs12916-014-0142-1/MediaObjects/12916_2014_142_MOESM3_ESM.pdf)

The study design feature HDI of the country in which the study was conducted was significantly associated with four predictors/correlates. Trust/satisfaction with the HIV care provider was more strongly associated with adherence in countries with a low or medium HDI than in countries with a high HDI (Figure 3 (1.2.3); Q-between=8,04, *P*=0.005). Daily dosing frequency was more strongly and negatively associated with adherence in countries with a medium or

low HDI than in countries with a high HDI (Figure 3 (1.2.2); Q-between=3,88, *P*=0.049). Older age was associated with higher adherence in countries with a high HDI but not in countries with a medium or low HDI (Figure 3 (1.2.1); Q-between=5,16, *P*=0.02). Depressive symptoms were more strongly associated with lower levels of adherence in countries with a medium or low HDI than in countries with a high HDI (Figure 3 (1.2.4); Q-between=4,38, P=0.04).

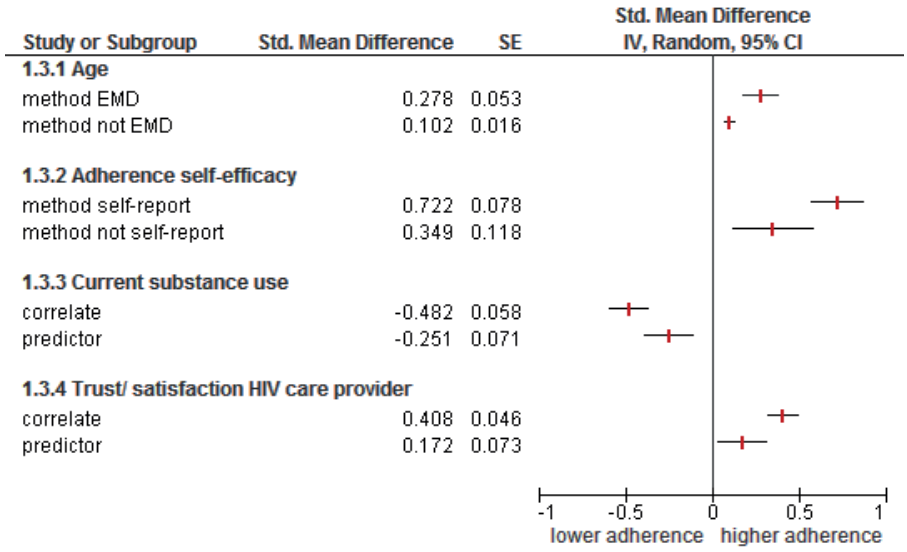
Figure 3: Countries' Human Development Index as moderator of the predictor-adherence relationship



The adherence assessment method was significantly associated with two predictors/ correlates. Adherence self-efficacy was more strongly associated with adherence in studies using self-report as adherence assessment method than in studies using another method (Figure 4 (1.3.2); Q-between =6,94, *P*=0.008). Higher age was more strongly associated with adherence in studies using EMD as adherence assessment method than in studies using another method (Figure 1.3.1; Q-between= 10,12, *P*=0.002).

Whether investigated factors were predictors or correlates yielded two significant associations. Trust/satisfaction with the HIV care provider was more strongly related with adherence if assessed as a correlate than as a predictor (Figure 4 (1.3.4); Q-between =7,44, *P*=006). Current substance use was more strongly and negatively related with adherence if assessed as a correlate than as a predictor (Figure 4 (1.3.3); Q-between= 6,34, *P*=0.012).

Figure 4: Adherence assessment method and study design as moderators of the predictor-adherence relationship



Discussion

In our meta-analysis based on 207 papers reporting on 103,836 patients, we provided a comprehensive overview of the relative importance of various predictors/ correlates of adherence to ART. Adherence to ART was most strongly associated with patients' beliefs, i.e., adherence self-efficacy beliefs, concerns about adverse effects of ART and beliefs about the necessity/utility of ART, and also with current substance use, trust or satisfaction with the HIV care provider, depressive symptoms, HIV stigma and social support. Aspects of regimen complexity such as daily dosing frequency, pill burden and whether the regimen included a PI, had smaller albeit significant effects.

Our findings are consistent with a recent meta-analysis among patients with various long-term medical conditions showing that patients' beliefs have an important influence on medication adherence (224). Results are also consistent with previous studies showing that substance use, depressive symptoms and HIV stigma are associated with lower levels of adherence, and trust or satisfaction with the health care provider with higher levels of adherence (7, 8, 181, 225). These results should be encouraging to HIV care providers as it suggests several avenues

for intervention that could result in improved adherence. Especially, the patients' adherence related beliefs and the relationship between patient and HIV care provider are factors that are in principle modifiable and thus possible targets for adherence-enhancing intervention. Eliciting and addressing the patients' beliefs and an improved relationship between patient and health care provider have previously been associated with improved levels of adherence (226, 227).

This study has several limitations. With the current study we aimed to provide a global overview of the relative importance of various predictors/correlates of adherence to ART. Therefore several predictors/correlates were aggregated into broad categories, i.e., social support, HIV stigma, trust or satisfaction with the HIV health care provider, financial constraints and substance use. Within these broad categories, distinct types of predictors/correlates may have a different impact on adherence that will remain undetected in the present global analysis, e.g. alcohol use could have a different impact on adherence than cocaine use.

Another limitation is that the search was done in a single database only, i.e., PubMed, and included only published English language papers. This may have influenced our results.

This meta-analysis has also several strengths. It provides a comprehensive overview of predictors/correlates of adherence to ART with quantitative estimates of their impact. Moreover this meta-analysis provides information about the relative importance of predictors/correlates.

Papers were included without restriction to geographical region, adherence assessment method or study design. This likely resulted in a consequent large heterogeneity in effect sizes for most predictors/correlates. Guidelines for the reporting of meta-analyses of observational studies have recommended using broad inclusion criteria and then to perform analyses relating design features to outcomes (228). We thus conducted meta- regression analyses to explore the impact of study design features on predictors/correlates of adherence.

The study design feature HDI of the country in which the study was conducted was significantly associated with four predictors/correlates. Trust/satisfaction with the HIV health care provider had a stronger positive effect on adherence in countries with a low or medium HDI than in countries with a high HDI. A possible explanation could be that in countries with a low or medium HDI, patients are more dependent on their HIV healthcare provider for information, support and care. Conversely, in countries with a high HDI, patients usually have more extensive access to health care providers and information about health, HIV and ART, making them less dependent on their HIV healthcare provider. There could also be cultural differences in the relationship between patients and healthcare providers with the healthcare providers having more authority in low or medium income countries.

Daily dosing frequency was more strongly and negatively associated with adherence in countries with a medium or low HDI than in countries with a high HDI. A possible explanation could be that achieving or maintaining high levels of adherence is more challenging in low or medium HDI countries. The added challenge of more frequent daily dosing could therefore more easily result in lower levels of adherence in these countries. However this explanation is in contrast with previous studies showing higher levels of adherence in low income countries than in high income countries. (3, 229)

Older age was associated with higher adherence in countries with a high HDI but not in countries with a medium or low HDI. This finding could simply reflect the fact that studies from low and medium HDI countries included few older patients. Finally, depressive symptoms were more strongly and negatively associated with adherence in countries with a medium or low HDI than in countries with a high HDI.

A remarkable finding was the limited effect of the adherence assessment method on effect sizes. Self-reports are known to overestimate adherence. We expected to find stronger associations between predictors/correlates and adherence in studies using electronic monitoring devices than in studies using self-reports because electronic monitoring devices are usually considered to be a more valid adherence assessment method (230). A possible explanation for the limited effect of the adherence assessment method could be that although self-reports overestimate adherence, the rank order of patients on an adherence scale is similar for self-report and electronic monitoring, thus yielding similar associations.

Duration of ART was not related to adherence in the present meta-analysis. It is usually assumed that adherence declines with time on treatment. A recent study investigating the natural history of changes in adherence to ART over time has shown that the decline is nonlinear with substantial heterogeneity across studies (231). In view of these results and the fact that the present meta-analysis included both patients already on ART and patients (re)starting ART, the absence of a relation between duration of ART and adherence is not surprising.

Conclusions

This meta-analysis of predictor/correlates of ART showed that adherence was strongly related with patients' adherence-related beliefs. These findings suggest that adherence-enhancing interventions should target psychological factors such as self-efficacy and necessity/concerns beliefs about ART. Additionally, simplification of regimens may have smaller, albeit significant effects.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the design of the study. NL and PN performed database searches, performed study selection and data extraction. NL performed quality assessment. PN conducted the meta-analyses and the moderator analyses. All authors reviewed and interpreted the study findings. All authors were involved in writing the manuscript. All authors read and approved the final version before submission.

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AIDS PATIENT CARE and STDs 2010, 24: 361-366

CHAPTER 3

Abacavir/Lamivudine/Zidovudine maintenance after standard induction in antiretroviral therapy-naıve patients: FREE randomized trial interim results

Abstract

Maintenance with a triple nucleoside reverse transcriptase Inhibitor (NRTI) regimen after successful induction with a dual NRTI/protease inhibitor (PI) combination may be advantageous, because of low pill burden, favourable lipids, and less drug interactions. This strategy to become free of PI-related problems without losing viral efficacy has not been formally tested. We performed a randomized, open-label, multicentre, 96-week comparative study in antiretroviral therapy (ART)-naıve patients with CD4 350 cells/mm3 and HIV-1 RNA concentrations (viral load [VL]) greater than 30,000 copies per millilitre. Patients were randomized after reaching VL less than 50 copies per millilitre on two consecutive occasions between 12 and 24 weeks after start of zidovudine/lamuvidine and lopinavir/ritonavir combination. Eligible subjects switched to abacavir/lamivudine/ zidovudine (TZV) or continued the PI-containing regimen. Here we present the 48-week data with virologic success rate (failure: VL>50 copies per millilitre). Two hundred seven patients had similar baseline (BL) characteristics: median CD4 180 cells/mm3, median VL 5.19 $\log^{10}$ copies per millilitre. One hundred twenty subjects (58%) met randomization criteria. Baseline VL differed significantly between dropouts and randomized subjects (median 5.41 versus 5.06 $\log^{10}$ copies per millilitre, p=0.017), as did CD4 cells (median 160 and 200 cells/mm^3, p=0.044). Sixty-one subjects received TZV and 59 subjects continued NRTIs/PI. At week 48, 2 patients in the TZV group and 5 in the PI group did not have a sustained virologic suppression (log rank test; p=0.379). CD4 counts increased significantly in both arms. In ART-naıve patients, TZV maintenance had similar antiviral efficacy compared to continued standard ART at 48 weeks after baseline. Patients on successful standard ART can be safely switched to a NRTI-only regimen, at least for the tested time period.

Introduction

Current standard therapy of HIV infection consists of a two-class combination of three antiretroviral (ART) agents1 (Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009, www.aidsinfo.nih. gov/ ContentFiles/AdultandAdolescentGL.pdf). Preferred starting regimens include a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) either combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI). In the backbone, one of two NRTIs may be a nucleotide reverse transcriptase inhibitor (NRTI). These combination antiretroviral therapies (cART) usually suppress HIV replication adequately, with increase of CD4 cell count and at least partial restoration of immunity. Triple-NRTI regimens are generally not re- commended, although in ART-naive patients, the combination of abacavir/lamivudine/zidovudine (TZV) demonstrated virologic activity comparable to indinavir-based,(1, 2) nelfinavir- based,(3) and atazanavir-based (4) regimens. In two of these studies (1, 4) virologic response to TZV was suboptimal in subjects with higher baseline viral loads (HIV1-RNA 100,000 copies per millilitre). In addition, the AIDS Clinical Trial Group (ACTG) 5095 study showed that TZV was inferior to an efavirenz (EFV)-based regimen regardless of baseline viral load (5). Current cART has been associated with significant short- and long-term adverse events, including hyperlipidemia, insulin resistance, and lipodystrophy syndrome (6-8). These metabolic side effects appear to translate into an increase of cardiovascular events in HIV-infected patients compared to HIV-seronegative individuals (8-11). Because of these and other toxicities, there is a need to explore other therapeutic approaches, including induction-maintenance strategies with simplified treatment regimens. Simplifying treatment regimens can also improve adherence, which in turn is pivotal to achieve optimal response to treatment (12). Complex regimens, higher daily pill burden, and higher dosing frequencies are predictors of nonadherence, with relatively low difference between once or twice daily dosing (13-15). PI-based regimens appear associated with lower adherence compared to triple NRTI regimens (16-18). Lower adherence to PI-based cART than to NNRTI-based regimens has also been shown (19, 20). Similar adherence was observed during maintenance phase between patients on a NRTI-only regimen or a NNRTI-based regimen (21). Compared to continued quadruple NNRTI-based treatment, adherence to triple NRTI maintenance therapy was better (22). Earlier studies addressing a switch to triple NRTI included patients who had not been ART-naıve from the start, resulting in suboptimal responses (18, 21, 23-27). Subsequent studies exploring the induction–maintenance concept in ART-naıve patients showed similar virologic success (i.e., noninferiority) for triple NRTI regimens compared to two-class cART (17, 21, 22, 28-31). However, some of these studies were not entirely prospective (17, 21, 29), or did not have a comparative design for the maintenance phase (28, 30), or used poorly tolerated quadruple regimens as induction

regimens (22, 32). Here we describe a randomized, prospective study in ART- naıve patients using a standard triple cART as induction therapy, followed by maintenance with TZV in those who reached an undetectable plasma viral load (less than 50copies per millilitre). We report the interim results at 48 weeks after baseline, specifically addressing the question of virologic efficacy of maintenance with single-class ART. and atazanavir-based (4)

Methods

Study population

HIV-1–infected, ART-naıve adults were eligible with a CD4 cell count 350 cells/mm^3 and an HIV-1 RNA level 30,000 copies per millilitre or more at screening. Exclusion criteria included diabetes mellitus or being treated for abnormality of the lipid spectrum. Laboratory exclusion criteria were hemoglobin<10g/dL (male) or 9g/dL (female), absolute neutrophil count<1000 cells/mm^3, platelet count <75,000 cells/mm^3, transaminases more than 5 times the upper limit of normal (ULN), total bilirubin >2mg/L, serum pancreatic amylase more than 1.5 times the ULN, fasting glucose >6.9 mmol/L or nonfasting glucose >11 mmol/L, fasting triglyceride level >4mmol/L, or fasting LDL cholesterol >5mmol/L or low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio >5. Patients were also excluded if they had a history of cardiovascular events or diabetes mellitus, combined with fasting triglyceride level >3mmol/L, or fasting LDL cholesterol >4mmol/L, or LDL/HDL ratio >4.

Study design and study sites

FREE is an investigator-initiated, randomized, open-label, 96-week study conducted at 10 sites in the Netherlands and 1 site in Belgium. During the induction phase, all patients were treated with 1 fixed-dose tablet of lamivudine (3TC) 150mg/ zidovudine (ZDV) 300mg (Combivir®; GlaxoSmtihKline, Zeist, The Netherlands, and Genval, Belgium) twice daily and with 3 capsules lopinavir (LPV) 133mg/ritonavir (r) 33mg (Kaletra®; Abott, Hoofddorp, The Netherlands and Louvain- La-Neuve, Belgium) twice daily. In 2005, the manufacturer changed the formulation of LPV/r, and the capsules were replaced by tablets x 200/50mg, 2 tablets taken twice daily. Only patients with HIV-1 RNA levels less than 50 copies per millilitre between week 12 and week 24, measured on two consecutive visits at least 4 weeks apart, were eligible for randomization into the maintenance phase. Patients were randomized on a 1:1 basis by computer-generated allocation to either continue 3TC/ZDV and LPV/r (PI arm) or to 1 fixed- dose tablet of Abacavir 300mg/3TC 150mg/ZDV 300mg (Trizivir®; GlaxoSmtihKline, Zeist, The Netherlands, and Louvain-La-Neuve, Belgium; the TZV arm), twice daily. A minimization rule was applied for the patient factor: HIV-1 RNA copy number. Patients were stratified in three groups: 30,000–100,000; more than 100,000–1,000,000; or more than 1,000,000 copies per millilitre at study entry. Screening evaluation

included a clinical assessment and laboratory evaluations: plasma HIV-1 RNA, CD4 cell count, haematology, clinical chemistries, and collections of a plasma sample for retrospective research for viral resistance mutations. Screening for the presence of the human leukocyte antigen (HLA)-B*5701 subtype was not performed. In recent years a statistically significant correlation with the abacavir hypersensitivity reaction and the presence of this allele has been shown (33). At the time this study was started routine genotyping for the HLA-B*5701 allele was not available. On-study evaluations included clinic visits at baseline and at week 4, 8, 12, 18, and 24, for the induction phase; and at weeks 36, 48,60, 72, 84, and 96 for the maintenance phase. HIV-1 RNA was assessed locally at each visit using the Roche Ultrasensitive Assay (Roche Diagnostics, Indianapolis, IN) with a lower limit of detection of less than 50 copies per millilitre.

End points

The primary end point of the study was antiviral efficacy at week 96, defined as plasma HIV-1 RNA less than 400 copies per millilitre. The purpose of the study was to assess treatment equivalence of this endpoint between both groups. Secondary end points included safety and tolerability; effect on absolute and cumulative $CD4^+$ cell count changes compared to baseline; use of cART related comedication, especially lipid-lowering agents; and time to treatment failure (HIV-1 RNA less than 50 copies per millilitre). Here we addressed the secondary end points at week 48: virologic efficacy (sustained viral load suppression less than 50 copies per millilitre), and premature discontinuation of allocated ART for any reason. We considered detectable viral load as well as treatment discontinuation as treatment failure for the present interim analysis.

Sample size

With an expected antiviral efficacy percentage of 80% at week 96 and an equivalence limit of 20 percent points (as assumed in the protocol), 50 randomized evaluable subjects per group are needed to show equivalence with 80% power, using a test size of 0.05 (one-sided).

Statistical analyses

Time to virologic failure was analysed using the Kaplan- Meier method, and the log-rank test was used to compare survivor functions (sustaining HIV-RNA less than 50 copies per millilitre) between groups. The 95% confidence interval was estimated for the difference in the percentages of treatment failure (virologic failure or premature discontinuation) between the two groups. All tests for secondary end points were two-sided with a confidence level of 95%. Changes in the absolute numbers of CD4 cells during the randomization phase were analysed using mixed-model analysis of variance (ANOVA). Statistical analyses were performed using SPSS version 16 (SPSS, Inc., Chicago, IL).

Ethics

The protocol was approved by Institutional Review Boards of all hospitals involved. All participants gave consent after written information had been given, in accordance with the national and international legislation, as well as the Declaration of Helsinki.

Role of sponsor

This was an investigator-driven study; the sponsor was not involved in the design, data analysis, draft of the paper, or in the decision to submit the paper for publication. The protocol (with revisions and updates) was registered at Clinicaltrials.com; Registration Identifier Number: NCT00405925.

Results

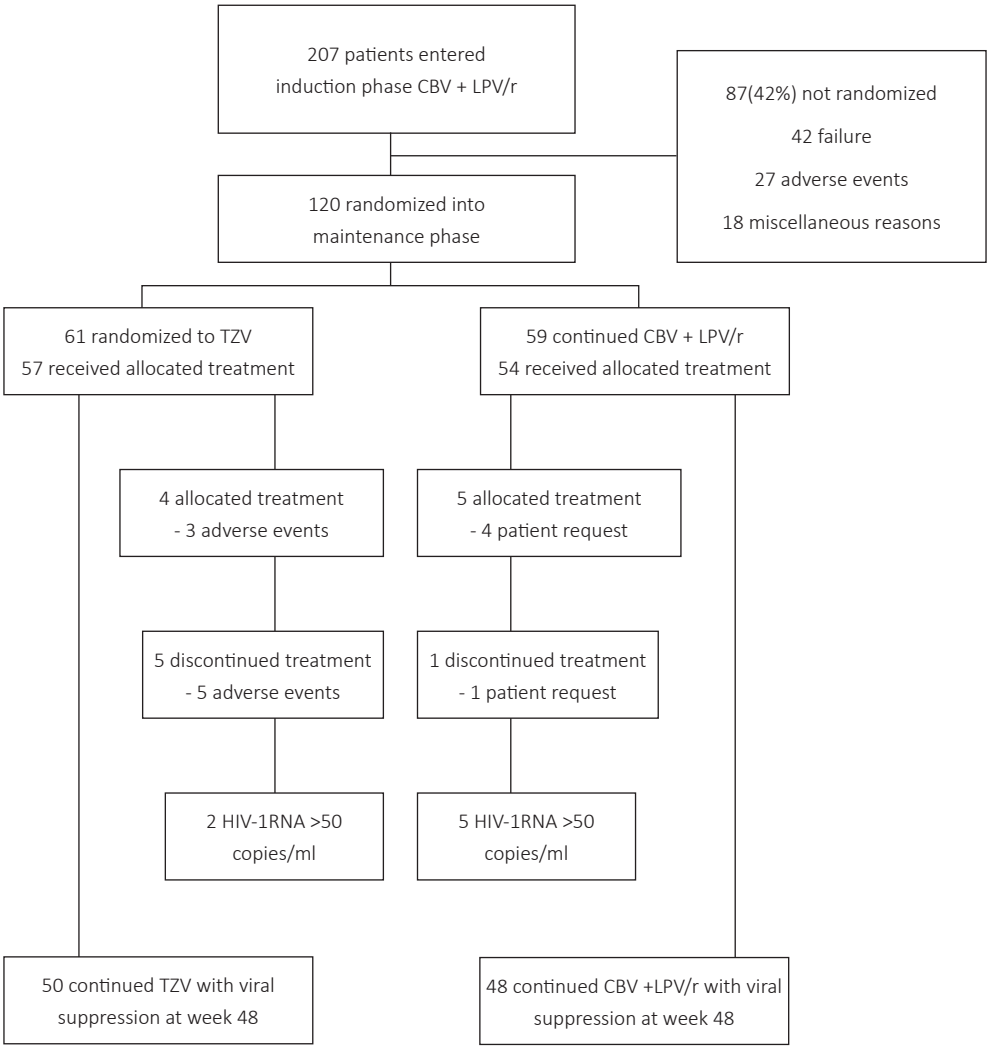
Patient disposition

Of 241 patients screened, 207 were enrolled in the induction phase. Table 1 shows their demographic and baseline characteristics. Patients at baseline were predominantly male, with a median age of 40.8 years (range, 19.4–78.1), had a median baseline HIV-1 RNA 5.19 $\log^{10}$ copies per millilitre (range, 2.97–7.45), and a median CD4 cell count 180/mm^3 (range, 10–440). Eighty-seven patients (36%) did not reach the maintenance phase (Fig. 1) primarily because they did not achieve virologic suppression (HIV-1 RNA less than 50 copies per millilitre on two occasions) before week 24 (47 patients, 54%), or because of side effects (22 patients, 25%). Of baseline variables only HIV-1 RNA level and CD4 cells differed significantly between the patients who did not reach the maintenance phase of the study (drop outs; HIV-1 RNA median 5.41 $\log^{10}$ copies per millilitre) and the patients who could be randomized (median 5.06 $\log^{10}$ copies per millilitre). Median CD4 cell count was 160 cells/mm^3 in the dropouts and 200 cells/mm^3 in the randomized group. A total of 120 patients were randomized to either continuation of the induction regimen (n=59) or to switch to TZV (n=61). The two groups were similar, and characteristics did not change between initial enrolment of participants and at randomization (Table 1). Nine patients were randomized, but did not start with the maintenance phase, 5 patients randomized into the PI arm, and 4 into the TZV arm. These 9 patients had no follow-up visits during the maintenance phase and were excluded from the analyses. Figure 1 provides details about these study participants that did not follow the allocated treatment regimen.

Table 1. Demographic and Baseline Characteristics of Patients

	Induction Phase	Maintenance Phase	
	CBV/LPV/r (n=207)	CBV/LPV/r (=59)	TZV (n=61)
Median age (range), yr	39.7 (19.4-78.1)	40.3 (24.7-62.0)	42.1 (21.9-68.6)
Male sex, n (%)	181 (87%)	52 (88%)	50 (82%
Median baseline plasma HIV-1 RNA Level (range), log_{10} copies/ml	5.19 (2.97-7.45)	5.03 (4017-6.61)	5.07 (2.97-6.18)
≥100.000 copies/ml	115 (60%)	29 (49%)	33 (54%)
Median CD4 cell count at baseline cells/mm^3 (range	180 (10-440)	207 (10-370)	195 (10-437)
<50 cells/mm^3, n (%)	31 (15%)	6 (11%)	9 (16%)
>50-<200 cells/mm^3, n (%)	73 (35%)	18 (34%)	20 (35%)
Median CD4 cell count at randomization cells/mm^3 (range)	NA	350 (50-610)	310 (50-780)

Figure 1: Flow chart and disposition of study participants in the FREE trial; interim results at week 48



Virologic response and treatment (dis-)continuation

At week 48, the proportion of patients with treatment failure(virologic or treatment discontinuation) was12%(7/57)in the TZV group and 11% (6/54) in the PI group. The difference between the TZV group and the PI group was 1.2 percentage points (TZV-PI; 95%CI–11.0 to +13.4). With these confidence limits lying wholly in the predefined range equivalence is demonstrated. In the TZV group most failures (5/7) were not virologic but premature discontinuations because of adverse events. Five patients in the PI group had HIV-1RNA 50 copies per millilitre or more at any one time before the end of week 48, compared to two patients in the TZV group (log rank test; p=0.379).In two of the patients in the PI group only a transient viral ‘‘blip’’ (defined as a single isolated or recurrent but transient episode of detectable low-level viremia greater than 50 copies per millilitre) was detected (at week 24 and at week 36), the three other patients had HIV-RNA greater than 50 copies per millilitre for the first time at their visit in week 48.In the TZV group one patient had HIV-1 RNA greater than 50 copies per millilitre in week 36, with no result known at week 48. The second patient in the TZV group had HIV-1 RNA greater than 50 copies per millilitre only at week 48. There was an increase of CD4 cells in both maintenance treatment arms at week 48 compared to their CD4 cell counts at randomization: in the PI group 95 (95% CI 42–149) CD4 cells/mm^3 (p=0.001), and in the TZV group 69 (95% CI 25- 113) CD4 cells/mm3 (p=0.002). The increase of CD4 cells at week 48 was not significantly different between groups (p=0.46).

Discussion

The FREE trial is the first study exploring a 100% prospective, well-designed induction-maintenance strategy in ART-naıve patients after induction therapy with standard cART. We show that viral suppression can be maintained by a single-class regimen after successful induction by two-class triple cART standard induction therapy. At week 48,virologic success rates with the triple NRTI regimen (TZV: 96.5%) and the continued standard PI-based cART regimen (90.7%) were similar. Our interim results confirm findings from two earlier studies showing that the induction-maintenance approach is effective (22, 32), but induction therapy in these studies consisted of four drugs, TZV, and EFV. In these studies the four-drug regimens had high discontinuation rates (24% and 37%). The Trizefal study (30) compared two quadruple induction regimens, TZV with either LPV/r or EFV, which after successful induction were followed by maintenance therapy with TZV. In the induction phase there was also a high discontinuation rate: 45% did not reach the maintenance phase primarily be- cause of adverse events. Although we show that a triple cART as induction therapy can be followed successfully by a single- class maintenance regimen, our dropout was fairly high, mainly because of strict inclusion criteria for the decision to switch to maintenance. Undetectable viral load (HIV-1 RNA<50 copies per millilitre) on two different visits 4–6 weeks

apart within 24 weeks after baseline was an unattainable goal for nearly half the patients; only 58% of patients enrolled at baseline could therefore be randomized. Patients (42%) who could not be randomized had significantly higher HIV-1 RNA copies per millilitre, and a lower CD4 count at baseline. Other studies used longer induction periods (24–48 weeks) (22, 30) and such policy would have increased the sample size of our study subjects. The rationale to determine a relatively short induction period was the fear to include subjects with pre-existing resistant mutant (quasi-)species virus with an enhanced chance to fail on a single class NRTI maintenance regimen. Since the average second phase HIV-1 RNA decay after cART initiation is 2–4 weeks on average (34), treatment of approximately 6–12 half-lives, or approximately 24–48weeks, would result in a substantially reduced residual viral burden at the time of treatment simplification. Our findings at 48 weeks suggest that such a policy to prolong the induction phase to reduce the risk for failure may not be necessary for those subjects that reach undetectable viral loads at week 20 and week 24, as virologic failure was equally uncommon in both arms of our study analysed at week 48. Potential weaknesses of our study are first, the limited sample size; had the design allowed for randomization with viral suppression after week2 4,this would have increased the sample size. Second, lack of concealment may have influenced failure rates, especially because the major source of failure was not virologic failure per se, but rather stopping study medication ‘‘for any reason.’’ Third, at this interim analysis at week 48, it is too early to predict the success of simplified treatment with TZV if such maintenance regimen were continued for longer periods of time. The simplification of cART after a successful induction period to a single-class regimen may be advantageous, even if such simplified treatment were only justified for limited periods of time. Triple NRTI regimens offer convenient dosing regimens with a very low pill burden (two pills per day) leading to better adherence, show favourable lipid pro- files (17, 22, 25), and result in fewer potentially serious drug interactions than standard cART. This may be helpful if during intercurrent medical or surgical events, drug–drug interactions need to be avoided, e.g., the use of rifamycin-based regimens for tuberculosis and non-tuberculous mycobacterial infections; anti-convulsive, anti-arrhythmic, or antimalaria therapy. Based on our observations, patients with viral suppression who need to interrupt PI or NNRTI agents, can be safely managed with single class NRTI—at least temporarily— with acceptably low chances of viral failure. With continued viral suppression less than 50 copies per millilitre, the chances of acquiring drug resistance are generally low (35). Although there was a low virologic failure rate after randomization in both arms in our study at week 48, results at week 96 have to be awaited to determine the safety and efficacy of single-class NRTI maintenance therapy during longer periods of time.

Acknowledgments

Presented in part at the Ninth International Congress on Drug Therapy in HIV Infection, November 9–13, 2008, Glasgow, UK.
Supported by an unrestricted grant from GlaxoSmithKline.

Author Disclosure Statement

No competing financial interests exist.

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CHAPTER 4

A simplified combination antiretroviral therapy regimen enhances adherence, treatment satisfaction and quality of life: results of a randomized clinical trial

Abstract

Objective: To investigate the effect of a simplified regimen, in terms of reducing pill burden, dietary requirements and possible adverse effects, on patients' adherence, treatment satisfaction and quality of life (QoL).

Methods: Antiretroviral naive patients who achieved a viral load <50 c/ml after induction therapy with bid lopinavir/ritonavir (LPV/r) and fixed dose AZT/3TC (CBV) were randomly assigned to continue CBV/LPV/r or switch to fixed-dose AZT/3TC/Abacavir (TZV). Patients completed standardized questionnaires on adherence, treatment satisfaction and QoL at randomization (between week 12 and 24) and at weeks 48, 72 and 96.

Results: Patients on CBV/LPV/r were more likely to have skipped medicines in the last week (p=0.035) and during the preceding weekend (p=0.027) than patients on TZV. Patients on CBV/LPV/r were significantly less satisfied with convenience of their treatment (p=0.004) and tended to be less satisfied with side effects of their treatment (p=0.091) and continuation of their present treatment (p=0.056) than patients on TZV. Patients on CBV/LPV/r reported significantly lower levels of role functioning (p=0.013) than patients on TZV.

Conclusion: In this randomized controlled trial, simplification of therapy to fixed-dose TZV among patients with suppressed HIV RNA was perceived to be more convenient, and resulted in improved adherence and better role functioning than continuing treatment with CBV/LPV/r

Introduction

The introduction of combination antiretroviral therapy (cART) has been accompanied with a significant decline in HIV- and AIDS-related morbidity and mortality. This significantly improved life expectancy has turned HIV-infection into a more chronic- than a fatal disease. The goal of cART is to suppress plasma viral load below the limits of detection and maintain this suppression as long as possible. To date, suppression of HIV is possible in the vast majority of patients with a wide variety of combination antiretroviral therapy (cART) regimens. Each of these effective cART regimens however may differ in their associated characteristics including the complexity of regimen and side effect profile Optimal adherence to cART is the key to success. It is generally assumed that simplification of cART regimens will lead to better adherence, higher treatment satisfaction and a better quality of life (QoL), but randomized studies demonstrating such advantages of simplified regimens are scarce.

Regimen complexity is considered to be composed of a number of regimen attributes including the number of prescribed pills ("pill burden"), the frequency of daily dosing, dietary requirements and adverse events (1). Most randomized studies investigating the advantages of simplified regimens have focussed on the effect of once daily dosing versus twice daily dosing on treatment adherence and treatment satisfaction, generally yielding more favourable outcomes for once daily regimens (2-6).

Whereas it is likely that reducing pill burden and dietary requirements also result in higher levels of adherence to cART, there is little empirical evidence to support this assumption. We could identify only two observational studies that have investigated the association between pill burden, adherence and patient's QoL (7, 8). The aim of our study was to investigate the effect of a simplified regimen in terms of reducing pill burden, dietary requirements and possible adverse effects on patient's adherence, treatment satisfaction and QoL within the context of a randomized trial

Methods

The FREE study was an investigator-initiated, randomized, open-label, 96-week study conducted at 10 sites in the Netherlands and 1 site in Belgium. During the induction phase, all patients were treated with one fixed-dose tablet of lamivudine 150 mg /zidovudine 300 mg (CBV) twice daily and three capsules lopinavir 133mg/ritonavir 33 mg twice daily (LPV/r). In 2005 the manufacturer changed the formulation of LPV/r and the capsules were replaced by tablets of 200/50 mg, taken as two tablets twice daily. After 12 to 24 weeks of induction therapy patients were randomized, after achieving a viral load <50 copies/ml at two consecutive visits. Group one switched to a fixed dose single tablet of zidovudine 150 mg/ lamivudine 300 mg/ abacavir 300mg (TZV) twice daily and group two continued LPV/r

and CBV. All patients were naïve to cART when entering the study. Both arms yielded similar antiviral efficacy after 48 weeks as reported previously (9).

Patients completed questionnaires on adherence, treatment satisfaction and QoL at randomization and after 48, 72 and 96 weeks. Adherence was measured with the Simplified Medication Adherence Questionnaire (SMAQ)(10). The SMAQ is a self-reported questionnaire containing 6 items. The questions ask how forgetful and careless patients are in taking their cART and if they stop taking medicines if they are feeling worse. It also asks about missed doses in the past seven days and in the last weekend and how many days within the past three months patients did not take their pills.
Treatment satisfaction was measured using the HIV Treatment Satisfaction Questionnaire (HIVTSQ) (11). The HIVTSQ consists of 10-items, which ask about satisfaction with current treatment, with control of HIV infection and with side effects of treatment. It also asks about the extent to which treatment is demanding and flexible, satisfaction with understanding HIV infection, with the extent to which treatment fits into life style and satisfaction to continue present treatment. It also asks if a patient would recommend their treatment to someone else. Items are scored on a 7-point scale, ranging from “very satisfied” to “very dissatisfied”, “very convenient” to “very inconvenient”, and from “yes, I would definitely recommend the treatment” to “no, would definitely not recommend the treatment”.
To measure QoL we used the Medical Outcome Study HIV (MOS-HIV) Health Survey. This questionnaire contains 10 subscales: physical functioning, pain, role functioning, social functioning, health perceptions, mental health, health distress, overall quality of life, cognitive functioning, and energy/vitality. All subscales range from 0-100 with higher scores indicating better QoL (12).

Statistical analyses

We compared characteristics at randomization between both study groups using Student t-tests, Mann-Whitney U tests, and Chi-squared tests for continuous variables with a normal distribution, for continuous variables with non-normal distribution and for categorical variables, respectively.
We used repeated-measures linear mixed models to test for differences between both study groups in treatment satisfaction and QoL over time. Model results were summarized by the estimated mean values. We used generalized estimating equations to investigate the difference between the 2 groups in treatment adherence over time. Model results were summarized by odds ratios and 95% confidence intervals.
Both linear mixed models and generalized estimating equation use all the available data, without excluding patients with missing observations. Both methods use maximum likelihood estimation for estimating missing data based on available data.

We conducted a sensitivity analysis to examine how our substantive results depend on the way we handled missing data. First, we conducted a complete cases analysis. Second, we repeated the analysis using last observation carried forward (LOCF) as imputation methods. Two-sided p values <0.05 were considered to indicate statistical significance. Data were analyzed using SPSS version 19 (SPSS, Inc., Chicago, Illinois).

Results

Of the 207 patients participating in the FREE study who were enrolled in the induction phase with CBV/LPV/r, 120 patients were randomized to either continuation of the induction regimen (N=59) or to switch to TZV (N=61). A total of 95 of these patients (79%) completed at least one questionnaire of whom 53 patients were allocated to the TZV group (87%) and 42 to the CBV/LPV/r group (71%). These patients were included in the present study on treatment satisfaction, treatment adherence and QoL.

There were no statistically significant differences between patients who completed at least one or no questionnaire(s) in gender, race, CD4 count and plasma HIV RNA concentration at start of the induction therapy and at randomization. Patients who completed questionnaires were, however, slightly older (mean age 43 years) than patients who did not complete questionnaires (mean age 37 years) (p=0.01). The characteristics at randomization of patients in both study groups who completed questionnaires are shown in Table 1.

A total of 65 patients completed a questionnaire at randomization (CBV/LPV/r: n= 22, TZV: n= 43), 53 patients completed a questionnaire at week 24 (CBV/LPV/r: n= 23, TZV: n= 30), 41 patients completed a questionnaire at week 48 (CBV/LPV/r: n= 19, TZV: n= 22) and 39 patients completed a questionnaire at week 72 (CBV/LPV/r: n= 19, TZV: n= 20).

Overall, 17% of the patients reported forgetting taking their medicines sometimes, 23% reported to be careless sometimes when taking medicines, and none of the patients reported to stop taking medicines when they were feeling worse. A total of 16% reported to have skipped medicines at least once during the past week, 5% reported skipping medicines during the last weekend and 1% reported not taking medicines on more than two days within the past three months.

Table 1: Patient characteristics at randomization

	LPV/r n = 42	TZV n = 53	P value
% males	83	81	0.50
% Caucasian race	82	76	0.61
Age (years), mean (SD)	43 (10)	44 (11)	0.51
CD4 count at start induction, (cells/uL) [median (IQR)]	220 (145-300)	180 (90-248)	0.03
CD4 count at randomization, (cells/uL) [median (IQR)]	387 (280-490)	300 (195-396)	0.09
HIV-1 RNA (log^{10} copies/ml) [median (IQR)] at start induction, mean (IQR)	5.00 (4.78-5.31)	5.00 (4.70-5.25)	0.63

Patients in the CBV/LPV/r group were significantly more likely to report skipping medication in the last week (OR: 1.81, 95% CI 1.04 to 3.14, p=0.035) and to report not taking medicines in the last weekend (OR: 2.87, 95% CI 1.13 to 7.29, p=0.027).
Patients in the TZV group found their present treatment more convenient (mean score 5.6 versus 5.1, p=0.004), tended to be more satisfied with the side effects of treatment (mean score 5.4 versus 4.9, p=0.091) (Figure 1A) and tended to be more satisfied to continue with their present treatment (mean score 5.6 versus 5.1, p=0.056) (Figure 1B) than patients in the CBV/LPV/r group.

Figure 1A

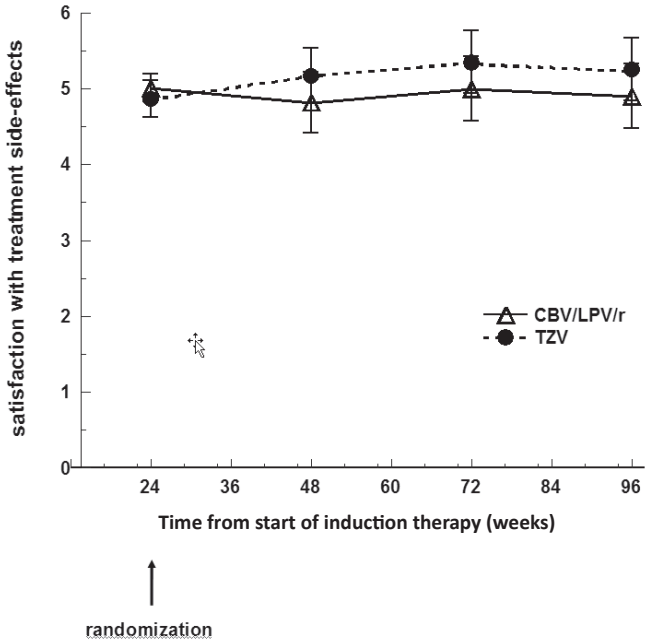
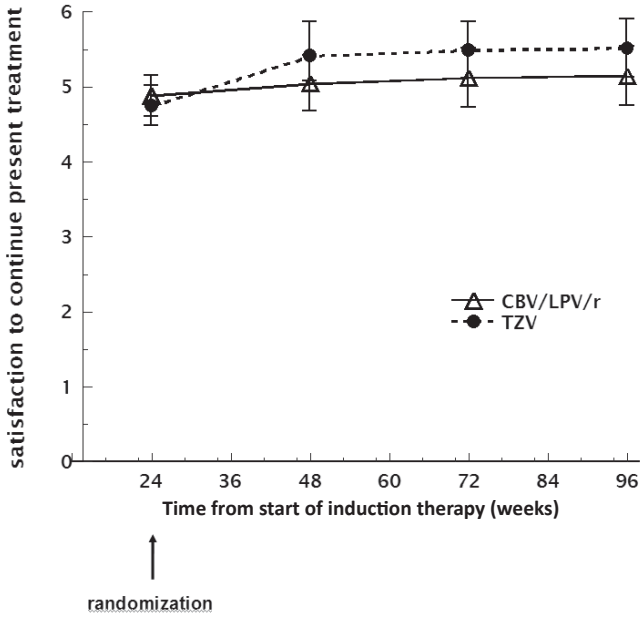


Figure 1B



Patients in the TZV group had a significantly better QoL with respect to role functioning than patients in the CBV/LPV/r group over follow-up (mean score 91 versus 80, p=0.013).
Overall, the results from our sensitivity analyses were in the same direction of our primary analysis and generally in favor of the TZV group. Using complete cases analysis, we observed no significant differences between both study groups in terms of treatment adherence, the same differences between both study groups with respect to treatment satisfaction and found patients in the TZV group to be significantly more inclined to recommend their treatment to someone else (mean score 5.8 versus 5.0, p=0.042). The complete cases analysis also yielded similar results with respect to QoL as the primary analysis.
The analysis using LOCF as imputation method yielded similar results with respect to treatment adherence and treatment satisfaction as our primary analysis with two exceptions. First, we found no difference between both groups in satisfaction with side effects. Second, patients in the TZV group tended to be more satisfied with the extent to which treatment fits in with their lifestyle (mean score 4.9 versus 4.6, p=0.088). However, using LOCF as imputation method, we observed the same difference between both groups in QoL as in our primary analysis, i.e., in role functioning. Additionally, we observed a better QoL in the TZV group with respect to energy/fatigue (mean score 66 versus 61, p= 0.021), but a lower QoL with respect to social functioning (mean score 81 versus 87, p=0.032) than patients in the CBV/LPV/r group.

Discussion:

In this randomized clinical trial, simplification of therapy to a fixed dose single class regimen resulted in higher treatment satisfaction, better adherence and better QoL than continuing a ritonavir-boosted PI-based regimen among patients with suppressed HIV-1 RNA.
To date, randomized studies investigating advantages of simplified regimens in terms of treatment satisfaction, adherence and QoL are scarce. We believe the present study entails a proof of principle that simplifying regimens in terms of pill burden, dietary requirements and potential side effects can lead to more favourable patient reported outcomes.
Our finding that a simplified regimen consisting of TZV resulted in better adherence than a standard PI- or NNRTI based regimen is consistent with two previous randomized studies (13, 14). Our finding that a simplified regimen consisting of TZV resulted in better adherence and in higher treatment satisfaction is consistent with one non-randomized switch study (15). Clearly, advantages of simplified regimens in terms of treatment satisfaction, adherence and QoL should be weighed against treatment efficacy and the choice for simplified regimens should be individualized.

Our study has several limitations. It had a relatively small sample size. Also, a considerable number of patients did not complete the questionnaire on treatment satisfaction, adherence

and QoL on one or more occasions. Moreover, patients enrolled in the CBV/LPV/r group more often missed the baseline measurement at randomization than did patients in the TZV group. We can only speculate why patients in the CBV/LPV/r group more often missed the baseline measurement. Possibly, patients themselves or the persons responsible for handing over the questionnaire to the patient perceived it to be more relevant in the TZV group. At randomization, patients in the TZV group had a change in their treatment regimen whereas patients in the CBV/LPV/r group just continued their prescribed regimen.
Patients who did complete questionnaires were on average five years older than patients who did not. Otherwise, we found no differences in demographic or clinical characteristics between patients who did and did not complete questionnaires.
Because of the relatively high number of missing questionnaires, we performed a sensitivity analysis to determine if different methods for handling missing observations would lead to different results than our primary analysis. The results of both our primary analysis and our sensitivity analysis were in the same direction and yielded evidence in favor of the simplified regimen. Nevertheless, we cannot rule out the possibility that the missing observations may have biased our results and overestimated the beneficial effect of the simplified regimen.
Another limitation is that we used a self-report measure of adherence, which is known to overestimate adherence. Because such possible overestimation was likely present in both study arms, we doubt whether this has influenced the comparison of adherence between the treatment arms.

Conclusion:

In this randomized controlled trial, simplification of therapy to fixed-dose TZV among patients with suppressed HIV RNA was perceived to be more convenient, and resulted in improved adherence and better role functioning than continuing treatment with CBV/LPV/r.
Although TZV is not a treatment of choice these days, this study is a proof of concept to show that simplification enhances treatment satisfaction, adherence and QoL. Increasing availability of single tablet combination cART regimens is a major advance, but food restrictions may still hamper optimal adherence. With expected treatment durations of over 30 years, convenience and treatment adherence will be of major importance to maintain patients on cART in the long term. As patients live different lives, individualization of therapy remains of the utmost importance.

Financial Support:

The FREE study was supported by an unrestricted grant from GlaxoSmithKline

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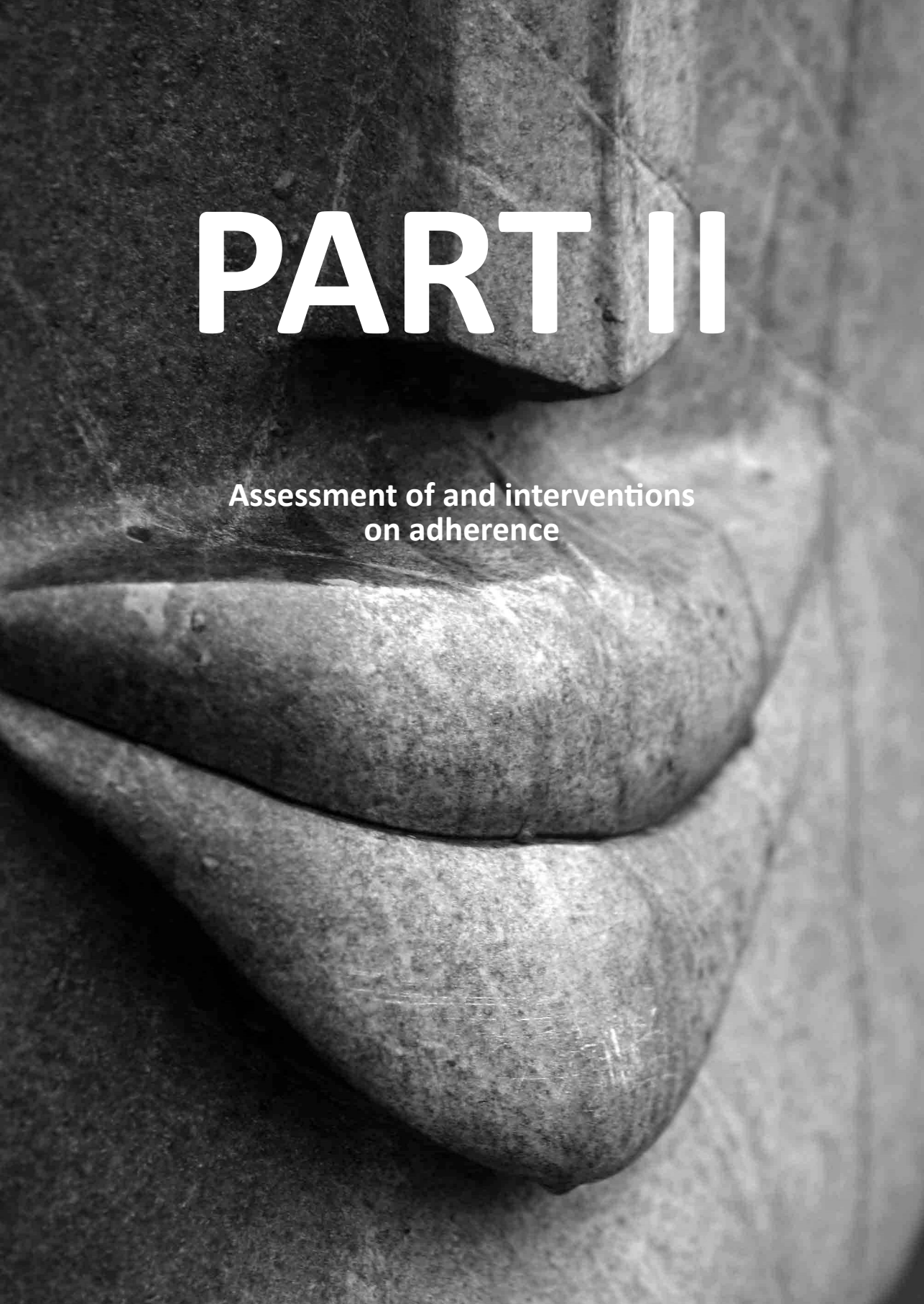

PART II

Assessment of and interventions on adherence

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Journal of Acquired Immune Deficiency Syndromes, 2002, 30: 324-334

CHAPTER 5

Assessment of adherence to HIV protease inhibitors: Comparison and combination of various methods, including MEMS (Electronic Monitoring), patient and nurse report, and therapeutic drug monitoring

Abstract

Background: Adherence to protease inhibitor-containing antiretroviral therapy is crucial, but difficult to measure. Objective: To compare and combine various methods of measuring adherence to the strict protease inhibitor-containing regimens.

Methods: The following methods were used: medication event monitoring system (MEMS) caps (electronic monitoring), therapeutic drug monitoring, pill count, pharmacy refill data, questionnaires, diaries (for registration of food patterns and special events related to the use of MEMS), adherence assessment by the physician and clinical nurse specialist, and in-depth interviews. In addition, ultrasensitive viral load and resistance testing was performed.

Results: Twenty-eight patients were included; data could be evaluated in 26. According to MEMS data, 25% of the patients took fewer than 95% of all doses, and two thirds of the patients took fewer than 95% of the doses on time. Only 43% of the patients showed good adherence with food restrictions. Methods that showed significant correlations with MEMS results were patients' self-reported adherence; therapeutic drug monitoring, indicating plasma levels outside predefined ranges; and estimation of adherence by a clinical nurse specialist, especially by in-depth interview.

Conclusion: Diary-corrected MEMS data gave a detailed insight into patients' adherence patterns. Patients' self-report and therapeutic drug monitoring were significantly correlated with the MEMS data, and the clinical nurse specialist may also play a role in identifying patients who are imperfectly adherent.

Introduction

Although protease inhibitor-containing antiretroviral therapy has dramatically improved the outcomes for HIV-infected patients, suboptimal adherence to these complex regimens decreases the likelihood of suppress-viral replication and increases the likelihood of developing resistance (1-15). High adherence seems necessary (1,8,12,14), which means ingestion of the correct number of pills at the right time according to the prescribed food requirements. Adherence is further complicated by adverse events and factors such as stigmatization (16-19). Whereas the virologic implications of suboptimal adherence are becoming increasingly clear, it is not yet apparent how adherence to these stringent regimens can best be measured. One problem in studying adherence is the lack of a gold standard (20-22). Thus far, self-report has predominantly been used (5,6,8, 10,13,23-27). Recently, a few studies using electronic monitoring have been presented (1,28-30). The medication event monitoring system (MEMS) records the opening and closing of a medication vial and thereby provides more detailed information. Nevertheless, it is still an indirect method because it does not measure drug ingestion. A direct, objective measure of ingestion of a drug is its plasma concentration (20,31), although it only gives short-time information. Adherence with food requirements can be measured with a diary or other kinds of self-report. The objective of our study was to combine several adherence-measuring methods to compare the information provided by these various methods. We aimed to find a set of methods that enables adherence monitoring of all relevant aspects of protease inhibitor-containing antiretroviral therapy. With the availability of tools to reliably monitor adherence, an important step toward developing effective interventions that improve adherence can be made.

Materials and methods

Patients

Two groups of outpatients were included in this study: 1) patients who were starting antiretroviral combination therapy including one or more protease inhibitors (naives) and 2) patients who were already using protease inhibitor-containing combination therapy for more than 48 weeks and who had an undetectable viral load (i.e., <400 or 500 copies/mL at the previous two measurements before start of the study; non-naives). In this descriptive study, the patient sample is a convenience sample, i.e., patient numbers were based on the availability of suitable patients in the two centers that participated, the University Medical Centre, Nijmegen and the Rijnstate Hospital, Arnhem. The goal was to include 20 naive and 20 non-naive patients, equally distributed over the two centers. Patients had to be between 18 and 65 years of age and able to read and speak Dutch. During follow-up evaluation, patients continued their original medication regimen, although changes according to standard of care

were allowed. Patients were monitored for 24 weeks during which three (for non-naives) or four (for naives) visits were planned, analogous to regular visits. Sociodemographic and other patient characteristics were registered during the first of these visits. If patients did not want to participate, the reasons for refusal, according to the patient and the nurse, were marked. All participants signed written informed consent, and the study was approved by the local Ethics Committees of both study centers. Medication Event Monitoring System In this study, the MEMS was used, more specifically the eDEMs Track caps (Aardex, Zug, Switzerland), in combination with 200-mL pill bottles. Medication dosing times were retrieved from the cap and analyzed by the Powerview program (Aardex, Zug, Switzerland). For our study, we used an intermediate version of Powerview that enabled us to insert and delete events to correct the MEMS data. These corrections were necessary because the bottle was also opened during study visits and for refills, although generally no medication was taken at those times. In these cases, data were corrected based on notes from the diary or on the study visit forms. Patients who used a medication cassette to organize their protease inhibitor ingestions and who were not willing to stop this practice during the study were excluded, although patients were allowed to take their medication out of the MEMS bottle before the actual ingestion time, if only sporadically. MEMS data were also corrected for these occurrences. The MEMS caps were supplied only for the protease inhibitors. During the study, regular prescriptions were used. Medication was supplied by the patient's local pharmacy and registered according to the regular method at that particular pharmacy. Patients performed the refills themselves. They were explicitly instructed only to use the MEMS bottle and to make notes of deviations. Also, they were told to ingest the medication directly after taking it from the bottle. Patients were aware of the function of the MEMS bottle. Parameters extracted from the Powerview report were percentage of prescribed medication taken, percentage of medication taken on schedule (i.e., within 1 hour before or after the scheduled time), and percentage of days on which the correct number of doses was taken. The calendar plot (overview of number of doses taken each day) and chronology plot (schematic report of dose-timing) were also visually inspected.

Questionnaires

Questionnaires were completed by patients at every planned study visit, i.e., at baseline and at 12- and 24-week follow-up evaluations. For naive patients, an extra questionnaire was supplied at week 4, and an adjusted questionnaire was given at baseline. The questions were completed without supervision of the physician or nurse. The names of antiretroviral agents used, with dosing regimen and food restrictions, were noted on the questionnaire. In addition, patients assessed their adherence based on ingestion of the correct number of doses and pills, the timing of ingestion, and adherence with food restrictions (visual analog scale from 1 [not precise] to 10 [very precise]). After completion, the questionnaires were placed in a sealed envelope and sent directly to the investigator. The mean estimate over the various visits was calculated.

Diaries

Patients were given six 31-day diaries. With respect to measuring adherence, the diary contained the following items: timing and composition of meals (scale 1-5 for amount and fat content, examples were given in the instructions) and specific issues related to MEMS use (participants had to mark refills, device use, and other unscheduled openings). The use of diaries in this study was not intended for measuring adherence regarding ingestion. Patients were asked to update their diaries four times a day. Analysis of adherence with food requirements was done by relating what the patient reported to consider as food requirements in the questionnaire to the data concerning food in the diary and the MEMS ingestion times. We looked at general food patterns over the entire study period and performed a detailed analysis of five randomly chosen days per patient. The interval between medication and food intake and the composition with respect to portion and fat content were compared with the requirements (indinavir, minor or no food intake 2 hours before and 1 hour after ingestion of medication; other regimens, intake of medication within 2 hours of food intake). Thus, patients were categorized into three groups: (I) good (no deviation), (2) moderate (minor deviations, irregularly), and (3) poor (frequent or major deviations) compliance with food restrictions.

Adherence Assessment by Treating Physician and Clinical Nurse Specialist

At each visit, the treating physician and clinical nurse specialist assessed the adherence of the patient in the same way the patient had done in the questionnaire (based on ingestion of correct number of doses and pills, timing of ingestion, and adherence with food restrictions; visual analog scale from I [not precise] to 10 [very precise]). The mean estimate over the various visits was calculated.

Plasma Drug Concentrations

Plasma samples were drawn at each visit, including unplanned visits, to determine protease inhibitor concentrations. Two weeks after start of the follow-up period, an 8-hour pharmacokinetic profile was recorded. The samples were analyzed with a validated high-performance liquid chromatography (HPLC) method, with a lower limit of quantitation of .04 mg/L (32). Random plasma concentrations were compared with the expected concentration at the corresponding time after ingestion, i.e., the interval between dose intake and plasma sampling according to the patient. For a comparison with the individual curve, deviation from the expected concentrations was calculated by determining the median absolute deviation from the expected ratio I (I = equal to concentration after observed ingestion). For a comparison with population curves, predefined limits, known as concentration ratio limits (CORALS), were used. CORALS generally reflect plasma concentrations 2-3 times higher than reference population values after observed ingestion or lower than one third to one sixth of these population values. Concentrations outside these limits have been found to be

predictive for nonadherence (33). For each patient, the percentage of samples outside these limits was determined.

Pill Count and Pharmacy Refill Data

At each visit, patients were asked to bring their antiretroviral medication to the hospital for a pill count. The number of pills in the MEMS bottle and those in the unopened and opened bottles were counted and registered separately. On the second part of the pill count form, the prescriptions given at that particular visit were registered. By combining pill count and prescription data, the percentage of doses taken of the protease inhibitor could be calculated. At the end of follow-up period, the pharmacy refill data for each patient were requested at the local pharmacy. Most pharmacy refill reports already include a calculation of the date on which the stock will be finished. From this refill report, the regularity of the refill pattern could be deduced. Pill count and refill data were combined to calculate the percentage of doses taken. The pill count at baseline reflected the initial stock; the one at the end of follow-up period, the final stock. The in-between refills reported by the local pharmacy reflected new stock. The following formula was used to calculate the percentage taken.

$$\frac{\text{(initial stock+ refilled amount) - final stock}}{\text{number of pills per day * number of days in follow-up}} \text{ X l 00 = \% of pills taken}$$

In-Depth Interview

An in-depth interview by the clinical nurse specialist was held with a subgroup of patients at the end of follow-up period. Patients had to give consent for the interview at the start of the study; patients who either refused or stopped prematurely were replaced. The interview was semi-structured: a list of questions was supplied to give direction to the conversation. The interviews were recorded on tape, and the patients were told that no one besides the investigators would hear the interview and that the interview would be processed anonymously. After transposition, statements regarding the patients' adherence were extracted by two researchers. By combining these statements, patients' adherence was categorized as 1) good (no deviations in ingestion, timing, or food requirements reported), 2) moderate (minor deviations reported), or 3) poor (patient admitting skipping doses, irregular drug intake, or deviations from food requirements).

Viral Load and Resistance Analysis

In addition to standard viral load measurements (cut off, 400 or 500 copies/mL), ultrasensitive measurements (cut-off, 25 copies/mL; Ultrasensitive HIV-1 Cobas Amplicor Monitor Assay, Roche Diagnostics, Pleasantin, CA, U.S.A.) were performed at baseline and at the end of follow-up period. If the viral load at the end of follow-up period was > 1000 copies/mL, genotypic resistance analysis was performed using an automated sequencer (ABI 377, PE Biosystems, Foster City, CA, U.S.A.) and Big-Dye-terminator chemistry (PE Biosystems). Population sequencing of the entire protease gene and of the RT gene from amino acid 1-300 was performed using polymerase chain reaction (PCR) amplified genome fragments derived from plasma virus RNA (34).

Statistics

Statistics were performed with SPSS for Windows (v. 9.0, SPSS Inc., Chicago, IL, U.S.A.). To compare the various methods with MEMS data, nonparametric Spearman correlation coefficients (r) were calculated with their corresponding levels of significance. Spearman r values of < .35 were regarded insufficient, whereas r values of 0.6--0.7 were high enough to consider the method comparable with MEMS data. $p < .05$ was regarded as significant. To compare a combination of methods with MEMS, categoric data of the specific methods were multiplied and then Spearman correlation coefficients were calculated again. Categorization of the data was done to increase the sensitivity of the methods to discriminate poor adherence from moderate or good adherence, although some methods did not result in numerical data. The categories were based on the literature or extracted from the data. The following cut-off points were used: MEMS % taken and % of days correct number of doses taken, I (good adherence): 2:95%, 2 (moderate): 95%-90%, 3 (poor): <90%; MEMS % on schedule, >90%, 90%- 80%, and <80%; self-reported adherence/physician and nurse estimate, >9.0, 9.0-8.0, :S:8.0; pill count/refill data, I: 2:95%, 2: 95%-90%, 3: <90%; plasma concentrations, I: 0% plasma concentrations outside CORALS, 3: >0%; in-depth interviews, categorized based on the statements of the patients concerning their own adherence.

Results

Patients

Twenty-eight patients were included in the study: 21 non-naive, 7 naive. Non-naive patients had a median duration of antiretroviral therapy use of 2.5 years (interquartile range [IQR], 2.0-3.3). Thirteen patients used a twice-daily regimen; the other 15 used a thrice-daily dosing frequency. Indinavir taken alone and the combination of ritonavir + saquinavir were the most frequently used protease inhibitors (12 and 10 patients, respectively). All patients but 1 were male, and all but 1 white; most (19 of 28) were homosexual. Twenty-six patients completed

follow-up week 12, and 24 completed follow-up week 24. Four of the 28 patients stopped prematurely (before follow-up week 24) because of protease inhibitor toxicity (1 naive, 2 non-naive patients) or patient request (I non-naive patient). Two of these patients stopped therapy before follow-up week 4 and were not included in the analyses.

Medication Event Monitoring System

According to the corrected MEMS reports (corrected for notes in diary, during visits, etc.), the median percentage of prescribed doses taken (% taken) was 98.9% (range, 10.1%-102.0%); the percentage of days on which the correct number of doses was taken (% correct days) was 94.6% (range, 4.1%-99.5%), and the percentage of doses taken on schedule (% on schedule, within 1 hour before or after the scheduled time) was 91.1% (range, 6.4%-100.3%). Twenty-five percent of the patients took fewer than 95% of all doses; 50% of the patients took the correct number of doses fewer than 95% of the days, and two thirds of the patients took fewer than 95% of the doses on time (Fig. 1). Figure 2 shows an example of perfect and imperfect compliance as depicted in MEMS chronology plots.

FIG 1. Distribution of adherence over the study population. Twenty-seven percent of the patients took fewer than 95% of all doses; 54% took the correct number of doses dor fewer than 95% of the days, and 69% took fewer than 95% of the doses on time (within 1 hour before or after the scheduled time)

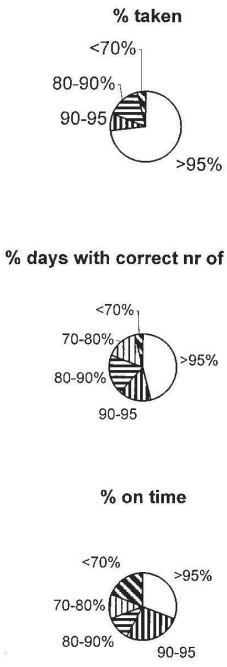
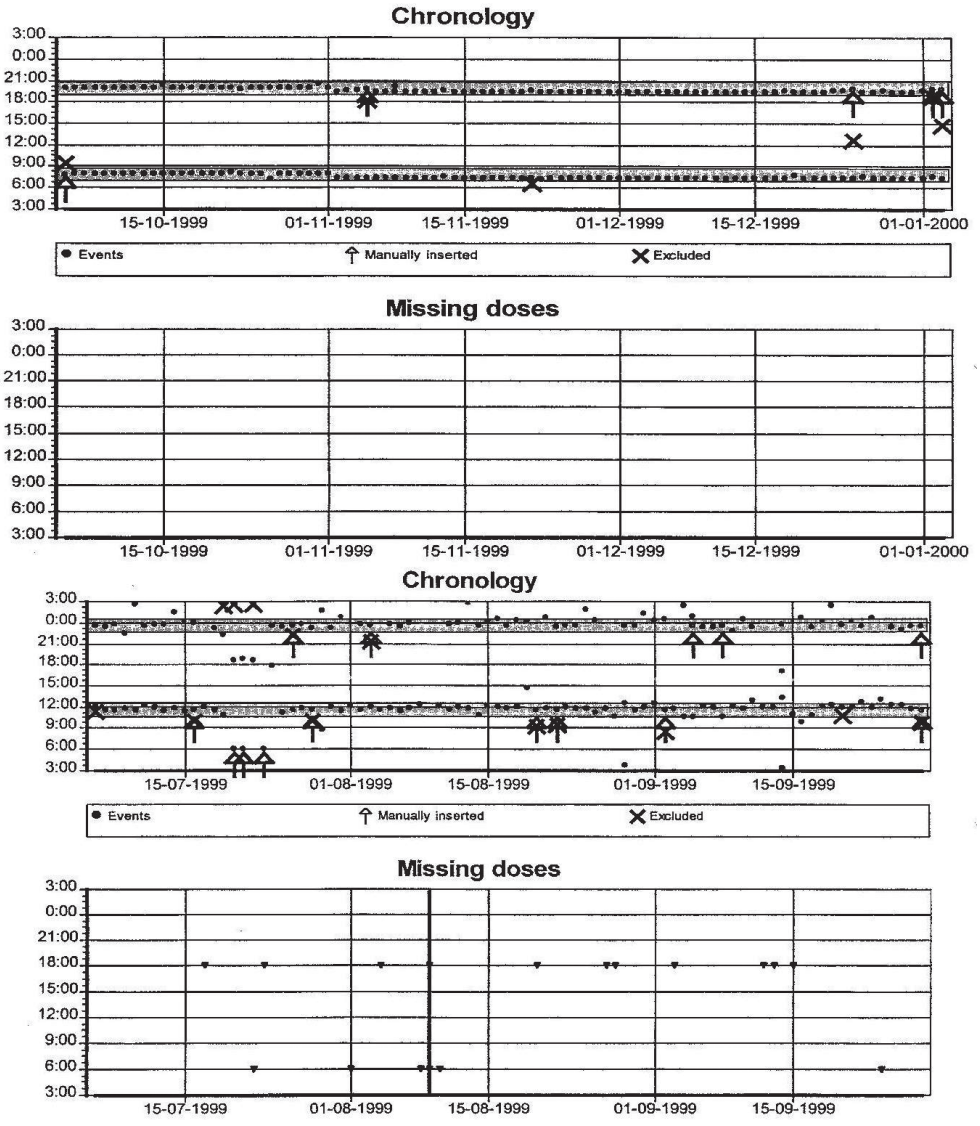


FIG 2. Chronology plot and missing doses of 2 patients on a twice-daily schedule. The upper two panels are form a patient with perfect adherence (taken, 101%; on schedule, 100%; days with correct number of doses, 99%). The lower two panel are form a patient with imperfect adherence (taken, 92%; on schedule, 77%; days with correct number of doses, 81%). Time is depicted on the Y axis; the date, on the X axis. Manually inserted and excluded events are based on notes in the diaries and visit forms. The grey horizontal bars represent the permitted time interval of the scheduled doses (± 1 hour).



Questionnaires

From the questionnaire, the patient's dosing regimen was extracted and used to analyze the MEMS data. In 4 cases (15%), food restrictions, according to the patients, were different than advised. Median patients' selfreported adherence (average of several measurements per patient) was 8.6 on a scale from 1 to l 0 (IQR, 8.0- 9.3). The lowest mark given was 5.7.

Diaries

Of the 26 patients, l patient did not take enough doses to analyze his accompanying food pattern, 1 did not sufficiently complete the food part of the diary, and 3 patients reported not to be restricted to food requirements. Of the other 21 patients, 9 (43%) complied well with the food restrictions, 4 (19%) complied moderately, and 8 (38%) poorly. Of the evaluative patients, 11 had to take their medication on (nearly) empty stomach, whereas 10 patients had to take their medication with (fat) food. Adherence with food restrictions in the first group was comparable with that in the second group (p = .495, Mann-Whitney U test). Adherence Assessment by Treating Physician and Clinical Nurse Specialist The median adherence as reported by the nurse was 8.8 (IQR, 7.9-9.3) and by the physician 9.0 (IQR, 8.3**-** 9.6). The nurses did not give anyone a score below 6.0 compared with the 7.1low score given by the physicians.

Adherence Assessment by Treating Physician and Clinical Nurse Specialist

The median adherence as reported by the nurse was 8.8 (IQR, 7.9-9.3) and by the physician 9.0 (IQR, 8.3- 9.6). The nurses did not give anyone a score below 6.0 compared with the 7.1low score given by the physicians.

Plasma Drug Concentrations

The mean number of plasma samples per patient was 5.5 (SD, 1.9). The number of evaluative samples was 143. Deviations in protease inhibitor concentrations compared with intrapatient reference values recorded under supervised ingestion ranged from 10% to 167%, with a median deviation of 36%. Using CORALS, the percentage of abnormal plasma concentrations among patients ranged from 0% to 88% (median, 0%), with 6 patients (23%) having one or more abnormal plasma concentrations. Two patients (8%) had one or more plasma concentrations below the lower limit of quantitation.

Pill Count and Pharmacy Refill Data

When pill count and pharmacy refill data were combined, the median percentage of pills taken was 100% (range, 71%-132%). Thirty percent of the patients were regarded as overadherent. In a small pilot study of 5 patients, a detailed analysis of the pill count and pharmacy refill data was performed. Several problems with these methods were encountered. First, there were strong indications that the pill count data had been manipulated, as has also been found

by others, by the patient with the poorest compliance according to the MEMS data (35). For example, MEMS openings were recorded shortly before visits, although no medication had been ingested at that time as was shown by undetectable plasma levels. Also, prescriptions were refilled shortly before visits, although the pill count forms indicated that this patient had had insufficient stock much earlier. Most likely the stock that the patient was assumed to have at home was brought to the hospital, and the excess was left at home. Nevertheless, it was difficult to determine the patient's actual behavior from the pill count and refill data, and the combination provides an enormous overestimation of the adherence according to MEMS (101 [pill count/refill] vs. 10% [MEMS] taken). Problems encountered with other patients from the pilot study were mixing of stocks among partners who used the same medication, inaccurate reporting of prescriptions by nurses, patients having old prescriptions at home, patients forgetting to bring the medication to the hospital, either purposely or accidentally.

In-Depth Interviews

The clinical nurse specialist held an in-depth interview with 14 of the 26 patients. One patient (7%) was categorized as having poor compliance; 6 (43%) were categorized as having moderate compliance, and the other 7 (50%) as having good compliance.

Correlation Between Different Methods

Table 1 shows all individual results as numeric values, if available, and categorized as well, as described in the Methods section. Table 2 lists the Spearman correlation coefficients (p) of the MEMS data compared with the other methods. According to the plasma concentration data obtained from the CORALS listed in the tables, protease inhibitor plasma concentrations deviated more from intrapatient reference values, recorded under supervised ingestion, in patients who were less adherent according to the MEMS data (% taken: Spearman p, -.426; $p < .05$; % on time: Spearman p, -.527; $p < .01$). In addition to assessing adherence in itself, plasma concentrations added relevant information to MEMS in cases where the MEMS data reported ingestion but plasma levels were undetectable or vice versa, and they were an objective check for the accuracy of the MEMS data. After adherence with food had been categorized as (1) good (no violation of food restrictions), (2) moderate (minor violations), or (3) poor (repetitive and more serious violations), the correlation with the categorized MEMS data was as follows: MEMS % taken: Spearman $p = .559$, $p < .01$; MEMS %on time: Spearman $p = .673$, $p < .01$. Methods that showed relatively high and significant correlations with the MEMS results were patients' self reported estimate of adherence in the anonymous questionnaire (p, .73; $p < .001$), plasma levels outside predefined ranges (p, .77; $p < .001$), and, to a lesser extent, estimation of adherence by the clinical nurse specialist (p, .57; $p < .01$). A combination of these methods did not increase the relation with the MEMS results (p, .57; $p < .01$, to p, .72; $p < .001$). The physician's estimate of adherence correlated less well (p, .43; $p < .05$), and the combination of pill count and pharmacy refill data only correlated

significantly with the MEMS data when overadherence was judged as poor adherence (categorized on the basis of the absolute deviation from 100%; p, .43; p < .05). In a subgroup, in-depth interviews with the clinical nurse specialist resulted in a high correlation with the MEMS results (p, .78; p < .01).

Table 1. Comparison of adherence measured by various methods (adherence category numbers in parentheses)

Patient	Protease inhibitor	BID/TID	Non-naive/ naive	MEMS, % taken	MEMS, % days	MEMS, % on time	Food (diary)	Questionnaire (self-report)	Physician estimate	HIV nurse estimate	Pill count + refills (%)	Plasma level[c]	Interview
1[a]	IDV	3	NN	97 (1)	87 (3)	80 (2)	2	9.0 (2)	10.0 (1)	9.0 (2)	ND[d]	0 (1)	ND
2	IDV	3	NN	100 (1)	99 (1)	92 (1)	1	7.0 (3)	9.0 (2)	8.6 (2)	100 (1)	0 (1)	ND
3	NFV + SQV	2	NN	86 (3)	74 (3)	78 (3)	3	8.0 (3)	8.7 (2)	8.3 (2)	86 (3)	50 (3)	ND
4[a,c]	NFV	2	NN	94 (2)	87 (3)	90 (2)	—	9.0 (2)	8.5 (2)	8.5 (2)	ND[d]	0 (1)	ND
5	RTV + SQV	2	NN	99 (1)	97 (1)	95 (1)	1	9.3 (1)	10.0 (1)	9.3 (1)	98 (1)	0 (1)	ND
6	IDV	3	NN	98 (1)	94 (2)	93 (1)	1	8.3 (2)	10.0 (1)	9.3 (1)	100 91)	0 (1)	1
7[c]	RTV + SQV	2	NN	99 (1)	99 (1)	99 (1)	—	9.3 (1)	9.0 (2)	10.0 (1)	99 (1)	0 (1)	1
8[c]	RTV + SQV	2	NN	10 (3)	4 (3)	6 (3)	—	8.0 (3)	7.9 (3)	7.7 (3)	101 (1)	88 (3)	ND
9	RTV + SQV	2	NN	88 (3)	76 (3)	67 (3)	3	7.7 (3)	8.5 (2)	8.0 (3)	126 (1)	50 (3)	3
10	RTV + SQV	2	NN	100 (1)	95 (1)	93 (1)	3	9.0 (2)	8.3 (2)	8.2 (2)	100 (1)	25 (3)	1
11	IDV	3	NN	99 (1)	88 (3)	83 (2)	1	8.0 (3)	8.3 (2)	8.8 (2)	71 (3)	0 (1)	ND
12	IDV	3	NN	98 (1)	95 (1)	78 (3)	3	5.7 (3)	8.8 (2)	7.4 (3)	98 (1)	0 (1)	2
13	IDV	3	NN	97 (1)	84 (3)	81 (2)	2	8.0 (3)	7.6 (3)	9.3 (1)	100 (1)	0 (1)	2
14	IDV	3	NN	99 (1)	98 (1)	87 (2)	2	9.0 (2)	9.8 (1)	9.4 (1)	ND[d]	0 (1)	2
15[c]	RTV + SQV	2	NN	83 (3)	71 (3)	31 (3)	—	7.7 (3)	7.1 (3)	6.0 (3)	121 (1)	14 (3)	ND[b]
16	SQV	3	NN	102 (1)	91 (2)	69 (3)	3	9.0 (2)	9.1 (1)	8.7 (2)	93 (2)	0 (1)	ND
17	RTV + SQV	2	NN	101 (1)	98 (1)	100 (1)	2	10.0 (1)	10.0 (1)	9.5 (1)	87 (3)	0 (1)	1
18[c]	RTV + SQV	2	NN	99 (1)	97 (1)	98 (1)	—	10.0 (1)	9.2 (1)	9.3 (1)	101 (1)	0 (1)	ND
19	IDV	3	NN	100 (1)	97 (1)	97 (1)	1	10.0 (1)	7.7 (3)	7.7 (3)	101 (1)	0 (1)	1
20	IDV	3	NN	99 (1)	97 (1)	92 (1)	3	10.0 (1)	9.3 (1)	10.0 (1)	100 (1)	0 (1)	2
21	RTV + IDV	2	NN	Stopped <4 weeks	x	x	x	x	x	x	x	x	x
22	IDV	3	NA	100 (1)	97 (1)	97 (1)	1	9.8 (1)	9.6 (1)	9.3 (1)	95 (1)	0 (1)	2
23	NFV	2	NA	99 (1)	98 (1)	96 (1)	1	8.5 (2)	9.1 (1)	9.8 (1)	132 (1)	0 (1)	1
24	IDV	3	NA	94 (2)	81 (3)	90 (2)	3	8.8 (2)	9.3 (1)	9.5 (1)	80 (3)	0 (1)	2
25	RTV + SQV	2	NA	100 (1)	100 (1)	93 (1)	1	8.8 (2)	8.2 (2)	7.5 (3)	126 (1)	0 (1)	ND
26	RTV + SQV	2	NA	99 (1)	98 (1)	97 (1)	1	9.0 (2)	9.6 (1)	8.8 (2)	100 (1)	0 (1)	1
27	NFV	2	NA	88 (3)	73 (3)	62 (3)	3	7.7 (3)	8.5 (2)	7.2 (3)	92 (2)	50 (3)	ND[b]
28	IDV	3	NA	Stopped <4 weeks	x	x	x	x	x	x	x	x	x

MEMS % taken: percentage of doses taken according to MEMS. MEMS % days: percentage of days on which the correct number of doses was taken. MEMS % on time: percentage of doses taken within 1 hour before or after the scheduled ingestion time.

Adherence categories: 1 = good adherence; 2 = moderate adherence; 3 = poor adherence.

[a] Patient 1 stopped medication between 12 and 24 weeks of follow-up observation; patient 4 withdrew consent at 12 weeks of follow-up observation.

[b] Patient 15 eventually refused cooperation, patient 27 was too depressed at the time of the interview.

[c] Patients 4, 7, and 18 reported to have no food restrictions, patient 8 had not enough ingestions to enable analysis of his food pattern, and the diary registration of patient 15 was too poor to enable analysis of his food pattern.

[d] No refill data available.

[e] Percentage of plasma concentration outside CORALS (concentration ratio limits).

IDV, indinavir; NFV, nelfinavir; RTR, ritonavir; SQV, saquinavir; NN, non-naive; NA, naive; ND, not done.

Table 2. Correlations between MEMS results and other methods to measure adherence

Method	MEMS (% taken)		MEMS (% taken on time)	
	Spearman rho numeric	Ordinal	Spearman rho numeric	ordinal
Questionnaire (self-report)	0.552[c]	0.538[c]	0.721[d]	0.731[d]
Plasma concentrations <> CORALS	−0.568[c]	0.768[d]	−0.593[c]	0.543[c]
Nurse estimate	0.287	0.472[b]	0.567[c]	0.530[c]
Physician estimate	0.273	0.426[b]	0.429[b]	0.387
Pill count/refill data				
Percentage	−0.074	0.284	0.027	0.382
Deviation from 100%	−0.146	0.414	−0.229	0.430[b]
In-depth interview[a]	x	0.550*	x	0.778[c]
Combination of methods				
Q × PI × N	x	0.618[c]	x	0.684[d]
Q × PI	x	0.642[d]	x	0.721[d]
Q × N	x	0.569[c]	x	0.705[d]
PI × N	x	0.610[b]	x	0.586[d]

For the ordinal results the categorization as listed in Table 1 is used. Additionally, the pill count/refill data are calculated as the absolute deviation from 100% and categorized by dividing the deviations into 3 equal groups.

[a] In-depth interviews were held in 14 of the 26 patients. CORALS, concentration ratio limits; Q, questionnaire; PI, plasma concentrations; N, nurse estimate. Combination of methods was calculated by multiplying the category numbers.

[b] $p < .05$.

[c] $p < .01$.

[d] $p < .001$.

Acceptance of Study Methods

The following comments on the study methods were made: the MEMS vial was too large to handle (200-mL bottles were used because of the large number of pills); having only one vial was inconvenient, and not being able to use a medication cassette was problematic. Keeping the diary was problematic, especially adding entries four times a day. Specific items with respect to MEMS were scored well, but items that had to be scored more often, such as the amount and fat content of food, were more difficult for some patients. As a result, several patients filled in all items once daily. The pill count was accepted well, although in practice, patients sometimes did not bring their pills with them.

Viral Load and Resistance Analysis

For 23 of the 26 patients, ultrasensitive viral load data (cut off 25 copies/mL) were available at the end of follow- up period. In 2 patients, the viral load was detectable. One of these patients (non-naive, number 14 in the table) had 1290 copies/ml. According to MEMS, this patient took 99% of the doses, and 87% were taken or time. Deviations in timing were small but occurred regularly. However, the viral load increase may also be explained by a relatively

low indinavir exposure, which was seen even after observed ingestion. Resistance analysis showed resistance to zidovudine and abacavir although zidovudine was only used before the study. A second non-naive patient (number 8 in the table) had 3635 copies/mL; this patient had the poorest adherence (10% taken according to MEMS and probably even less according to undetectable plasma concentrations after MEMS opening). This patient's virus was resistant for zidovudine, abacavir, and lamivudine but not for pro tease inhibitors. He had used zidovudine and lamivudine during the study and long before. The viral loads of the other 21 patients were undetectable (<25 copies/mL) although 5 patients (3 non-naive and 2 naive) had taken fewer than 95% of their doses (the lowest % taken was 83%) and 8 (7 non-naive, 1 naive) had taken fewer than 90% of their doses on time (31 %-83%) according to MEMS.

Discussion

In this study, diary-corrected MEMS data gave a detailed and accurate insight into adherence patterns of HIV -infected patients using protease inhibitor containing antiretroviral therapy. Patients' self-report and therapeutic drug monitoring were significantly and highly correlated with adherence according to MEMS, as was the case for the in-depth interviews held by the clinical nurse specialist.

Medication Event Monitoring System

The MEMS caps were only supplied for the protease inhibitors because this class of medication has the most stringent requirements with respect to dose frequency, timing, and food intake. Nucleoside reverse transcriptase inhibitors are less vulnerable, and although nonnucleoside analogs are at high risk for development of resistance, their long elimination half-lives make them less prone to nonadherence. Because of the different appearance of the MEMS bottle and cap and the refill necessity at home, telling the patients about the function of the MEMS caps could not be avoided. For this reason, and others, a follow-up period of 24 weeks was chosen: we assumed it to be unlikely for patients to mimic perfect adherence for a long period (36,37). By using MEMS caps, various patterns of adherence were seen among different patients. Specific problems such as missing afternoon doses, variation in the timing of the bedtime dose, and changed timing during weekends were seen. Such detailed information will enable a targeted intervention to improve adherence (38).

Self-Report and In-Depth Interview

Self-report is often regarded as a method that overestimates adherence (13,29,30). However, an estimate of poor adherence by a patient should be regarded seriously (21); several studies have demonstrated an association between self-report and viral outcome (10, 12,23,29). When patients were asked anonymously about their adherence in our study, their estimate

corresponded relatively well with the results from the MEMS caps. Particularly, patients who repeatedly gave themselves an 8 or lower on a visual analog scale from 1 to 10 appeared to be imperfectly adherent, which proves that it is useful to ask patients about their adherence. This request may be done in writing by a third party, i.e., not by the treating physician, but, for example, by a pharmacist. The physician too often gave a wrong estimate of the patient's adherence to turn his or her judgment into a useful method, as has been shown before (1,28). The nurse was better able to judge the patient's adherence. When the nurse held an in-depth interview with the patient and remarks with respect to adherence were extracted to categorize the patients' adherence, a rather strong correlation with adherence according to MEMS was found. This finding could mean that the approachability of and the close relationship with the nurse, as mentioned by patients in their interviews, reveals detailed and reliable information on adherence.

Therapeutic Drug Monitoring

When looking at plasma concentrations drawn after unobserved ingestion, the patients with larger deviations from their individual pharmacokinetic profile after observed ingestion appeared to be less adherent according to MEMS. Additionally, we saw a strong relation between having plasma concentrations outside predefined population concentration limits assessed after observed ingestion (i.e., CORALS) (33) and nonadherence, especially with respect to the number of doses taken. Five of the 6 patients with one or more plasma concentrations outside the CORALS took less than 90% of their medication according to MEMS, and thus were detected by repeated therapeutic drug monitoring. These 5 patients were the only ones who were categorized as having poor compliance (MEMS, <90% taken, category 3). A disadvantage of plasma sampling is that patients could mimic perfect adherence by taking doses shortly before a visit (37 ,39). Although this still may cause abnormal plasma concentrations, for example, because no auto induction has occurred during the days of nonadherence, dose-timing is wrong, or extra doses are taken to compensate for missed doses (40), there is a chance that nonadherence will not be detected. Nevertheless, the results of the current study show that when patients knew that their plasma concentrations were determined, deviating plasma concentrations were found that correlated with imperfect adherence according to MEMS. This result agrees with the observation that the MEMS reports did not show an improvement in adherence shortly before study visits. The absence of this "toothbrush effect" has been described before (36).

Pharmacy Refill Data and Pill Count

Only a rough estimation of the refill pattern could be extracted from the pharmacy refill data (3). Most patients in this study were in the non-naive group and may have had a stock of pills at home. The number of pills in this stock is unknown if no pill count is performed, and thus the exact situation cannot be assessed with refill data alone (35). Only a combination of pill count

and pharmacy refill data could give an estimation of adherence in this study. Nevertheless, even by combining pill count and pharmacy refill data, a percentage of adherence could be calculated that may appear rather good, but that, when reviewing the stocks at several time points, shows overuse or underuse, indicating that the overall calculation is actually inaccurate. This finding agrees with the poor correlation between adherence according to MEMS and adherence according to pill count and refill data in the current study and with the limitations of the methods recognized by others (3,4,20,31,40,41).

Diaries

Analysis of adherence with food restrictions registered in the diaries was based on the food requirements reported by the patient in the questionnaire because instructions may have been incorrect. From the analysis of food patterns in the diaries, it became clear that violation of the requirements occurred for the drugs that had to be taken with food (fat) and those that had to be taken on a nearly empty stomach. It was found that keeping a diary, especially when it has to be completed several times per day, is problematic for patients and therefore cannot be applied to larger patient groups. Monitoring adherence with food restrictions is difficult to perform. One approach is to have the clinical nurse specialist discuss this issue with the patient.

Adherence Rate

Our patient group may seem highly adherent compared with the adherence rates found by others (1,3,13, 29,36), but we suspect that 11%-16% of the patients who refused to participate would have been nonadherent; in other words, we did not select an extremely adherent patient group. A more likely explanation for the relatively high adherence may be found in the inclusion criteria: only patients without communication problems were included, and in the majority of the participants, their therapy thus far had been effective-one of the causes of good efficacy may be good adherence.

Viral Load

From the viral load data in this study, it is noted that virologic failure occurred only in the patient with the poorest compliance during the 24-week study period. Other patients reached or kept undetectable viral loads even though adherence was sometimes lower than the threshold necessary for virologic suppression as suggested by others (1,8,12,14). However, the viral load results from this study are only indicative because the study group is heterogeneous, with respect to duration of therapy, kind of pretreatment, and pretreatment viral load. The latter was not always known and may be important for the grade of adherence needed to reach and maintain viral suppression. Nevertheless, patients with lower adherence are at risk for virologic failure and possible development of virologic resistance (1-14),

although no thresholds can be determined from this study, and exact relations are not yet fully understood.

In conclusion, the MEMS data give a detailed insight into patients' adherence patterns. Notes about special events occurring in relation to MEMS caps, such as visit openings, refills at home, or device use, should be used to correct the MEMS data to improve their accuracy (42). Therapeutic drug monitoring can be used as a direct measure to objectify the MEMS results, whereas plasma concentrations outside predefined limits are highly correlated with the MEMS results and thus can be used to detect nonadherent patients. Another method that showed a highly significant correlation with the MEMS results was the patients' self-reported estimate of adherence in an anonymous questionnaire and, to a lesser extent, the estimation of adherence by a clinical nurse specialist. In a random subgroup, in-depth interviews with the clinical nurse specialist resulted in a high correlation with the MEMS results, which could mean that by allowing patients talk to a person they trust and who is easily accessible may help to reveal nonadherence. Thus, therapeutic drug monitoring, patients' self-report, and clinical nurse specialist assessment of adherence after an in-depth interview with the patient can be used to detect patients who have a problem with adherence, and MEMS can be used in problematic patient groups in whom interventions are planned because MEMS give a real insight into adherence patterns. In addition to MEMS, diaries should be used, plasma concentrations should be measured, and patients should always be asked about their adherence, preferably by a clinical nurse specialist or a third party, such as a pharmacist.

Acknowledgments

The authors thank clinical nurse specialists: Arnold Coors, Yvonne Vincken, and Karin Grintjes for their help in realizing this study. The authors also thank the HIV internists of the UMC Nijmegen and Rijnstate Hospital Arnhem for their adherence judgments, and the technicians of the Department of Clinical Pharmacy for measuring the plasma drug concentrations. The authors thank Aardex for providing the intermediate Powerview version. Additionally, the authors thank Roche Diagnostics for the supply of materials for the ultrasensitive viral load test, and clinical psychologist Jan Vercoulen for his advice on the questionnaires and diaries. The authors also thank Marijcke Schoots van de Siepkamp for transposition of the in-depth interviews.

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Frontiers in Public Health 2015, 3; article 139

www.frontiersin.org

CHAPTER 6

Electronic monitoring-informed counselling to improve adherence to combination anti-retroviral therapy and virologic treatment outcomes: a meta-analysis

Abstract

Background: Adherence to combination antiretroviral therapy (cART) for HIV infection is a primary determinant of treatment success, but is often suboptimal. Previous studies have suggested that electronic medication monitoring-informed counselling is among the most effective adherence intervention components. Our objective was to review available evidence about the effectiveness of monitoring-informed counselling and to aggregate findings into quantitative estimates of the effect of such intervention on medication adherence and virologic treatment outcomes.

Methods: We searched PubMed for papers reporting on randomized controlled trials (RCTs) comparing intervention groups receiving monitoring-informed counselling as one of the intervention components versus control groups not receiving such counselling for their effect on medication adherence and viral load concentrations. The standardized mean difference (SMD) in adherence and the odds ratio (OR) of undetectable HIV RNA in intervention versus control groups were the common effect sizes. Random-effect models with inverse variance weights were used to aggregate findings into pooled effect estimates with 95% confidence limits.

Results: A total of 13 studies were included. Adherence was significantly higher in intervention groups than in control groups (SMD 0.51, 95% CI 0.31 to 0.71). Patients in intervention groups were significantly more likely to have undetectable HIV RNA concentrations than patients in control groups (OR 1.35, 95% CI 1.12 to 1.63). However, in studies in which monitoring-informed counselling was the only intervention component, the difference in adherence and virologic response between intervention and control groups was not statistically significant.

Conclusion: Electronic monitoring-informed counselling improved adherence and virologic response compared with control groups not receiving such counselling in studies in which it was one out of multiple intervention components, but not in studies where it was the only intervention component.

Keywords: adherence, compliance, HIV infection, antiretroviral therapy, meta-analysis .

Introduction

Adherence to combination antiretroviral therapy (cART) is a primary determinant of antiretroviral treatment success. Sufficiently high levels of adherence to cART are necessary to achieve and sustain viral suppression and to prevent disease progression and death (1-3). Yet, many HIV infected patients do not succeed in achieving or maintaining adequately high levels of adherence to cART (4). Adherence to cART is potentially amenable to intervention. Since the advent of cART, numerous interventions aimed at enhancing adherence to cART have been developed and evaluated. Several systematic reviews have reviewed and synthesized the effectiveness of such interventions to improve adherence and virologic treatment outcomes (5-8). Overall, these reviews have shown that various types of interventions can significantly increase adherence, but effects vary considerably across studies and most types of interventions have also been found not to produce significant effects in other studies.

An appreciable number of adherence enhancing intervention studies have provided patients and/or their health care providers with objective information about the patients' medication taking behavior as one of the intervention components. In these studies, medication adherence is typically measured using an electronic medication monitoring device. Electronic medication monitoring devices register the time and date of each opening of the device which is assumed to represent medication ingestion. The date and time of openings of the device over a long-time period can be shown to patients in the form of a graphical display. Such graphical feedback could make medication taking behavior and the occurrence of non-adherence more concrete or real to the patient who may be unaware of suboptimal adherence. Personalized feedback based on the pattern of medication use could open discussions between patients and health care providers about adherence barriers and potential solutions to deal with these.

Research conducted across medical conditions have suggested that feedback on adherence performance and the accompanying counselling informed by recent adherence performance are among the intervention components that improve adherence most consistently (9-11). However, studies investigating the effectiveness of such monitoring-informed counselling among patients with chronic HIV infection have yielded inconsistent results. Some studies (12) have found significantly improved adherence and virologic treatment outcomes whereas others have found no beneficial effects (13).

Our objective was to review available evidence about the effectiveness of monitoring-informed counselling among patients who are prescribed cART for a chronic HIV infection and to aggregate findings into quantitative estimates of the effect of such intervention on medication adherence and virologic treatment outcomes. Moreover, we aim to identify study design features that are associated with stronger intervention effects.

Materials and methods

Literature search

We searched PubMed for papers published from August 1996 to October 2014 using the following strategy:

((“intervention” [tiab]) OR (“intervention” [tw])) AND (HAART[title/abstract] OR CART[title/abstract] OR ART[title/abstract] OR ARV[title/abstract] OR ARVs[title/abstract] OR antiretroviral[title/abstract] OR anti-retroviral[title/abstract] OR anti-viral[title/abstract] OR antiviral[title/abstract] OR “Antiretroviral Therapy, Highly Active”[Mesh] OR “Anti-Retroviral Agents”[Mesh])) OR ((HIV Infections[MeSH] OR HIV[MeSH] OR hiv[title/abstract] OR hiv-1[title/abstract] OR hiv-2*[title/abstract] OR hiv1[title/abstract] OR hiv2[title/abstract] OR hiv infect*[title/abstract] OR human immunodeficiency virus[title/abstract] OR human immune deficiency virus[title/abstract] OR human immuno-deficiency virus[title/abstract] OR human immune-deficiency virus[title/abstract] OR ((human immun*) AND (deficiency virus[title/abstract])) OR acquired immunodeficiency syndromes[title/abstract] OR acquired immune deficiency syndrome[title/abstract] OR acquired immuno-deficiency syndrome[title/abstract] OR acquired immune-deficiency syndrome[title/abstract] OR ((acquired immun*) AND (deficiency syndrome[title/abstract])) or “sexually transmitted diseases, viral”[mh]) OR HIV[title/abstract] OR HIV/AIDS[title/abstract] OR HIV-infected[title/abstract] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title])) AND (adhere*[tiab] OR complian*[tiab] OR adhere*[tw] OR complian*[tw] OR Patient Compliance[MeSH] OR Medication Adherence[MeSH])) AND (“1996/01/01”[PDat] : “2014/12/31”[PDat])))

The reference lists of the papers retrieved were reviewed for additional relevant publications. Additionally we searched abstracts from the International AIDS conference (years 2006, 2008, 2010, 2012, 2014), the IAS Conference on HIV Pathogenesis, Treatment and Prevention (years 2007, 2009, 2011, 2013), the HIV Drug Therapy Glasgow Meeting (years 2008, 2010, 2012, 2014) and the International Conference on HIV Treatment and Prevention Adherence (years 2010 to 2014).

Eligible studies met the following criteria 1) randomized controlled (cross-over) trial 2) comparing monitoring-informed counselling as one of the intervention components versus not receiving such counselling. Intervention groups could thus consist of multi-component and single component interventions 3) outcomes are medication adherence and/or viral load concentrations 4) participants are HIV infected persons prescribed cART for a chronic HIV infection. We included English language papers only.

Data extraction

We extracted the following information from each study: name of the first author, year of publication, sample size, whether patients were initiating, restarting or switching a cART regimen or were already on ART, whether the intervention was only administered to patients with low pre-intervention adherence levels (yes/no), or if patients were triaged to different levels of intervention intensity depending on their adherence level (yes/no), the percentage of patients with undetectable viral loads at baseline, duration of the intervention period (weeks), number of intervention sessions and intervention components. The categorization of intervention components was adapted from two previous systematic reviews of antiretroviral adherence interventions (6, 8). Intervention components additional to 1) monitoring-informed counselling were coded as: 2) didactic provision of information about HIV, cART and adherence, 3) behavioral, cognitive behavioral, or motivational counselling, 4) provision of reminder devices, 5) social support enlistment, 6) depression screening, treatment or referral, 7) financial incentives for good adherence, and 8) substance use screening, treatment or referral. We calculated the number of intervention components per study. Both authors independently extracted information and discrepancies were resolved through discussion. When more than one type of intervention was tested, data from each arm of the intervention were considered as separate data points.

Statistical analysis

We defined adherence as the percentage of prescribed doses of cART taken. We used the standardized mean difference (SMD) as the common effect size to express the difference in adherence between intervention and control groups. If studies did not provide the SMD, we contacted authors to get additional data. If no additional data were available, we calculated the SMD from correlation coefficients, means and standard deviations, odds ratios, t-, x^2-, or F-statistics, contingency table data or exact P values (14). When studies reported an insignificant effect on adherence without data we assigned a value to the SMD of 0.01. Values of the SMD of 0.2 to 0.49, 0.5 to 0.79, and ≥0.8 can be interpreted as small, medium and large effects, respectively (15).

We used the odds ratio (OR) as the common effect size to express the difference in the percentage of patients with an undetectable viral load in intervention versus control groups. When studies reported an insignificant effect of the intervention on viral load without data, we assumed an OR of 1.01.Random effect models with inverse variance weights were used to aggregate individual SMDs and ORs into pooled effect estimates with 95% confidence limits (CI) using Review Manager 5.3.

We compared pooled effect estimates of adherence and undetectable viral loads between studies in which monitoring-informed counselling was the only intervention component

with studies in which monitoring-informed counselling was one out of multiple intervention components. We conducted a sensitivity analysis to examine potential bias resulting from over-representation of studies with more than one intervention arm. We examined the extent to which results would change when studies with more than one intervention arm were excluded from the analysis or if only a single intervention arm was included.

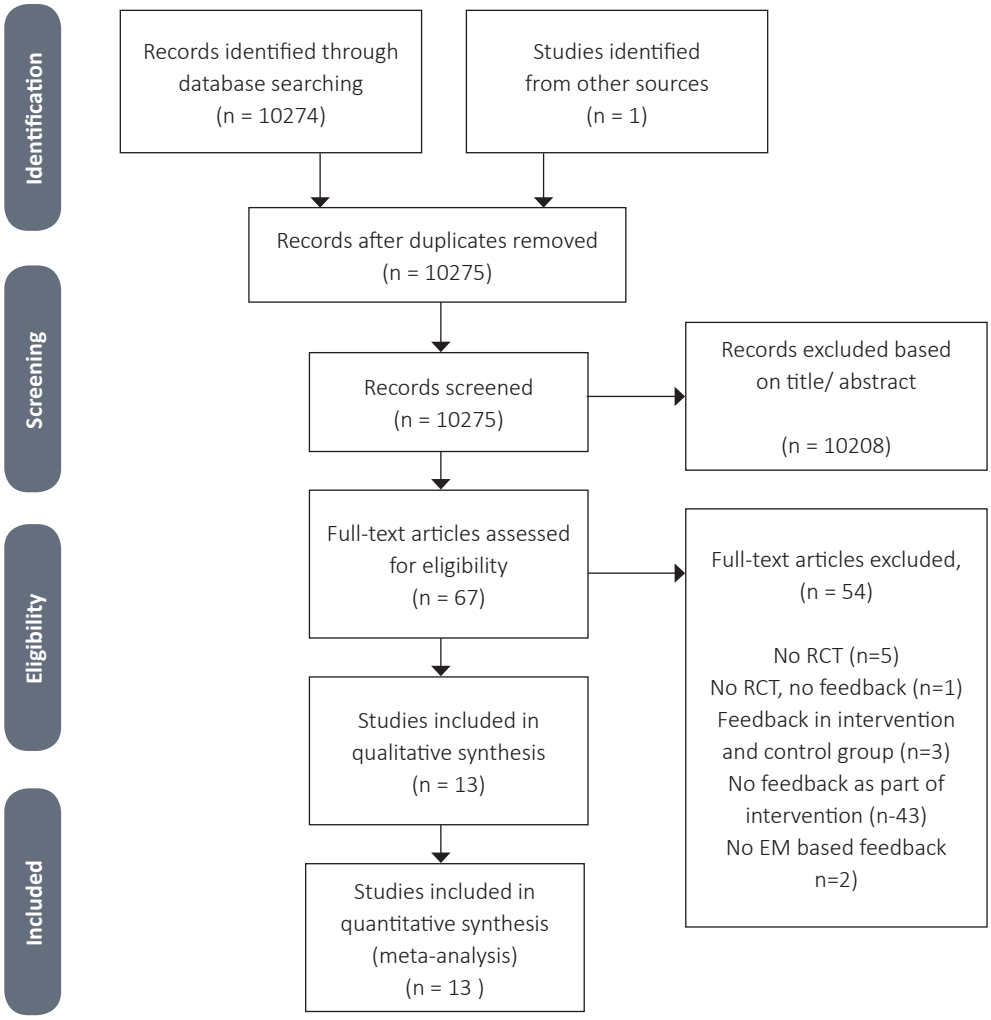
We examined whether variation in effect sizes of adherence and viral load were significantly associated with study design features. We investigated the effect of the following study design features: whether patients were initiating, restarting or switching an cART regimen (yes/no) or were already on ART, the percentage of patients with undetectable viral loads at baseline, whether the intervention was only administered to patients with low pre-intervention adherence levels (yes/no), or if patients were triaged to different levels of intervention intensity based on their adherence level (yes/no), duration of the intervention period (weeks), number of intervention contacts, whether intervention components administered to the intervention group included the following: didactic provision of information about HIV, cART and adherence (yes/no), behavioral, cognitive behavioral, or motivational counselling (yes/no), provision of reminder devices (yes/no), social support enlistment (yes/no), depression screening/treatment/referral (yes/no), financial incentives for good adherence (yes/no), and substance use screening/treatment/referral (yes/no).

Subgroup analysis were performed by grouping effect sizes for adherence and viral load by study design feature and assessing heterogeneity between groups using the between-group Q statistic (Q-between) within a mixed effects model using the method of moments estimation. These analyses were conducted using the SPSS macro's MetaF and MetaReg from Lipsey and Wilson (14, 16). We performed meta-regression analysis with method of moment estimation to assess the relationship of the number of intervention components per study with the SMD in adherence and the log odds ratio of undetectable HIV RNA using Comprehensive Meta-Analysis version 2. We examined the presence of publication bias by the visual inspection of funnel plot symmetry and formally with Egger's regression intercept.

Results

Our literature search yielded a total of 10274 potentially relevant articles. We found an additional article from another data source, resulting in a total of 10275 potentially relevant articles. All articles were subsequently screened on the title and abstract. After reading the full text of 67 articles, we excluded 54 articles mainly because the intervention did not consist of monitoring-informed counselling. Thus, a total of 13 articles, reporting on 1419 patients, were found to meet inclusion criteria and were entered in our meta-analysis (Figure 1).

Figure 1: Flow diagram



Characteristics of the included studies are shown in Table 1. We contacted three authors, but couldn't get any additional data

Table 1: Characteristics of included studies

Study	n	**Starting/ switching cART**	**Low pre-intervention adherence**	**% with undetectable baseline VL**	**Intervention components**	**Intervention duration (weeks)**	**Number of intervention sessions**
Davies et al 2010 (14)	145	no	no	-	1	48	-
De Bruin et al 2010 (12)*	133	no	no**	84%	1, 2, 3	36	4
Engelbrecht 2010 (16)	88	no	no	69%	1, 4	16	4
Gross et al 2013 (17)*	180	yes	no	0%	1, 2, 3, 5, 6, 8	52	22
Koenig et al 2008 (18, 19)	139	yes	no	0%	1, 2, 3, 4, 5, 6, 8	24	11
Rigsby et al 2000 (20)*	55	no	no	35%	1, 3	4	5
Rosen et al 2007 (21)*	56	no	yes	57%	1, 3, 7 1, 3, 7, 8	16	16
Sabin et al 2010 (22)*	64	no	no**	88%	1	24	6
Sabin et al 2014 (23)*	116	no	no**	99%	1, 4	24	6
Safren et al 2009 (24)*	45	no	no	-	1, 2, 3, 4, 6	48	10 to 12
Smith et al 2003 (25)*	43	yes	no	0%	1, 2, 3, 5	12	4
Wagner et al 2006 (26)*	199	yes	no	15%	1, 3	48	5
Wilson et al 2010 (13)	156	no	no	0%	1	-	2

1) monitoring-informed counselling 2) didactic provision of information about HIV, cART and adherence 3) behavioral, cognitive behavioral or motivational counselling 4) provision of reminder device 5) social support enlistment 6) depression screening/treatment/referral 7) financial incentives for good adherence 8) substance use screening/treatment/ referral. * The study had reported significant improvement in adherence due to the intervention of interest. ** Patients were triaged to different levels of intervention intensity depending on their level of adherence.

Overall, we found adherence was significantly higher in intervention groups which had received monitoring-informed counselling as part of the intervention compared with control groups that did not receive such counselling (SMD 0.51, 95% CI 0.31 to 0.71) (Figure 2). This represents an improvement of a moderate magnitude in terms of effect sizes. Moreover, patients in these intervention groups were more likely to have undetectable HIV RNA concentrations than patients in control groups that did not receive such counselling (OR 1.35, 95% CI 1.12 to 1.63) (Figure 3). We identified three studies in which monitoring-informed counselling was the single intervention component and was compared with a control group not receiving such counseling (13, 14, 22). In these three studies, the effect of the intervention on adherence (SMD 0.24, 95% CI -0.17 to 0.66) (Figure 2) and on the likelihood of undetectable HIV RNA concentrations (OR 0.94, 95% CI 0.64 to 1.38) (Figure 3) were not statistically significant.

Figure 2: Effect of interventions on adherence

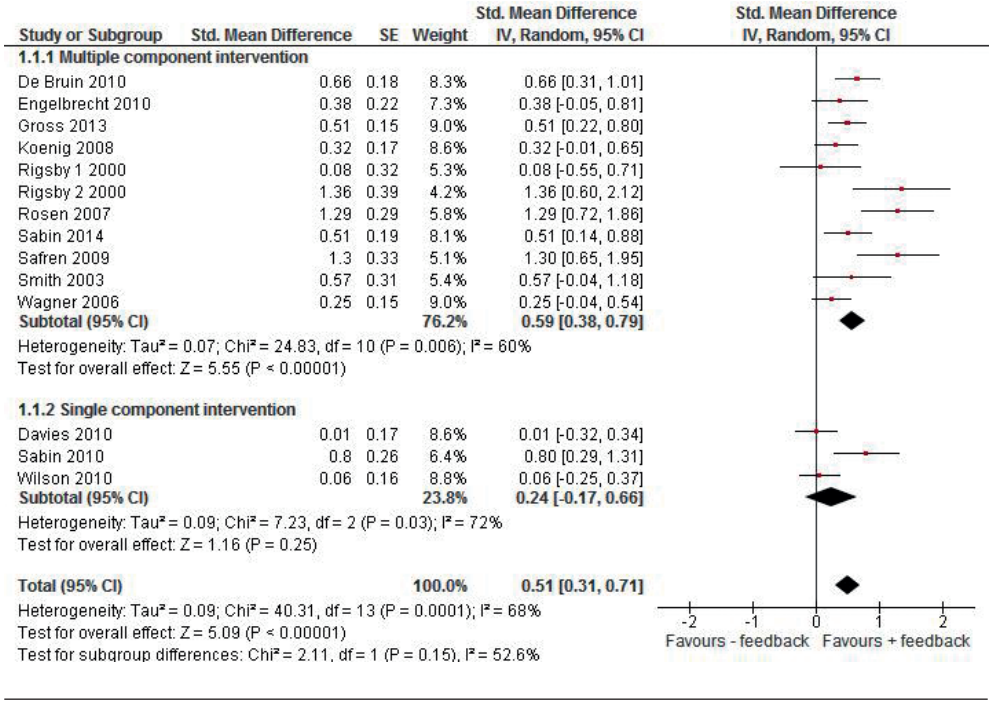
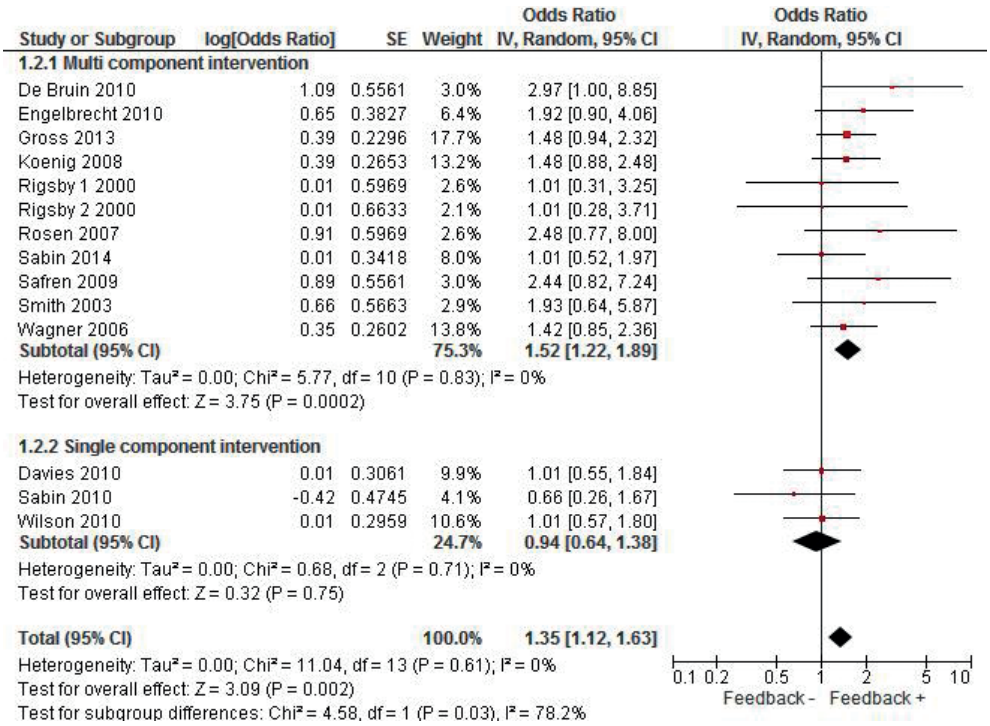


Figure 3: Effect of interventions on the likelihood of undetectable HIV RNA



A total of 12 out 13 studies included, compared a single intervention arm with a control group. In one study, two intervention arms were compared with the same control group (20). One of the intervention arms of this study provided financial incentives for good adherence in addition to the other intervention components, whereas the other intervention arm did not provide financial incentives. Excluding this study from our analysis or including only the intervention arm without financial incentive resulted in pooled effect estimates for adherence of SMD: 0.49 (95% CI 0.30 to 0.69) and SMD: 0.47 (95% CI 0.28 to 0.66), respectively, and for the likelihood of achieving undetectable viral load of OR: 1.37 (95% CI 1.13 to 1.66) and OR: 1.36 (95% CI 1.12 to 1.64), respectively.

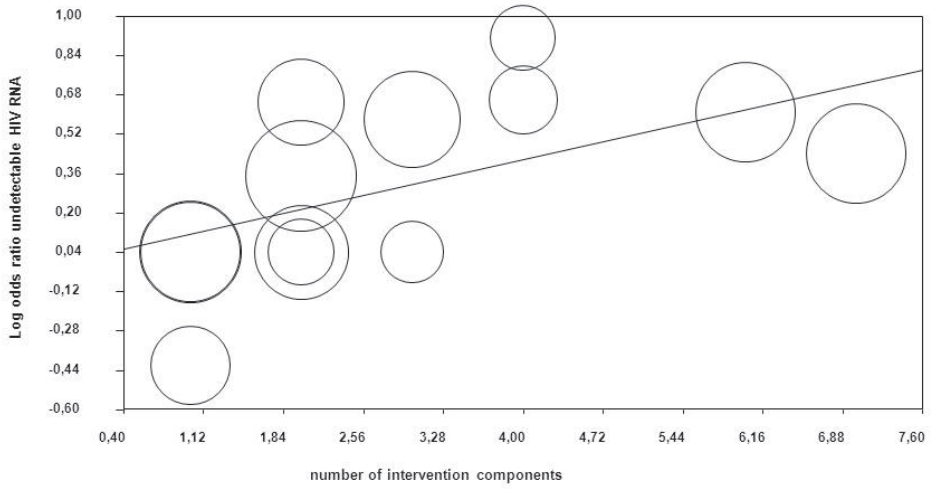
Variation in effect sizes of adherence were significantly associated with the study design features; percentage of patients with undetectable viral load at baseline and providing financial incentives for good adherence. Studies with a lower percentage of patients with undetectable viral loads at baseline (dichotomized at the median of 35%) yielded larger effect sizes than

studies with a higher percentage of patients with undetectable viral loads at baseline (SMD 0.65 (versus 0.31, Q= 6.87, p=0.009). Studies providing financial incentives for good adherence (22, 23) yielded larger effect sizes than studies without financial incentives (SMD 1.32 versus 0.40, Q=10.83, p=0.001). Both effects remained statistically significant in a multivariate model.

Variation in effect sizes for undetectable viral loads were significantly associated with whether the intervention components included didactic provision of information about HIV, cART and adherence, or behavioral, cognitive behavioral, or motivational counselling. Studies in which the intervention components included didactic provision of information about HIV, cART and adherence yielded higher effect sizes than studies not including this intervention component (OR 1.81 versus OR 1.19, Q=9.91, p=0.0016). Studies in which the intervention components included behavioral, cognitive behavioral, or motivational counselling yielded higher effect sizes than studies not including this component (OR 1.64 versus OR 1.08, Q=11.89, p=0.0006). We were unable to include both variables in a multivariate model due to high collinearity.

Meta-regression analysis showed that a higher number of intervention components was significantly associated with a higher likelihood of undetectable HIV RNA (Figure 4), but not with higher adherence in the intervention groups.

Figure 4: Meta-regression of number of intervention components on the logg odds of undetectable HIV RNA



Slope=0.10, Q=6.48, df=1, p=0.011. The circle size reflect the weight that a study obtained in the meta-regression.

The funnel plot for the outcome measure medication adherence was suggestive of publication bias (Egger's regression intercept p=0.04), with an absence of small studies yielding negative effects (Figure 5). The funnel plot for the outcome measure virologic treatment response was not suggestive of publication bias (Egger's regression intercept p=0.99) (Figure 6).

Figure 5: Funnel plot medication adherence

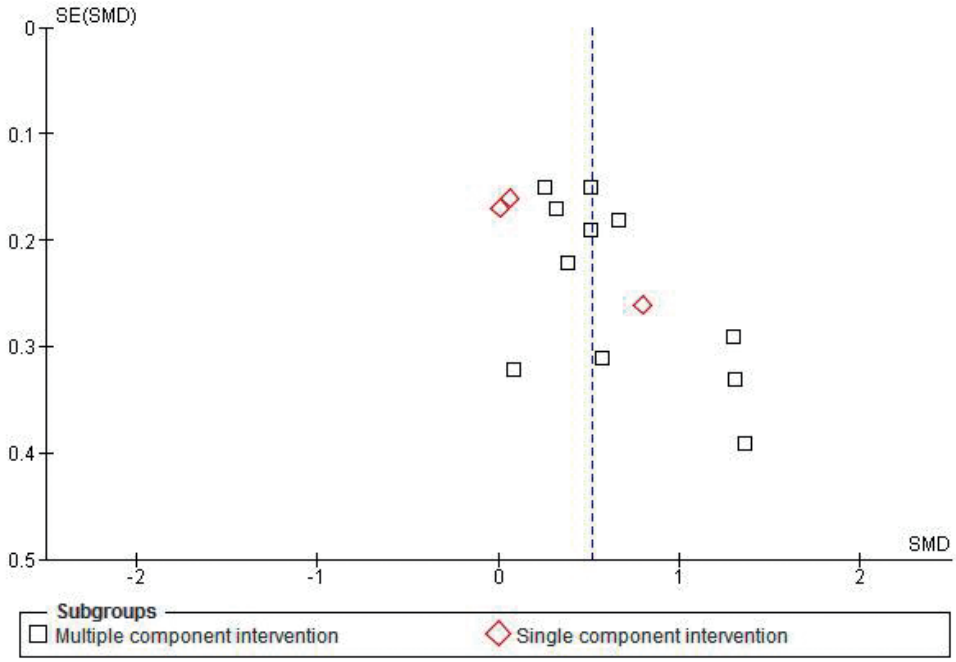
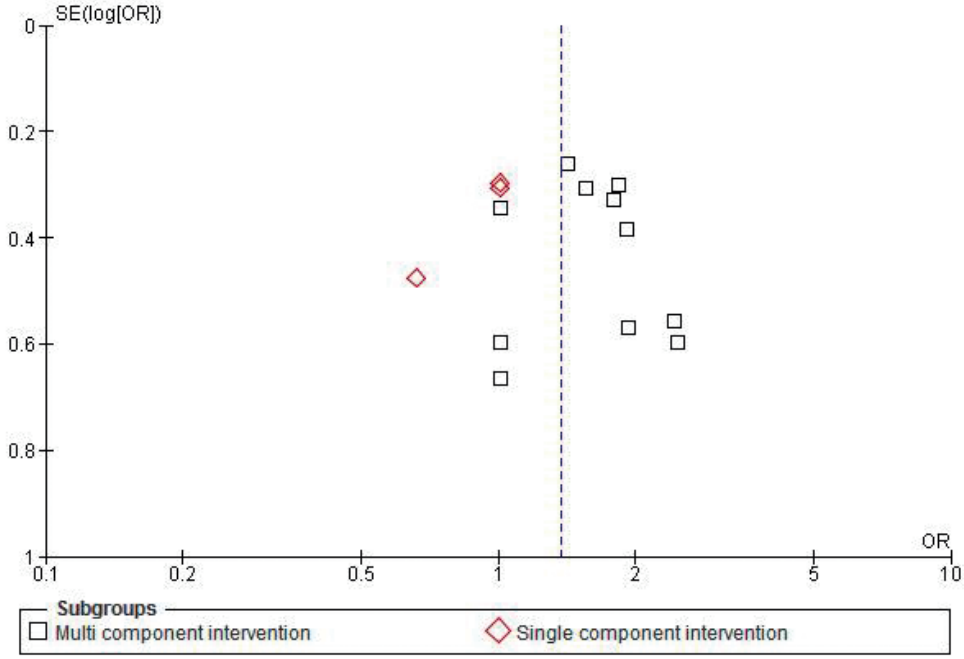


Figure 6: Funnel plot undetectable HIV RNA



Discussion

Our meta-analysis of randomized controlled trials investigating the effect of monitoring-informed counselling on treatment adherence and virologic treatment response, yielded significantly improved adherence and virologic treatment response only when such counselling was part of a multi-component intervention. The improvement in adherence constituted a medium sized effect. The improvement in medication adherence achieved in the intervention groups was clinically relevant as it was accompanied by an increased likelihood of having an undetectable viral load.

We distinguished between studies in which monitoring-informed counselling was the only intervention component and studies in which monitoring-informed counselling was one out of multiple intervention components. In the vast majority of studies included, monitoring-informed counselling was one out of multiple intervention components that patients received. Consequently, the separate contribution of monitoring-informed counselling to the improved

levels of adherence and virologic treatment response is difficult to establish. However, this reflects the current state of the art in hiv adherence support research in which most interventions consist of multiple components (29). Moreover, it reflects the clinical reality that adherence is behavior that may be affected by multifactorial barriers that may best be addressed by comprehensive interventions (9). Multicomponent interventions may increase the likelihood of having an impact on adherence and treatment outcomes compared with single component interventions. Researchers may first combine approaches to document an effect and in later studies attempt to isolate effects of intervention features.

We identified only three single component studies with divergent results. Two single component studies found insignificant effects of the intervention on adherence (13, 14). In contrast, one single component study found significantly improved adherence in the intervention group (22). In one of the single component studies with insignificant results, the lack of effect of the intervention was attributed to inadequate adherence counselling techniques of the health care providers who delivered the intervention (13). Although the amount of adherence-related dialogue increased in the intervention group, little of that dialogue was problem solving in nature but tended to have a scolding or lecturing quality (13).

In contrast, the single component study that yielded improved levels of adherence in the intervention group mentioned that participating health care providers had received practice and role-playing training sessions during which it had been emphasized that the goal of counselling was to help subjects to improve their medication-taking behavior, not to scold them about poor adherence (22). The authors speculated that for patients with adherence problems, monitoring-informed counselling offered an opportunity for meaningful discussion about medication-taking issues specific to the individual and point in time, which may have provided patients just the focused discussion of behavior changes that they needed (22). Given the quest for effective and practical interventions to promote medication adherence (30), it would be most interesting to see if future studies employing a similar relatively simple monitoring-informed counselling with prior training of health care providers would also result in improved adherence.

We aimed to identify study design features that were associated with larger effect sizes for adherence and virologic treatment response. Lower percentage of patients with undetectable viral loads at baseline and providing financial incentives for good adherence were significantly associated with larger effect sizes for adherence but not for virologic treatment response. The clinical relevance of these findings is therefore uncertain. Studies including the didactic provision of information about HIV, cART and adherence, or behavioral, cognitive behavioral, or motivational counselling as intervention components yielded larger effect

sizes for virologic treatment response than studies that did not include these intervention components. We were unable to assess the independent effect of these two intervention components in a multivariate model, due to the low number of included studies and due to the fact that many studies including one of the two intervention components also included the other component. While the multiple component studies were associated with larger improvements in adherence and virologic treatment response than the single component studies, it remains thus largely unknown which intervention components are responsible for this difference.

There is also more a fundamental reason why it could be difficult to determine which adherence intervention components are most responsible for improvements in adherence than others. It is increasingly recognized that multifactorial barriers may influence patient adherence and that these barriers may differ between patients and change within patients over time. There is also increasing recognition that interventions should be targeted to people who are clearly identified as needing that specific intervention. By analogy with a medical condition that can only be adequately treated when an accurate diagnosis is established, the treatment, i.e., adherence intervention, should be matched to the diagnosis, i.e., barriers to adherence that the patient is experiencing (31). For example, reminder devices aren't that likely to help people whose adherence barriers aren't related to problems remembering doses. Consequently, adherence intervention components that are highly effective for a particular patient may be largely ineffective for another patient depending on the specific problems with adherence a particular patient is experiencing. The most effective interventions are probably those that carefully tailor the intervention components to the adherence problems an individual patient is experiencing.

There has been attention in the field to the content of adherence care that is provided in control groups of adherence intervention studies. It was previously found that the difference in adherence intervention components provided in the intervention and control groups was a significant predictor of the difference in viral load and adherence success rates between intervention and control groups (32). In the present study, the difference in adherence intervention components provided in the intervention and control groups was not a significant predictor of the difference in virologic success nor of the difference in adherence between intervention and control groups (data not shown). This finding may have been due, however, to a limited description of adherence care provided to control groups in many of the included studies.

The present study has several limitations. First, because in the vast majority of studies monitoring-informed counselling was one out of multiple intervention components, the

separate contribution of such counselling to the improved levels of adherence and virologic treatment response is difficult to establish.

Second, we searched a single electronic database only, i.e., PubMed, which may have resulted in publication bias. However, we supplemented this database with searches in abstracts of the most relevant HIV conferences for the subject of medication adherence.

Third, if studies reported insignificant differences in adherence or virologic response between intervention and control groups without data, we assumed an effect size of 0.01. This may have been a too conservative estimate which may have resulted in an underestimate of the effectiveness of the concerning interventions.

Fourth, we categorized adherence intervention components in several broad categories, for example, behavioral, cognitive behavioral or motivational counselling. Within these broad categories, distinct types of intervention components may have had a different impact on adherence and virologic response that will remain undetected in the present global analysis, e.g. cognitive behavioural counselling could have had a different impact on adherence and virologic response than motivational interviewing.

Fifth, when more than one type of intervention was tested within a single study, we considered data from each arm of the intervention as separate data points. This may have resulted in an over-representation of a study with more than one intervention arm. However, a sensitivity analysis in which we excluded this study from our analysis or included only one of the intervention arms did not change our overall results.

In conclusion, monitoring-informed counselling improved medication adherence and virologic response compared with control groups not receiving such counselling in studies in which it was one out of multiple intervention components, but not in studies where it was the only intervention component.

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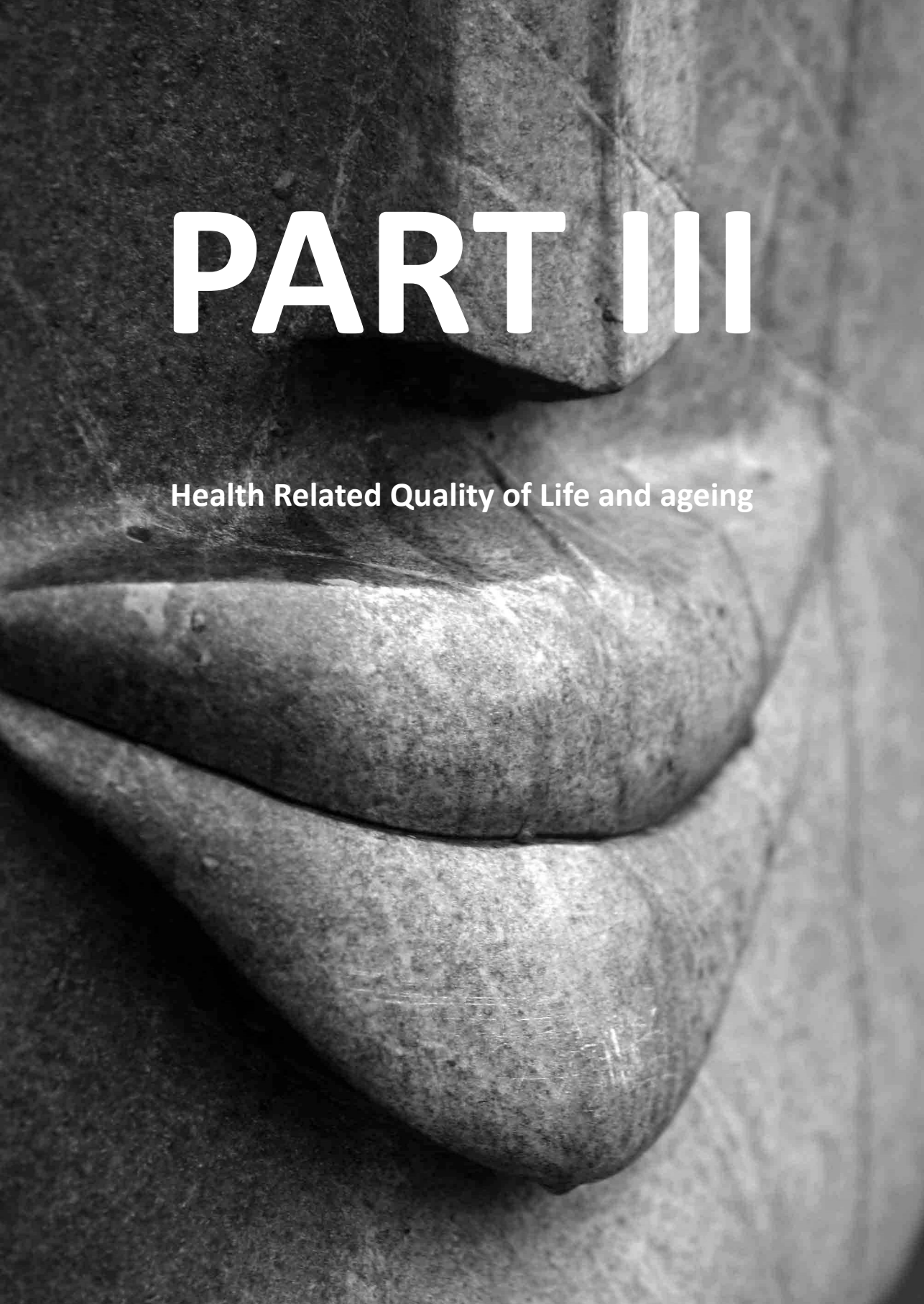

PART III

Health Related Quality of Life and ageing

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Submitted

CHAPTER 7

Impact of co-morbidity and ageing on health-related quality of life in HIV-positive and HIV-negative individuals

Abstract

Background: HIV-infected individuals may be at risk for the premature onset of age-associated non-communicable co-morbidities. Being HIV-positive, having comorbidities and being of higher age may adversely impact health-related quality of life (HRQL). We investigated the possible contribution of HIV infection, co-morbidities, and age on HRQL and depression.

Methods: HIV-infected individuals and uninfected controls from the AGE_hIV Cohort Study were screened for the presence of co-morbidities. They completed the Short Form 36-item Health Survey to assess HRQL and the nine-item Patient Health Questionnaire to assess depression. Linear and logistic regression were used to investigate to which extent co-morbidities, aging and HIV infection were independently associated with HRQL and depression.

Results: HIV-infected individuals (*n*=541) reported significantly worse physical and mental HRQL and had a higher prevalence of depression than HIV-uninfected individuals (*n*=526). A higher number of co-morbidities and HIV-positive status were each independently associated with worse physical HRQL, whereas HIV-positive status and younger age were independently associated with worse mental HRQL and more depression. The difference in physical HRQL between HIV-positive and HIV-negative individuals did not become greater with a higher number of co-morbidities or with higher age.

Conclusions: In a cohort of largely well-suppressed HIV-positive participants and HIV-negative controls, HIV-positive status was significantly and independently associated with worse physical and mental HRQL and with an increased likelihood of depression. Our finding that a higher number of co-morbidities was independently associated with worse physical HRQL reinforces the importance to optimize prevention and management of co-morbidities as the HIV-infected population continues to age.

Key words: HIV infection, health-related quality of life, ageing, comorbidity, cohort study, depression

Introduction

HIV-associated morbidity and mortality have dramatically declined since the introduction of combination antiretroviral therapy (cART) (1, 2). As a result, the number of HIV-1 infected adults living into old age is steadily increasing wherever access to cART is ensured. However, even among well-treated HIV-infected individuals without comorbidity or AIDS-defining events, life-expectancy remains lower than in the general population (3). Currently, approximately 50% of individuals in care with HIV in the Netherlands are 45 years or older (4). In view of a longer life expectancy, the care for people living with HIV should increasingly be aimed at not only improving the quantity but also the quality of life.

Several studies have shown that people diagnosed with HIV have impaired health-related quality of life (HRQL) compared with the general population (5, 6). However, HIV-infected individuals may differ from general population samples with respect to background and behavioral characteristics. Sexual- and ethnic minorities are more prevalent in the HIV-infected population than in the general population. Differences in lifestyle factors, notably substance use, have also been demonstrated between HIV-infected and uninfected populations (7, 8). Both minority status and lifestyle factors have previously been associated with a lower level of HRQL (9). The contribution of HIV on HRQL is therefore preferably studied by comparing individuals with HIV to uninfected individuals with similar demographic- and lifestyle characteristics.

HIV-infected persons are at increased risk of age-associated non-communicable co-morbidities compared to the general population (10). Such co-morbidities were previously shown to have a negative impact on the physical dimension of HRQL among persons with HIV infection (11-13). Previous research has demonstrated that HIV infection (5, 6, 15, 16) and aging (15, 16) also negatively impact HRQL both in general terms and concerning the physical dimension of HRQL. Older HIV-infected individuals were previously shown to have a worse performance on physical function tests such as walking speed and grip strength than older HIV-uninfected individuals. Lower walking speed and grip strength were associated with lower levels of physical HRQL and an increased mortality rate (17-19). Furthermore, depression is more prevalent among HIV-infected individuals than among HIV-uninfected individuals (20, 21). The inflammatory pathway is a possible contributor to the high incidence of depression in HIV positive individuals (22). Chronic inflammation is inherent to HIV infection, while elevated levels of inflammatory markers have been associated with depression in HIV positive and HIV negative individuals (23).

The objectives of the present study were to compare HRQL and depression between HIV-infected and HIV-uninfected controls while adjusting for a range of socio-demographic,

clinical/biological and lifestyle characteristics. Additionally, we aimed to investigate the independent contribution of co-morbidity, age and HIV infection to HRQL and depression.

Methods

Participants

The AGE$_h$IV Cohort Study is an ongoing, prospective comparative cohort study. Between 2010 and 2012, a total of 598 HIV-1 infected individuals were recruited from the HIV outpatient clinic of the Academic Medical Center in Amsterdam, the Netherlands. As a control group, 550 HIV-uninfected individuals were recruited from the sexual health clinic and the Amsterdam Cohort Studies on HIV/AIDS at the Amsterdam Public Health Service, from the same geographical region and with similar socio-demographic and behavioral (risk) factors. The inclusion criteria were age ≥45 years and laboratory confirmed presence or absence of HIV-infection. After obtaining informed consent participants were screened for the presence of the following age-associated non-communicable co-morbidities: hypertension, angina pectoris, myocardial infarction, peripheral arterial disease, ischemic cerebrovascular disease, diabetes mellitus type 2, obstructive pulmonary disease, impaired renal function (i.e. estimated glomerular filtrate rate <60ml/min), non- AIDS cancer and atraumatic fractures/ osteoporosis (10).

At enrolment, participants were asked to complete an extensive questionnaire to collect data on socio-demographics, lifestyle factors, HRQL, and depressive symptoms.

Detailed information concerning HIV and cART history was obtained from the Dutch HIV Monitoring Foundation. The study protocol was approved by the local ethics review committee and registered at www.clinicaltrials.gov (identifier NCT01466582).

For the present study, we included 541/598 (90%) of the HIV-infected participants and 524/550 (95%) of the HIV-uninfected participants who completed the questions on HRQL and depressive symptoms at enrolment.

Dependent variables

HRQL was measured using the Medical Outcomes Study Short Form 36-item health survey (SF-36) (24). The SF-36 contains eight subscales from which a physical health summary (PHS) and mental health summary (MHS) score can be calculated. The subscales physical functioning, role- physical, bodily pain and health perceptions contribute most to PHS and vitality, social functioning, role-emotional and mental health contribute most to MHS. All subscales and summary scores range from 0–100, with higher scores indicating better HRQL. The summary

scores are transformed into a standardized scale with a mean of 50 and standard deviation of 10. The SF-36 subscales and the PHS and MHS yield high levels of reliability and validity (25).

Depressive symptoms were assessed using the nine-item Patient Health Questionnaire (PHQ-9) (26). Scores may range from 0-27 with higher scores indicating more depressive symptoms. Scores equal to or higher than 10 are indicative of clinically relevant levels of depression (26). Depressive symptoms were also assessed by the Centers for Epidemiologic Studies Depression scale (CES-D) consisting of 20 items (27). Scores may range from 0 to 60 with higher scores indicating more depressive symptoms. Scores equal to or higher than 16 are indicative of clinically relevant levels of depression.

Independent variables

Individuals with laboratory confirmed HIV infection were categorized as HIV-infected and individuals with laboratory confirmed absence of HIV infection were categorized as HIV-uninfected. We counted the number of non-communicable co-morbidities per participant and categorized them into 0, 1, 2 or >2. Participants' age was categorized into the following categories: 45 to 49, 50 to 54, 55 to 59, 60 to 64 and 65 years or older (10).

Demographic, clinical/biological and lifestyle covariates

We considered a range of demographic, clinical/biological and lifestyle characteristics, previously shown or suspected to be related with HRQL and/or depression as potential covariates. We considered the following socio-demographic characteristics: gender (male/female), Dutch origin (yes/no), being married/cohabiting (yes/no), men who have sex with men (MSM) (yes/no) and educational level (low-middle/high).

We considered the following clinical/biological measures: mean CD4 cell count in the year prior to enrolment, being hepatitis B serum antigen (HBsAg) positive (yes/no) and being hepatitis C virus (HCV) RNA positive (yes/no).

In the context of a frailty assessment (28) we performed two physical functioning tests: grip strength and walking speed. Maximum grip strength was assessed using Jamar handheld dynamometer (Jamar Plus + Digital Hand Dynamometer, Jamar, USA), the mean value of three consecutive measurements of the dominant hand was used for analysis. Walking speed was determined by asking the participants to walk a distance of 4.57 m (15ft) at their own usual pace. The average of two consecutive measurements was used. Grip strength and walking speed were categorized according to the strata described by Fried (29). Stratification of grip strength was based on gender and BMI. Stratification of walking speed was based on gender and body height. Persons in the per stratum lowest quintile were considered to have low grip strength (yes/no) or low walking speed (yes/no).

Because depression may be driven by inflammation and immune activation, we also considered measures of inflammation and immune activation that were assessed in the AGE_hIV Cohort Study, i.e., high sensitivity C-reactive protein (hs-CRP), soluble (s)CD163 and sCD14, as potential covariates.

We considered the following lifestyle characteristics: being a current smoker (yes/no), heavy daily drinking (yes/no), defined as (almost) daily intake of at least 3 (females) or 5 (males) alcoholic consumptions, ever injecting drug use (IDU) (yes/no), and daily to monthly use of cannabis (yes/no), cocaine (yes/no) or XTC (yes/no).

Within the HIV-infected group, we also considered the following HIV and ART-related factors: years known to be HIV-1 seropositive, years since start of first ART, HIV diagnosis prior to 1996 (yes/no), exposed to nucleoside reverse transcriptase inhibitor mono/dual therapy prior to cART initiation (yes/no), nadir CD4 cell count, history of AIDS (yes/no), undetectable viral load in the year prior to enrolment (yes/no), duration of suppressed plasma HIV RNA, and duration of CD4 count <200 cells/mm^3.

Statistical analysis

Differences in characteristics at enrolment between HIV-infected and uninfected participants were examined with Chi-square tests for categorical data and Wilcoxon rank-sum tests or Student t-tests for continuous data, where appropriate. We calculated SF-36 and PHQ-9 scale scores according to standard scoring instructions.

To examine the magnitude of potential differences in HRQL between HIV-infected and uninfected individuals, we calculated effect sizes by dividing mean differences by the pooled standard deviation. Effect sizes of 0.2, 0.5 and 0.8 were interpreted as small, medium and large, respectively (30). The magnitude of the difference in depression (PHQ-9 score ≥10) between HIV-infected and uninfected individuals was expressed as odds ratio (OR). ORs of 1.44, 2.47 and 4.25 were interpreted as small, medium and large, respectively (30). To examine if potential differences between HIV-infected and uninfected individuals were attenuated after adjustment for the independent variables and covariates, we first calculated unadjusted effect sizes (model 1). Next, we calculated effect sizes that were adjusted for the number of comorbidities (model 2). Next, subsequent models were additionally adjusted for age (model 3), demographic factors (model 4), clinical/biological factors (model 5) and for lifestyle factors (model 6).

To investigate factors independently associated with HRQL, we conducted multiple linear regression analyses with the PHS and MHS as the dependent variables. To investigate factors independently associated with depression (PHQ-9 score ≥10), we conducted multiple

logistic regression analysis. The independent variables were HIV infection, the number of co-morbidities and age. The demographic-, clinical/biological and lifestyle variables were treated as covariates. First we conducted series of bivariate analyses. Factors that yielded bivariate associations with HRQL or depression with p-values <0.20 were subsequently entered in a multivariate model using a backward selection of variables for the final model. We checked for violations of necessary assumptions in multiple regression by examining normal plots of the residuals of the linear regression models and by examining the possible presence of collinearity (Tolerance/Variance Inflation Factor statistics). In a sensitivity analysis, we used the Center for Epidemiologic Studies Depression scale (CESD) score ≥16 instead of a PHQ9 score ≥10 to define depression.

We explored if age and the number of co-morbidities had a different impact on HRQL and depression in HIV-infected versus uninfected individuals by including an interaction term in the models, i.e., age by HIV status, and co-morbidities by HIV status. Two sided p-values <0.05 were considered statistically significant. Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics at enrolment

The characteristics at enrolment of the HIV-infected and uninfected participants are shown in Table 1. HIV-infected participants were less likely to be of Dutch origin and to have a high educational level. HIV-infected participants were more likely to be married/cohabiting, to have chronic HBV infection, low grip strength and low walking speed, a higher number of age associated non-communicable co-morbidities, a lower CD4 cell count and higher concentrations of measures of inflammation and immune activation (hs-CRP, sCD163, sCD14) than HIV-uninfected participants. HIV-infected individuals were more likely to be a current smoker and to have ever used intravenous drugs and less likely to use XTC daily to monthly. Virtually all HIV-infected participants were on cART and had undetectable HIV-1 plasma viral loads.

Table 1: Characteristics of HIV infected and HIV uninfected study participants.

Characteristic	HIV-infected participants (n=541)	HIV-uninfected participants (n=524)	P value
Demographic characteristics			
Age (yrs), median (IQR)	52.9 (48.2 to 59.6)	52.1 (47.9 to 58.5)	0.19
Male sex, No (%)	497 (89%)	446 (85%)	0.12
MSM, No (%)	400 (74%)	365 (70%)	0.14
Dutch origin , No (%)	391 (72%)	425 (81%)	**0.001**
High educational level , No (%)	217 (42%)	285 (56%)	**<0.001**
Married/cohabiting, No (%)	268 (50%)	221 (42%)	0.017
Clinical/biological factors			
Hepatitis B serum antigen (HBsAg) positive, No (%)	34 (6.3%)	3 (0.6%)	**<0.001**
Hepatitis C virus (HCV) RNA positive, No (%)	15 (2.8%)	5 (1.0%)	0.052
Low grip strength, No (%)	129 (24%)	72 (14%)	**<0.001**
Low walking speed, No (%)	154 (29%)	66 (13%)	**<0.001**
Number of age associated non-communicable co-morbidities, median (IQR)	1 (0-2)	1 (0-1)	**<0.001**
Number of age associated non-communicable co-morbidities, mean (SD)	1.29 (1.2)	0.96 (0.96)	**<0.001**
Mean CD4 cell count in year prior to enrolment, median (IQR)	565 (435-745)	840 (660-1050)	**<0.001**
hs-CRP (mg/L), median (IQR)	1.5 (0.7-3.5)	1.0 (0.6-1.9)	**<0.001**
sCD14 (ng/mL), median (IQR)	1574 (1297-2011)	1353 (1079-1738)	**<0.001**
sCD163 (ng/L), median (IQR)	289 (207-419)	252 (182-342)	**<0.001**

Lifestyle characteristics			
Heavy daily drinking, No (%)	26 (5%)	38 (7%)	0.13
Current smoker, No (%)	173 (32%)	129 (25%)	**0.009**
Ever intravenous drug use, No (%)	19 (3.6%)	6 (1.1%)	**0.017**
Daily to monthly use of cannabis, No (%)	74 (14%)	60 (12%)	0.32
Daily to monthly use of XTC, No (%)	23 (4%)	45 (9%)	**0.006**
Daily to monthly use of cocaine, No (%)	20 (4%)	15 (3%)	0.55
HIV /ART specific factors			
Currently on cART, No (%)	517 (96%)		
Years know to be HIV-1 seropositive, median (IQR)	12 (6-17)		
Years since start first cART, median (IQR)	10 (4-15)		
Exposed to nucleoside reverse transcriptase inhibitor mono/dual therapy prior to cART initiation	114 (24%)		
Nadir CD4 cell count, median (IQR)	180 (78-260)		
Duration of CD4 < 200 cells mm^3, median (IQR), months	0.7 (0-8)		
History of AIDS, No (%)	173 (32%)		
HIV diagnosis prior to 1996, No (%)	173 (32%)		
Years since last plasma HIV RNA >200 copies/mL, median (IQR)	5.8 (2.5-10.2)		
Plasma HIV RNA <200 copies/mL in the year prior to enrolment, No (%)	495 (92%)		

Differences in HRQL and depression between HIV-infected and uninfected individuals

HIV-infected individuals reported significantly worse HRQL than HIV-uninfected individuals on eight out of the ten SF-36 scales and they reported significantly more depression on the PHQ-9 in the unadjusted analysis (Table 2, model 1). The difference in HRQL on subscales related to physical functioning and the physical health summary score between HIV-infected and uninfected individuals was slightly attenuated after adjustment for comorbidities (model 2) and was attenuated even more after adjustment for the biological/clinical covariates (model 5). The difference in HRQL on subscales related to mental health, the mental health summary score and depression between HIV-infected and uninfected individuals became more pronounced after adjustment for the biological/clinical covariates (model 5). This was mostly due to adjustment for sCD14 concentrations. The difference between HIV-infected and uninfected individuals in HRQL and depression remained significant on six of the SF-36 scales and on the PHQ-9 after adjustment for all independent variables and covariates (model 6). These differences were of a small to medium magnitude with effect sizes ranging from 0.17 for role-physical and the mental health summary score, to 0.32 for vitality and 0.40 for health perceptions and an OR indicative of a medium effect for depression.

Table 2: Differences between HIV-infected and HIV-uninfected participants in HRQL and depression

	HIV-infected participants (n=541)	HIV-uninfected participants (n=524)	Effect size, Model 1	Effect size, Model 2	Effect size, Model 3	Effect size, Model 4	Effect size, Model 5	Effect size, Model 6
HRQL (SF-36), mean (SD)[1]								
Physical functioning	85 (20)	90 (16)	0.27**	0.20**	0.20*	0.20**	0.10	0.08
Role functional-physical	75 (38)	84 (32)	0.25**	0.20**	0.20**	0.24**	0.19*	0.17*
Bodily pain	80 (22)	82 (21)	0.12*	0.10	0.10	0.06	0.02	0.02
Social functioning	81 (22)	86 (19)	0.21**	0.19**	0.19**	0.23**	0.22**	0.20**
Mental health	75 (18)	77 (17)	0.11	0.10	0.09	0.11	0.16*	0.12
Role functioning-emotional	79 (35)	83 (32)	0.11	0.09	0.09	0.12	0.10	0.07
Vitality	65 (20)	72 (18)	0.31**	0.30**	0.30**	0.33**	0.36**	0.32**
Health perceptions	63 (21)	73 (18)	0.51**	0.45**	0.45**	0.47**	0.42**	0.40**
Physical health summary score	49 (9)	52 (8)	0.35**	0.29**	0.29**	0.29**	0.20**	0.18*
Mental health summary score	50 (10)	51 (10)	0.12*	0.12*	0.12	0.16*	0.21**	0.17*
Depression (PHQ-9 score ≥10), No (%)[2]	78 (14.5%)	42 (8.0%)	1.94**	1.85**	1.85**	2.08**	3.23**	2.90**

* $p \leq 0.05$, ** $p \leq 0.01$

1 effect sizes for difference between HIV infected and HIV uninfected participants on SF-36 scales are standardized mean differences

2 effect sizes for difference between HIV infected and HIV uninfected participants on PHQ-9 are odds ratios

Model 1: unadjusted differences

Model 2: differences adjusted for number of comorbidities

Model 3: differences adjusted for number of comorbidities and age

Model 4: differences adjusted for number of comorbidities, age, and demographic characteristics

Model 5: differences adjusted for number of comorbidities, age, demographic characteristics and clinical/biological factors

Model 6: differences adjusted for number of comorbidities, age, demographic characteristics, clinical/biological factors and lifestyle characteristics.

Association between HIV-status, comorbidities and age with HRQL and depression

Table 3 shows the factors that were independently associated with physical- and mental HRQL and with depression in a multivariate model. HIV-positive status was independently associated with worse physical HRQL (Figure 1A, Table 3), worse mental HRQL (Figure 2A, Table 3) and with a higher likelihood of depression (Table 3). A higher number of co-morbidities was significantly associated with worse physical HRQL (Figure 1A, Table 3) but not with mental HRQL (Figure 2B, Table 3), or depression (Table 3). Younger age was significantly associated with worse mental HRQL (Figure 2B, Table 3) and with an increased likelihood of depression (Table 3) but not with physical HRQL (Figure 1B, Table 3).

Table 3: Multivariate model of factors associated with physical- and mental HRQL and depression.

	Physical HRQL score	p-value	Mental HRQL score	p-value	Odds Ratio depression score ≥10	p-value
Main study parameters						
HIV infection (0=no, 1=yes))	-1.6	0.002	-1.7	0.009	1.60	0.002
Number of chronic co-morbidities (0, 1, 2, >2)	-1.4	<0.001	-	-	-	-
Age (per 10 yrs increase)	-	-	1.8	<0.001	0.76	0.007
Demographics						
Gender (0=male, 1=female)	-	-	-2.2	0.02	-	-
MSM (0=no, 1=yes)	1.4	0.02	-	-	-	-
Dutch origin (0=no, 1=yes)	-	-	-	-	0.68	0.018
High educational level (0=no, 1=yes)	1.0	0.045	-	-	0.70	0.011
Married/cohabiting (0=no, 1=yes)			2.4	<0.001	0.60	<0.001
Clinical/physiological/ biological factors						
Current HBV infection (0=no, 1=yes)	-	-	-	-	-	-
Current HCV infection (0=no, 1=yes)	-4.8	0.012	-	-	-	-
Low grip strength (0=no, 1=yes)	-1.8	0.008	-	-	-	-
Low walking speed (0=no, 1=yes)	-2.7	<0.001	-	-	1.45	0.032
Mean CD4 cell count in year prior to enrolment	-	-	-	-	-	-
Log hs-CRP (mg/L)	-	-	-	-	-	-
Log sCD14 (ng/mL)	-	-	4.5	0.02	0.35	0.016
Log sCD163 (ng/L)	-	-	-	-	-	-
Lifestyle factors						
Heavy daily drinking (0=no, 1=yes)	-	-	-3.4	0.007	-	-
Current smoker (0=no, 1=yes)	-	-	-1.7	0.02	1.58	0.003
Ever IDU (0=no, 1=yes)	-	-	-	-	-	-
Daily to monthly cannabis (0=no, 1=yes)	-	-	-	-	-	-
Daily to monthly XTC (0=no, 1=yes)	-	-	3.6	0.004	-	-
Daily to monthly cocaine (0=no, 1=yes)	-	-	-	-	-	-

A higher physical and mental HRQL score indicates a better HRQL. A depression score ≥10 indicates clinically relevant depressive symptoms.

There was no evidence that the difference in HRQL between HIV-infected and HIV-uninfected individuals became more pronounced with a higher number of co-morbidities (Figures 1A, 2A), or at an older age (Figure 2B). In fact, the difference in physical HRQL between HIV-infected and HIV-uninfected individuals tended to become smaller with increasing age (interaction HIV status by age, p=0.07) (Figure 1B).

Figure 1B

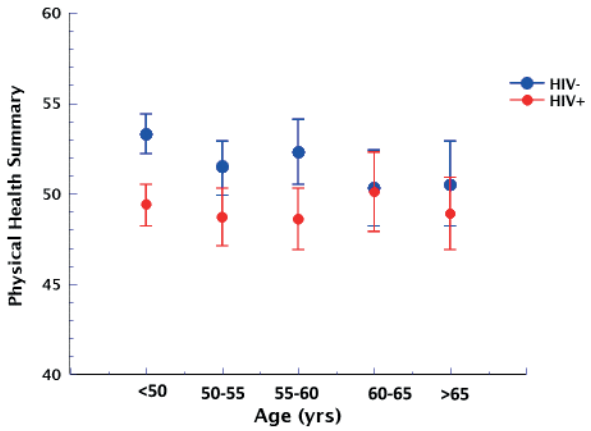


Figure 1A

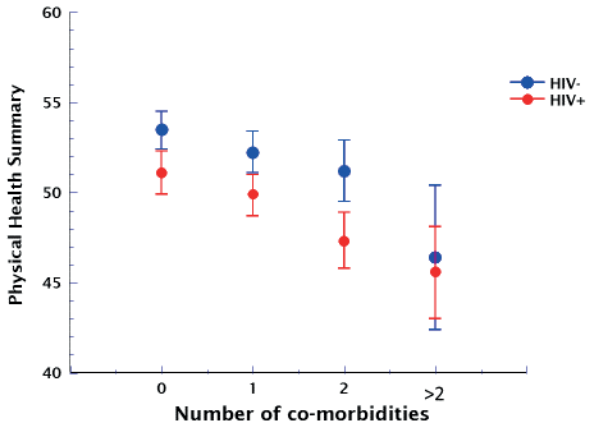


Figure 2A

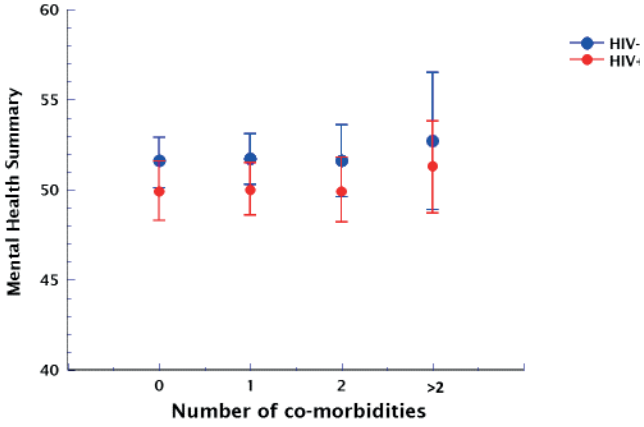
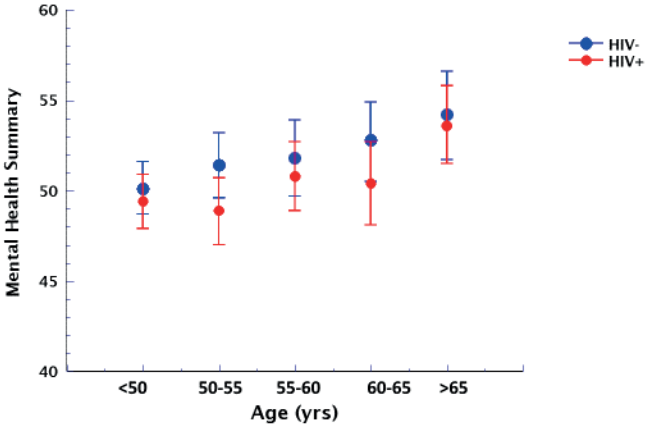


Figure 2B



Demographic, clinical/biological and lifestyle covariates associated with HRQL and depression

Covariates independently associated with a worse physical HRQL were a low grip strength, a low walking speed, HCV infection, lower educational level and not being MSM. Covariates independently associated with a worse mental HRQL were female gender, not being married or cohabiting, lower sCD14 concentrations, heavy daily drinking, being a current smoker and not using XTC daily to monthly. Covariates independently associated with an increased likelihood of depression were being of non-Dutch origin, having a low educational level, not being married or cohabiting, low walking speed, lower sCD14 concentrations and being a current smoker (Table 3). A sensitivity analysis using a CESD score ≥16 to define depression, yielded fairly similar results with two exceptions. Using the CESD, female gender was significantly associated with depression, whereas being a current smoker was not associated with depression according to the CES-D (data not shown).

Of the HIV/cART specific covariates, not being exposed to nucleoside reverse transcriptase inhibitor mono/dual therapy prior to cART initiation was independently associated with a better physical HRQL (2.7 point higher HRQL, p=0.005). None of the HIV/ART specific covariates were associated with mental HRQL or depression.

Discussion

In this cohort of HIV-positive individuals with largely suppressed viremia on cART and HIV-negative controls, all aged ≥45 years, we found that HIV-positive status was significantly and independently associated with worse physical- and mental- HRQL, as well as with an increased likelihood of depression. Differences in HRQL between HIV-positive and HIV negative individuals, however, were of a small to medium magnitude. The difference in HRQL between HIV-positive and HIV negative individuals did not become more pronounced with a higher age or with a higher number of comorbidities. A higher number of comorbidities was independently associated with worse physical HRQL. Younger age was independently associated with worse mental HRQL and a higher likelihood of depression.

Our finding that a higher number of comorbidities (12, 13), reduced walking speed (17) and grip strength (18) are associated with lower physical HRQL are in line with previous studies among HIV-infected and uninfected controls. It has previously been suggested that HIV-infected individuals may age more rapidly than their HIV negative counterparts. We therefore investigated whether the difference in HRQL between HIV-infected and HIV-uninfected individuals became greater with a higher age. We did not find such an age effect. Conversely, we observed the opposite trend in that the difference in physical HRQL between HIV-positive

and HIV-negative persons decreased somewhat with higher age, which is in line with findings from a previous study (5). However, we cannot rule out survival bias, i.e., persons with poorest HRQL may not have lived long enough to be part of the oldest age categories. We found that the difference in HRQL between HIV-positive and HIV negative individuals was statistically independent and did not become more pronounced with a higher number of comorbidities. This suggests that the negative impact of HIV on HRQL is not only entirely mediated through the increased risk of developing co-morbidities with HIV-infection.

If one of the main aims of health care is to enhance patients' HRQL, then it is important to understand which factors may be associated with impaired HRQL. HIV-positive status, a higher number of comorbidities, low walking speed, low grip strength and being HCV infected were all significantly and independently associated with a reduced physical HRQL. To the extent that these factors are modifiable, our findings suggest that optimizing the prevention and management of comorbidities and treatment of HCV co-infection may contribute to enhancing patients' HRQL. However, our findings also suggest that a negative impact of HIV-infection on HRQL will remain even in the presence of optimized prevention and management of co-morbidities and HCV co-infection, because the impact of HIV-infection was statistically independent of all other variables.

Mental HRQL and depression were independently associated with HIV-positive status, lifestyle factors, i.e., substance use, and demographic characteristics. Substance use can be both a cause and a consequence of a low mental health or depression. Given the cross sectional nature of our analysis we cannot make inferences about the direction of this relationship. Female gender, non-Dutch origin, a low educational level, and living alone were all associated with an increased risk of having a low mental HRQL and/or depression. HIV health care providers need to be alert to individuals with one or more of these characteristics as they may require more additional support or referral to mental health services.

Our finding that HIV-positive status was significantly and independently associated with lower mental HRQL and more depression is in line with a large body of evidence showing a high prevalence of depression in HIV. Negative affect in HIV infection has previously been linked to stressors such as HIV stigma and discrimination and also to poverty, unemployment, and social isolation, which are disproportionately prevalent in the HIV-infected population (31).

There is nowadays an extensive body of data showing significant associations between depression and increased inflammation and immune activation in persons with and without somatic conditions (23, 32), although some investigations have reported a lack of association, or occasionally an inverse relationship (33, 34). A few studies in HIV-infection have investigated the relationship between inflammation and immune activation and depression, with some

studies finding support for this relationship (22, 23, 35), while others did not (6, 36). Contrary to our expectation, we found that higher sCD14 concentrations were independently associated with better mental HRQL and a decreased likelihood of depression. This finding remained when we used the CES-D instead of the PHQ-9 to assess depression. In a previous study also finding such inverse relationship among a general population sample of middle aged adults, it was hypothesized that persons with better mental health might be more likely to take on physiologically demanding occupational or social roles or tasks. These demanding roles or tasks could, in turn, have resulted in increased systemic inflammation even in the absence of emotional distress (33). Another study among patients with established coronary heart disease (CHD) found that depression was associated with lower levels of inflammation. In this study, it was hypothesized that elevated levels of cortisol associated with depression might explain this relationship because cortisol has anti-inflammatory properties (34). Another explanation for the inverse relationship is the cross-sectional nature of our analysis that may not allow for properly capturing longitudinal relationships between variables. Finally, our finding might simply be due to chance.

The present study has limitations. As previously mentioned, the cross-sectional nature of our analysis does not allow for making causal inferences. Also, the present study attempted to include HIV negative controls with comparable demographic and lifestyle characteristics. Although the HIV-positive and HIV-negative study groups were largely comparable, differences in some demographic and life-style related factors were present, which was addressed by adjusting all regression analyses for a broad range of demographic and lifestyle-related factors. Nevertheless, we cannot rule out the possibility of unmeasured confounders potentially influencing our results.

In conclusion, HIV-infected individuals have a worse physical and mental HRQL and more depression than HIV-uninfected individuals. Our findings suggest that optimizing the prevention and management of comorbidities and treatment of HCV co-infection may contribute to enhancing patients' HRQL. Nevertheless, our findings also suggest that the negative impact of HIV-infection on HRQL will remain even in the presence of optimized prevention and management of co-morbidities and HCV co-infection, because the negative impact of HIV-infection was statistically independent. Future studies should continue to search for modifiable factors associated with HRQL with the aim to develop strategies tailored to the needs of the growing population of HIV-infected persons of older age to enhance their HRQL.

Acknowledgements

Funding

Funding This work was supported by The Netherlands Organization for Health Research and Development (ZonMW) together with AIDS Fonds [grant numbers 300020007 and 2009063, respectively]. Additional unrestricted scientific grants were received from Gilead Sciences; ViiV Healthcare; Janssen Pharmaceutica N.V.; Bristol-Myers Squibb and Merck&Co. None of these funding bodies had a role in the design or conduct of the study, the analysis and interpretation of the results, the writing of the report, or the decision to publish.

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CHAPTER 8

Discussion and Future Perspectives

This thesis is the result of research based on questions we encountered in treating and supporting patients in daily clinical practice. It describes the results of investigating adherence, quality of life and ageing in patients with HIV infection.

Introduction

Thirty years ago, in 1986, when I started my career as a nurse in HIV care, I only knew that we were dealing with a lethal infectious disease. Especially young homo-and bisexual men and intravenous drug users were victims of this disease as well as people who had received blood or blood products, e.g. people with hemophilia. The median time after seroconversion to the development of AIDS was seven to ten years, and with the diagnosis of AIDS, the median time till death was 2,5 years. My work as a nurse in those days was mainly to support patients, provide terminal care, and give support to their family and friends. Additionally, educating other healthcare providers about HIV and the way the virus could be transmitted was essential to help take away their anxiety to care for persons with HIV or AIDS.

The knowledge we gained in those days was mainly based on the results of medical research and on exchange of experiences with other clinicians and nurse colleagues. In those early days of the AIDS epidemic, nursing research in HIV was scarce.

Advances in AIDS research, especially the development of zidovudine (ZDV) and effective chemoprophylaxis against Pneumocystis carinii (now named Pneumocystis jiroveci) Pneumonia (PJP) have brought major changes to the clinical management of persons with HIV (1, 2). In 1987, ZDV was the only agent licensed for use in HIV disease. Soon after the introduction of ZDV, more agents became available from the same class (NRTI's) and dual-therapy became the norm. The importance and impact of adherence on the outcome of the disease was something we as nurses became increasingly aware of. In the early nineties of the last century, more and more publications became available that described nursing research on adherence, its influencing factors and the interventions needed to enhance adherence (3-6).
With the introduction of HAART in 1996, a new era started for HIV treatment. HIV changed from a lethal infectious disease into a chronic disease. However it remained very important for patients to take medication at the right time and follow the correct dietary requirements in order to avoid the selection of a resistant virus.

Being completely adherent to HAART was very difficult for patients due to the complicated regimens and the number of pills they had to take. Most medication needed to be taken three times a day, every eight hours. In addition, some protease inhibitors had to be taken on an empty

stomach (indinavir) and some with fat food (ritonavir), and one of the NRTIs, i.e., didanoside, was not allowed to be taken at the same time as one of the PIs, i.e., indinavir. This meant that some patients had to fast nine hours a day due to their treatment regimen. It is therefore not difficult to imagine that many patients experienced difficulties with adherence to this regimen. Some patients forgot a dose, others forgot to eat while taking the medication, and some others chose to take a 'drug holiday' to forget that they had a chronic illness. In the course of time, we also learned that drug-resistance could be a serious problem due to the existence of cross-resistance among the available medicines from the same class. Consequently, it became more and more difficult to give patients new combinations. To avoid resistance a high level of adherence (>95%) (8) was necessary. Adherence therefore became a hot issue in daily clinical practice. Nurses were now not only confronted with the importance of adherence, but also with the problems their patients encountered to achieve these high levels of adherence. New devices were launched to help patients take their pills at the right time and in the right way, including different types of alarms, pillboxes and computer programs (7).

We learned from studies in other chronic diseases that adherence levels were usually suboptimal. Fifty to sixty percent of patients with a chronic disease were found to be adherent to their medication and/or the required lifestyle. The question raised was how much adherence was necessary to avoid HIV resistance? Paterson and colleagues were the first researchers to publish data about viral suppression and adherence rates. They found that a level of more than 95% adherence was needed to reach viral suppression and to avoid the selection of resistant virus (8).

Adherence therefore became an even bigger challenge for nurses: coaching and supporting patients to reach and maintain these high levels of adherence. The factors that adversely impact adherence became more important; depressive feelings, lack of social support, and the experienced stigma of the HIV disease. More studies were launched on how to best measure adherence, and to evaluate adherence enhancing interventions (9-12).,

Increasingly, the perspectives of patients were taken into account, and research evolved around questions such as: What do patients think is needed to reach the high levels of adherence? What kind of support do they need? (13, 14)

In the course of those years, medication regimens also changed and became easier to take. Fixed-dose combinations were introduced, thereby reducing pill burden and once or twice daily regimens became available, which made it easier for patients to adhere. (15-19)

At the time of completion of this thesis, most newly identified patients will start cART with a once daily fixed-dose single-pill combination regimen. Despite these advances, long-term adherence still remains a challenge.

Furthermore, as a result of improved treatment options, the life expectancy of HIV-infected patients has increased tremendously. The profession of HIV-nursing has changed accordingly. Initially we knew everything about the treatment of HIV-associated infections, now we need to be aware of common co-morbidities and their treatments which patients will face as they age with HIV. Co-morbidities like hypertension, diabetes mellitus, cardiovascular disease and other common co-morbidities that occur when people grow older (20). Also the management of side-effects of the medication regimens, such as depression, osteoporosis and renal disease, needs our attention. Nurses still need to discuss medication adherence with their patients to avoid poor health maintenance habits as well as dangerous drug-drug interactions and side effects, but also lifestyle changes to prevent co-morbidities such as cardiovascular disease. Co-morbidities may be aggravated by cART. Moreover, they also require medicines, thereby making adherence an even more important focus of our attention. With HIV infection becoming a chronic instead of a lethal disease, patients' HRQL has become an increasingly important treatment outcome. Whereas antiretroviral medication may prevent full-blown AIDS, the medication and underlying chronic condition can interfere with HRQL. HIV and ageing become key issues influencing HRQL, providing nurses a unique challenge how to facilitate resilient aging in this growing population.

The impact of this thesis in daily practice

Adherence

According to Vervoort et al. the nurse plays a central role in the adherence support of HIV-infected patients (21). The results of the meta-analysis (chapter 2) can be used by nurses to prepare patients starting or switching to cART. For example, nurses may take into consideration the relevant predictors and correlates such as depressive symptoms, self-efficacy, beliefs about necessity and/or utility of cART and concerns about cART. Tailor-made interventions based on these psychological factors can be useful to support patients' adherence. The use of education and counseling of patients before and during therapy can decrease the negative influence of the above mentioned predictors/correlates on adherence, and can enhance or maintain the necessary high levels of adherence. To date cART regimens are much simpler than the regimens described in chapters 3, 4 and 5. In the induction-maintenance trial (chapter 4) we saw that simplification of the regimen -- a single tablet regimen (STR) twice daily -- resulted in higher adherence levels, treatment satisfaction and quality of life. The particular STR used in this study proved less successful after a period of time and is nowadays rarely used. The availability of novel highly effective STR's makes it possible for patients to start or switch to a once daily STR. So simplification with a STR or with the available once-daily regimen has been found to be successful in enhancing or maintaining high adherence levels (15, 18, 22, 23).

Combining various adherence measures leads to a better prediction of adherence than examining each measure separately (24, 25). The combination of patient self-reports, compared with the estimation of nurses and therapeutic drug monitoring (TDM) as seen in our study (chapter 5), and is still successfully used in our daily practice. The advantages of self-reports are the low costs and the ease of administration, and their applicability in clinical and research settings.

Electronic Drug Monitoring (EDM) is not only used as an adherence measure tool, but can also be used as an intervention, in combination with counseling to enhance adherence levels (chapter 6). The results of EDM can be used to give patients insight into their adherence levels (26-29). However, EDM is expensive, labor intensive and has a low patient acceptability, and is therefore rarely used in daily practice.

Health Related Quality of Life

UNAIDS has launched the '90-90-90' targets for the year 2020 (90% of the people are tested, 90% of those treated and 90% of those virally suppressed) but they do not mention HRQL

(30). For this reason Lazarus et.al. proposed a 'fourth 90' target – ensure that 90% of people with viral suppression have a good HRQL (31).

With the improved treatment options for HIV infection, not only adherence needs our attention, but also HRQL. As patients with HIV grow older, they are at an increased risk for age-associated non-communicable co-morbidities compared to uninfected individuals (20) which may have a negative impact on HRQL (32-37).
Furthermore, depression is more prevalent among HIV-infected persons, and can also interfere with good adherence and HRQL. Co-morbidities due to HIV-infection, ageing and cART may not only impact HRQL, but also adherence. These co-morbidities often need pharmacological interventions, which may lead to poly-pharmacy (accompanying use of multiple medications for health conditions). This increases the risk of drug-drug interactions, which may lead to drug toxicity and loss of efficacy due to suboptimal medication adherence (17). Again, the increased number of pills may affect adherence levels negatively. Given the problems related to poly-pharmacy, more non-medication approaches, such as diet, exercise, stress reduction and health education should be encouraged and evaluated with respect to their possible positive influence on HRQL.

Future HIV nursing care and research

Nurses treating patients with HIV need to be aware of the common co-morbidities patients may face as they age with HIV. The implementations of effective measures to prevent diseases, to maintain or enhance HRQL of HIV-infected patients who age, are necessary and urgent. Nursing interventions such as management of HIV and its co-morbidities, in particular to social and psychological support, may minimize negative effects on HRQL. Despite the availability of a new generation of HIV medicines and the possibilities of the STR's once daily regimen, interventions to reduce the negative effects of the above mentioned psychosocial factors thwarting adherence remains an important focus in counseling patients.
Nurse researchers need to examine new strategies to improve and maintain adherence levels in this changing population of ageing HIV-infected individuals, and find strategies tailored to their needs to maintain an acceptable HRQL.

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CHAPTER 9

Summary

This thesis contains three parts: Factors influencing adherence, assessment of and interventions aimed at adherence, and health related quality of life (HRQL) and aging.

Part I: Factors influencing adherence

The objective of the study described in **chapter 2**, was to carry out a meta-analysis of the current research evidence on: socio-demographic, treatment-related, condition-related, patient-related and interpersonal predictors and correlates of adherence to cART. We extracted quantitative estimates of the impact of these factors on adherence to cART with the aim to assess the relative importance of predictors and correlates of adherence. We included 207 studies reporting on a total of 103,836 patients. This meta-analysis showed that adherence was most strongly associated with patients' adherence-related beliefs. Other predictors which proved to be of importance were: adherence self-efficacy beliefs, concerns about adverse effects of ART and beliefs about the necessity or utility of ART, current substance use, trust in or satisfaction with the HIV care provider, depressive symptoms, HIV stigma, and social support. Aspects of regimen complexity such as daily dosage frequency, pill burden, and whether or not the treatment regimen included a protease inhibitor (PI) , yielded smaller, but still significant effects. These findings suggest that adherence-enhancing interventions should target psychological factors such as self-efficacy and necessity/concerns beliefs about cART. The results suggest several potential options for interventions to improve adherence.

The FREE study described in **chapter 3**, investigated the efficacy and safety of induction with a triple therapy consisting of a protease inhibitor (PI) and two nucleoside reverse transcriptase inhibitors (NRTIs), followed by a simple maintenance therapy with a fixed-dose single tablet combination triple NRTI regimen twice daily. This strategy of a PI-sparing therapy without losing viral efficacy had not yet been formally tested. Patients were randomized after reaching HIV-RNA less than 50 copies/ml on two consecutive occasions between 12 and 24 weeks after starting lopinavir/ritonavir (LPV/r) plus zidovudine/lamivudine (CBV). Eligible subjects switched to the fixed dose combination of abacavir/lamivudine/zidovudine (TZV) or continued the PI regimen with LPV/r and CBV. A total of 120 patients were randomized to either continuation of the induction regimen (n=59) or switching to TZV (n=61). At week 48, the proportion of patients with treatment failure (virological or treatment discontinuation) was 12% (7/57) in the TZV group and 11% (6/54) in the LPV/r/CBV group. The CD4 cell count had increased in both treatment groups at week 48 compared to their CD4 cell counts at randomization, without a significant difference between the groups (p=0.46).

After the induction phase , the patients enrolled in the FREE study were given self-report questionnaires to measure their adherence, treatment satisfaction and quality of life (Qol). These results are described in **chapter 4**. Patients completed these questionnaires at randomization, week 48, 72 and 96. Of the 120 patients who were randomized, 95 patients (79%) completed at least one questionnaire, of which 53 patients were allocated to the TZV group (87%) and 42 to the LPV/r/CBV group (71%). In this study, simplification of therapy to a fixed-dose TZV among patients with suppressed HIV-RNA was perceived to be more convenient, and resulted in improved adherence and better role functioning than continuing treatment with LPV/r/CBV. Although TZV is not a treatment of choice any longer, this study shows that simplification may enhance treatment satisfaction, adherence and QoL. Increasing the availability of single-tablet cART regimens has a major advantage, but food restrictions could still hamper optimal adherence. With patients being expected to take treatment for 30 years or longer, convenience and treatment adherence will remain of major importance to maintain patients on cART. Due to the diversity of the patients, individualization of therapy remains of the utmost importance.

Part II: Assessment of and interventions on adherence

A problem when assessing adherence, is the lack of a gold standard. Self-reports have been used most commonly since they are relatively easy to use and inexpensive. However, patients generally overestimate their adherence compared to more objective methods. In **chapter 5**, a combination of adherence measurement methods were compared amongst patients prescribed with unboosted PIs as part of their cART regimen. This study aimed to identify a set of methods that enabled adherence monitoring of all relevant aspects, including: Electronic Monitoring Devices (EMD), patient diaries, self-reports, adherence assessment by physician and clinical nurse specialist's, pill-counts and pharmacy refill data, in-depth-interviews, and therapeutic drug monitoring (TDM) indicating PI plasma levels outside predefined ranges. In addition, ultrasensitive viral load and resistance testing were performed. The study duration was 24 weeks. Twenty-eight patients were included: 21 were already taking cART and 7 were treatment naive and subsequently started cART. Twenty-six patients completed 12 weeks of follow-up and 24 completed 24 weeks of follow-up. At the end of 24 weeks in-depth interviews were conducted by the clinical nurse specialist in a subgroup of patients (14 of 26). Twenty-five percent of the patients took fewer than 95% of all doses, and two-third (32%) of the patients took fewer than 95% of the doses on time. Only 43% of the patients showed good adherence together with food restrictions.

Based on 24 patients who were followed for 24 weeks, the diary-corrected EMD-data were found to give a detailed and accurate insight into adherence patterns of the patients. In this

study the patients' self-reported estimate of adherence corresponded relatively well with the results from the EMD. There was a strong correlation with adherence according to EMD and the in-depth-interviews taken by the clinical nurse specialist. The conclusions of this study were that EMD data give detailed insight into patients' adherence patterns and TDM can be used as a direct measure to objectify the EMD results. Additionally, the study showed that patients' self-reported estimates of adherence and the estimation of the nurse, correlated strongly with the EMD data. The disadvantage of using EMD in daily practice is that it is expensive. Therefore, patients' self-reports, the estimation by the nurse and the combination with TDM are easy to implement and can be used successfully in daily practice.

EMD combined with informed counselling has been found to be a potent adherence-enhancing intervention. In **chapter 6** we describe a meta-analysis to assess the effectiveness of EMD combined with informed counselling. It aggregates the findings into quantitative estimates of the effect of such interventions on medication adherence and virological treatment outcomes.

In this meta-analysis, 13 articles reporting on 1419 patients, were used. Overall, we found that adherence was significantly better in the intervention groups which had received EMD monitoring-informed counseling as part of the intervention, compared to the control groups that did not receive such counseling. In the majority of the studies included, EMD monitoring-informed counseling was one out of a multiple of intervention components that patients received. Consequently, the contribution of just monitoring-informed counseling to improve levels of adherence and virological treatment response is difficult to establish. It reflects the clinical reality that adherence is behavior that may be affected by a multitude of factors that may best be addressed by multi-component interventions.

Part III: Health Related Quality of Life (HRQL) and Ageing

Since the introduction of cART in 1996, AIDS – associated morbidity and mortality has declined dramatically. Therefore the number of HIV-1 infected adults living into old age is steadily increasing. With this increasing age the onset of age-associated co-morbidities also increases, and these co-morbidities may negatively affect HRQL.

In **chapter 7** we investigate the possible contribution of co-morbidities, age and HIV-related factors on HRQL and depression. HIV-infected individuals and uninfected control individuals aged 45 years or older, participating in the AGE_hIV Cohort Study were screened for the presence of co-morbidities. They completed the Short Form 36-item Health Survey (SF-36) questionnaire to assess HRQL, and the nine-item Patient Health Questionnaire (PHQ-9) to assess depressive symptoms. HIV-infected individuals (*n*=541) reported significantly worse physical and mental HRQL and had a higher prevalence of depression than HIV-uninfected individuals (*n*=526). A higher number of co-morbidities and HIV-positive status were each independently associated with worse physical HRQL, whereas HIV-positive status and younger age were independently associated with worse mental HRQL and more depression. There was no evidence that the difference in HRQL between HIV-infected and HIV-uninfected individuals became more pronounced with a higher number of co-morbidities, or at an older age. In this cohort of largely well-suppressed HIV-positive and HIV-negative individuals, the HIV-positive status was significantly and independently associated with poor physical and mental HRQL and with an increased likelihood of developing depression.

The discussion (**chapter 10**) is a reflection on thirty years of clinical practice as a nurse in HIV care. The introduction of HAART in 1996 changed HIV infection changed from a lethal infectious disease into a chronic disease and therefore also changed the profession of HIV-nursing. Recent developments in the treatment of HIV and the meaning of these for nursing care are described as well as considerations for future research.

Appendix

Nederlandse Samenvatting

Inleiding

Sinds de introductie van combinatietherapie voor de behandeling van een HIV- infectie in 1996, is de levensverwachting van met HIV geïnfecteerde mensen aanzienlijk toegenomen. HIV kan nu dan ook getypeerd worden als een chronische infectieziekte in plaats van een dodelijke infectieziekte.
Sinds 1996 zijn de ontwikkelingen op het gebied van combinatie therapie doorgegaan en is de hoeveelheid pillen die men in moet nemen aanzienlijk verminderd. Ondanks deze verbetering is het voor veel mensen moeilijk om therapietrouw te zijn en voor succes van de behandeling is een hoge mate van therapietrouw (>85%) noodzakelijk. Bij een te lage therapietrouw bestaat de kans op resistentie tegen het gebruikte middel, waardoor dit zijn werkzaamheid verliest.
Door deze ontwikkelingen op het gebied van behandeling worden mensen met HIV ouder en kunnen daardoor geconfronteerd worden met andere niet-HIV gerelateerde aandoeningen, zoals verhoogde bloeddruk, suikerziekte en verhoogd cholesterol. Tevens kunnen zij nog steeds last hebben van bijwerkingen van de medicijnen, zoals verminderde nierfunctie en botontkalking. Voor de behandeling van deze co-morbiditeiten zijn vaak weer andere medicijnen nodig. Hierdoor neemt de hoeveelheid in te nemen pillen en vaak ook het aantal inname momenten toe. Ook kunnen deze co-morbiditeiten een negatieve invloed hebben op de kwaliteit van leven. Dit alles kan dan weer meer kans geven op een verminderde therapietrouw.
Dit proefschrift bestaat uit drie delen. Deel I beschrijft factoren die therapietrouw beïnvloeden en tevens of simplificatie van therapie een betere therapietrouw geeft en van invloed is op de therapie-tevredenheid en op de kwaliteit van leven van de patiënt. In deel II wordt er gekeken welke effectieve methoden er gebruikt kunnen worden om therapietrouw te meten, dan wel uit te vragen bij de patiënt en welke interventie mogelijkheden er zijn om de therapietrouw te verhogen of de hoge mate van therapietrouw voort te zetten. Deel III handelt over de kwaliteit van leven en het ouder worden met HIV.

Deel I: Factoren die therapietrouw beïnvloeden

De meta-analyse, beschreven in **hoofdstuk 2**, is uitgevoerd om factoren die therapietrouw beïnvloeden te vinden binnen de bestaande wetenschappelijke literatuur en te kijken welke factoren het meest van belang zijn bij therapietrouw. Hierbij ging het om socio-demografische gegevens, therapie-gerelateerde, conditie-gerelateerde, patiënt-gerelateerde

en interpersoonlijke factoren. Deze meta-analyse laat zien dat therapietrouw het meest beïnvloed wordt door de overtuiging van de patiënt van het belang van therapietrouw, het geloof dat men therapietrouw kan zijn (zelf-effectiviteit), ongerustheid over bijwerkingen en de overtuiging van het nut en noodzaak van de medicijnen. Verder waren ook middelengebruik (zoals alcohol en/of drugs), vertrouwen in en tevredenheid over de hulpverlener, het HIV stigma en sociale steun uit de naaste omgeving van de patiënt in hoge mate van invloed op de therapietrouw. Aspecten van complexiteit van de behandeling, zoals de dosis frequentie, hoeveelheid pillen en of er een proteaseremmer in het regime opgenomen zat, zijn ook van invloed op de therapietrouw. De invloed hiervan was kleiner dan de eerder genoemde factoren, maar bleken wel significant te zijn.
De resultaten uit de meta-analyse geven voldoende handvatten om interventies in te zetten om de negatieve invloed van deze factoren weg te nemen en daarmee de therapietrouw te verhogen en te handhaven op een hoog niveau.
In **hoofdstuk 3** wordt een klinische studie beschreven waarin twee regimes met elkaar zijn vergeleken op veiligheid en effectiviteit. Patiënten in deze studie starten allemaal met lopinavir/ritonavir (LPV/r) en lamivudine/zidovudine (CBV). Tussen week 12 en 24, bij twee maal een ondetecteerbare viral load, worden patiënten gerandomiseerd naar of doorgaan met het huidige regime of over naar een klasse sparend regime, bestaande uit een combitablet van abacavir/lamivudine/zidovudine (TZV) beiden twee maal daagse inname. Beide regimes bleken op week 48 veilig en effectief.
Binnen deze studie (**hoofdstuk 4**) hebben patiënten vragenlijsten ingevuld naar therapietrouw, therapietevredenheid en kwaliteit van leven. Hieruit kwam naar voren dat het vereenvoudigede regime van TZV een betere therapietrouw liet zien, grotere therapietevredenheid en een hogere kwaliteit van leven. Deze studie toont aan dat simplificatie van therapie, in dit geval minder pillen, een factor is die de therapietrouw verhoogd.
Bovenstaande studie is al wat ouder en de regimes die hierin onderzocht zijn, worden niet meer gebruikt. Tegenwoordig zijn het bijna allemaal eenmaal daagse regimes en veel combinatie zijn inmiddels verwerkt in combinatiepillen.

Deel II: Methoden om therapietrouw te meten en interventies om therapietrouw te verhogen

De studie die beschreven wordt in **hoofdstuk 5** is al in de beginjaren van de combinatietherapie uitgevoerd. Hierbij werden nog de oude regimes met ongebooste proteaseremmers gebruikt. In deze studie is gekeken naar gecombineerde meetmethoden voor therapietrouw. Er blijkt geen gouden standaard te zijn om therapietrouw te meten. In de meeste gevallen wordt gebruik gemaakt van vragenlijsten die patiënten zelf invullen, de zogenaamde zelf-rapportage. Dit is een makkelijke en goedkope methode, maar kan nog wel eens overschatting

geven van de therapietrouw. In deze studie is er een combinatie van verschillende methoden gebruikt. Naast zelf-rapportage is er gebruik gemaakt van elektronische monitoring, welke registreert wanneer de pot waar de medicatie inzit geopend wordt, en de inschatting van de therapietrouw door de arts en de verpleegkundig specialist. In een subgroep van deze patiënten zijn bovendien diepte-interviews afgenomen. Daarnaast is er in het bloed gekeken naar de medicatiespiegels (TDM) en HIV-RNA. In deze studie hebben zowel startende patiënten en patiënten die al op therapie stonden meegedaan. Er wordt in de literatuur vanuit gegaan dat elektronische monitoring en TDM objectieve metingen zijn, en dat de andere metingen meer subjectief zijn.
Uit de studie komt naar voren dat een combinatie van de verschillende metingen een goed beeld geeft van de mate van therapietrouw van een patiënt. Een combinatie van zelf-rapportage, inschatting van de therapietrouw door de verpleegkundig specialist en TDM blijkt een goede en praktische methode te zijn om ook in de dagelijkse praktijk de mate van therapietrouw bij een patiënt te meten.
Elektronische monitoring, in combinatie met counseling, wordt ook gebruikt in studies als interventie om patiënten inzicht te geven in hun medicijn inname patroon. Van deze interventie wordt verwacht dat hierdoor de therapietrouw hoger zal worden. Om te kijken of dit inderdaad de therapietrouw bevordert, hebben we een meta-analyse uitgevoerd (**hoofdstuk 6**) waarin studies met deze interventie met elkaar zijn vergeleken om zicht te krijgen of deze interventie inderdaad de therapietrouw verhoogd.
Hiervoor hebben we 13 studies gevonden waar in totaal 1419 patiënten aan deelnamen. Hierbij zagen we dat elektronische monitoring in combinatie met counseling inderdaad een hogere mate van therapietrouw laat zien in vergelijking met de controlegroepen die geen counseling ontvingen. Echter in de meeste studies werden meerdere interventies ingezet, dus het is lastig om te concluderen dat elektronische monitoring in combinatie met alleen counseling deze resultaten geeft.

Deel III: Kwaliteit van Leven en de ouder wordende HIV patiënt

Sinds de introductie van combinatie therapie in 1996 is HIV een chronische ziekte geworden. Dit betekent dat patiënten tegenwoordig ook ouder worden dan in het verleden. Met het stijgen van de leeftijd worden patiënten nu geconfronteerd met ziektes die horen bij het ouder worden, zoals bijvoorbeeld hypertensie en suikerziekte. Ook de medicatie kan hierop van invloed zijn en op de langere termijn andere aandoeningen geven zoals verminderde nierfunctie, botontkalking en een verhoging van de bloedvetten, waardoor de kans op hart- en vaatziekten toeneemt. Deze aandoeningen kunnen van invloed zijn op de kwaliteit van leven (**hoofdstuk 7**).

Binnen de AGE$_h$IV Cohort studie, waarin een groep HIV patiënten van 45 jaar en ouder (n= 541) is vergeleken met een vergelijkbare groep niet-geïnfecteerde personen ook van 45 jaar en ouder (n=526), worden de mensen gescreend op de aanwezigheid van co-morbiditeiten en hebben zij vragenlijsten ingevuld over de kwaliteit van leven en de aanwezigheid van depressieve symptomen. Een groter aantal co-morbiditeiten en een HIV positieve status waren beiden onafhankelijk geassocieerd zijn met een verminderde fysieke kwaliteit van leven. Een HIV positieve status en een jongere leeftijd waren onafhankelijk geassocieerd aan een slechtere mentale kwaliteit van leven en meer depressieve symptomen. Er werd geen bewijs gevonden dat het verschil in kwaliteit van leven tussen HIV-geïnfecteerden en niet-HIV geïnfecteerden duidelijker werd met een hoger aantal co-morbiditeiten. Belangrijk is wel dat co-morbiditeiten zoveel mogelijk voorkomen moeten worden en indien aanwezig, zo goed mogelijk behandeld, waardoor de negatieve invloed op de kwaliteit van leven af zou kunnen nemen. Dat neemt echter niet weg HIV een negatieve impact blijft houden op de kwaliteit van leven, ook wanneer preventie maatregelen worden genomen om co-morbiditeiten te voorkomen of deze optimaal te behandelen.

In de discussie (**hoofdstuk 8**) wordt terug gekeken op de dertig jaar dat ik als verpleegkundige in de HIV zorg werk. Een zeer belangrijke de ontwikkeling in die dertig jaar is de introductie van combinatie antiretrovirale therapie. Hierdoor is HIV veranderd van een fatale ziekte naar een chronische ziekte. De regimes van de antiretrovirale therapie zijn in de loop der jaren sterk vereenvoudigd en in veel gevallen kan er volstaan worden met een combinatietablet eenmaal daags. Toch blijft therapietrouw een belangrijk aandachtspunt binnen de verpleegkundige zorg.

Doordat patiënten tegenwoordig ouder worden als gevolg van deze antiretrovirale therapie, worden zij nu geconfronteerd met co-morbiditeiten als gevolg van een hogere leeftijd en langdurig medicatie gebruik.

Voor deze co-morbiditeiten hebben mensen vaak weer andere medicijnen nodig, waardoor het positieve effect van eenmaal daags één tablet wegvalt en de therapietrouw weer moeilijker wordt. Door deze co-morbiditeiten kan ook de kwaliteit van leven minder worden. Verpleegkundige interventies gericht op effectieve maatregelen om co-morbiditeiten te verminderen, therapietrouw te verhogen en de kwaliteit van leven te handhaven of te verbeteren, blijven noodzakelijk.

Toekomstig verpleegkundig onderzoek zou dan ook gericht moeten zijn om nieuwe strategieën te onderzoeken therapietrouw te verhogen in deze veranderde en ouder wordende patiëntenpopulatie en strategieën te vinden gericht op de behoeften van patiënten om de kwaliteit van leven te handhaven of te verbeteren.

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PHD Portfolio

Name PhD Candidate:	Nienke Langebeek
PhD period:	2012 - 2017
Supervisors:	Prof. M.A.G. Sprangers and Prof. P. Reiss
Co-supervisor:	Mw. Dr. P.T. Nieuwkerk

General courses:
NSPOH – Summercourse Epidemiology, Zweeloo
GCP-WMO, EWMO, Rijnstate Ziekenhuis Arnhem
Scientific writing in English, Post- Amsterdam Graduate School

Presentations:
Does a simplified regimen give a better adherence, treatment satisfaction, and quality of life? (*posterpresentation*)

HIV Drug and Therapy Conference Glasgow 2012

A simplified combination antiretroviral therapy (cART) regimen enhances adherence, treatment satisfaction and quality of life: results of a randomized clinical trial

V&VN VS Congres, Papendal 2013 (*oral presentation*)
European HIV Nursing Conference Barcelona 2013
Wetenschaps Symposium Ziekenhuis Rijnstate 2013

Predictors and correlates of adherence to combination antiretroviral therapy (cART): meta-analysis (*oral presentations*)

NCHIV Amsterdam, 2013
V&VN VS Congres, Papendal 2013
European HIV nursing Conference, Barcelona 2013

Impact of co-morbidity and ageing on health related quality of life in HIV-positive and HIV-negative individuals (*oral presentations*)

NCHIV Amsterdam, 2015
SOAAIDS Congres Amsterdam, 2015
European HIV Nursing Conference, Barcelona 2016

Impact of co-morbidity and ageing on health related quality of life in HIV-positive and HIV-negative individuals (*powerpoint presentation*)

VS Symposium Ziekenhuis Rijnstate Arnhem – innovatie en wetenschapsmarkt, 2016
Teaching activities:

Lectures:
Hepatitispoli: de rol van de verpleegkundige, Hepatitis Course Janssen BV, Utrecht 2012

HIV & AIDS: 1982 – heden: DIVAS, Rijnstate Hospital Arnhem, 2012

Evidence Based Medicine: Refereeravond Verpleegkundig Specialisten, Rijnstate Hospital Arnhem, 2013

Therapietrouw bij chronisch medicatie gebruik: Master Advanced Nursing Practice

Lustrumcongres Hogeschool Utrecht, Driebergen 2014

Psychiatrische klachten en hiv: Praktische ervaring vanuit de AGZ, HIV op de Agenda, Amsterdam 2014

SOA screening, Workshop voor dokterassistenten, Medische Microbiologie, Rijnstate Hospital Arnhem, 2015

International Course HIV and Food and Nutrition Security - Medical Aspect of HIV and Aids, Wageningen University, Wageningen 2016

Supervising:
Praktijkopleider voor Verpleegkundig Specialisten in opleiding, Rijnstate Hospital and Hogeschool Arnhem-Nijmegen, 2013 - ongoing

Dankwoord

Dit proefschrift was niet tot stand gekomen, zonder de hulp van een aantal mensen. Hoewel ik ongetwijfeld mensen zal vergeten wil ik toch een poging wagen om zo volledig mogelijk te zijn.
Allereerst wil ik Clemens Richter bedanken. Clemens, mede door jouw enthousiasme ben ik geïnteresseerd geraakt in het doen van onderzoek. Daarbij gaf je mij een kans om binnen de FREE studie als subinvestigator een onderzoek te doen naar therapietrouw, therapietevredenheid en kwaliteit van leven. Dit is de eerste stap geweest tot promoveren en als je dit leest, dan is het ook daadwerkelijk gelukt. Dank dat ik al die jaren met je heb mogen samenwerken. Het waren mooie en leerzame jaren.

Mirjam Sprangers en Peter Reiss, mijn beide promotoren, wil ik bedanken. Mirjam, heel veel dank dat je het destijds zag zitten om als promotor op te treden. Na een jaar watertrappelen en proberen mijn hoofd boven water te houden, zorgde jij en Pythia ervoor dat ik in een warm bad belandde en dat ik gekomen ben tot het schrijven van dit proefschrift.
Peter, jij ook dank, dat je mijn promotor wilde zijn. Jij gaf destijds aan, toen ik je vroeg, dat je het een eer vond dat ik je hiervoor gevraagd heb. Nou Peter ik vond het zeker een eer dat je het wilde doen. Veel dank hiervoor.

Pythia, dat jij samen met Mirjam, alles in kannen en kruiken had, toen ik voor een eerste gesprek bij je kwam, was heel bijzonder, en ik ben je daar nog steeds dankbaar voor. Fijn dat je het al die jaren met mij hebt uitgehouden. Het resultaat is er uiteindelijk gekomen. Ik zal onze lunches, om 11.30, op de dinsdagen missen. Ik hoop dat we in de toekomst nog eens wat samen kunnen doen.

Tevens wil ik de leden van de promotiecommissie, Prof. Burger, Prof. Kaasjager, Prof. Brinkman, Prof. Geerlings, Prof. De Haan, Prof. Roodbol danken voor de kritische beoordeling van mijn manuscript.
David, Karin, Kees, Suzanne, Rob en Petrie, dank dat jullie direct positief hebben gereageerd op mijn verzoek om plaats te nemen in de commissie. Het voelde heel goed dat jullie zo enthousiast reageerden.

Petra, Gerjanne en Marja, heel erg veel dank dat jullie mij hierin gesteund hebben en zo af en toe mijn chagrijnige buien hebben getrotseerd. Het was fijn dat ik elke week een dag of in Amsterdam of thuis mijn gang kon gaan en kon werken naar dit uiteindelijke resultaat. Gerjanne dank ook dat jij als paranymf naast me wil staan.

Jet Gisolf, dank dat je zo af en toe eens een zetje gaf om toch vooral door te zetten, al viel dat zo nu en dan niet mee. Het heeft uiteindelijk wel geleid tot dit resultaat.

Robert-Jan en Mark, jullie hebben natuurlijk alleen het laatste stukje meegemaakt. Robert Jan, jij zat even in dezelfde situatie, en het was fijn om zo nu en dan eens te checken of ik de "regelen der promotie" wel goed invulde.
Mark, fijn dat je bij ons bent komen werken, je bent een waardige vervanger van Clemens. Ik waardeer je enthousiasme enorm en hoop nog een tijd te mogen samenwerken.

Hella Grandjean, ik mis je op de werkvloer, heerlijk af en toe die cynische humor van je te horen, dank dat je mijn paranymf wil zijn. Ik hoop dat je het heel erg naar je zin hebt op je nieuwe werkplek (bij je oude maatje).

Maria van der Linden, heel veel dank dat je bereid was om mijn Engelse teksten ook echt Engels te maken. Het zal af en toe wel lastig zijn geweest, maar je commentaar gaf vaak aan, dat ik zaken anders moest opschrijven, wilde het voor de buitenstaander ook leesbaar zijn.

Katherine, Ferdinand en Peter, wat fijn dat ik mocht inhaken bij het AGEhIV Cohort en daar de invloed van co-morbiditeiten op de kwaliteit van leven bij hiv-geïnfecteerden en niet-geïnfecteerden mocht opschrijven. Het heeft me zeker geïnspireerd om hier in de toekomst mee door te gaan. Zeker gezien het feit, dat mijn patiëntengroep veel mensen van 45 jaar en ouder bevat. Ik zal zeker nog wel contact met een van jullie hierover opnemen, om te kijken hoe de verpleegkundige praktijk voor deze groep patiënten kunnen verbeteren. Want dat daar een aantal zaken opgepakt moeten worden, dat is mij wel duidelijk geworden.

Alle medewerkers van de afdeling Klinische Psychologie van het Academisch Medisch Centrum wil ik bedanken voor de gastvrijheid, die ik heb ondervonden. Jullie gaven mij direct het gevoel dat ik erbij hoorde, terwijl ik toch maar een dag per week en later nog maar af en toe van jullie gastvrijheid gebruik heb gemaakt. Jullie enthousiasme tijdens de onderzoeksbijeenkomsten hebben mij er mede toe aangezet om te kijken of dit ook binnen de verpleegkundig specialisten groep georganiseerd kan worden.

Patricia Hugen, het is lang geleden dat jij bezig was met je promotie en dat ik betrokken raakte bij jouw onderzoek. Dank dat ik hieraan mee mocht doen en dat ik als tweede auteur in een aantal artikelen vermeld sta, wat mede ook te danken is aan David Burger. Dit was toch wel de allereerste aanzet voor mijn promotie.

Jeroen Heijnen, dank dat je me op de valreep hebt geholpen, nadat ik de wanhoop nabij was met het invoegen van de kopteksten. Dank zij jou is het me uiteindelijk gelukt!

Alle artsen, verpleegkundig consulenten en researchverpleegkundigen die deel hebben genomen aan de FREE studie, heel veel dank voor jullie medewerking binnen de studie en het verzamelen van de gegevens. Zelfs na afsluiting van de studie waren jullie bereid om de deelnemers nogmaals om toestemming te vragen om nog verdere gegevens op te vragen. Sorry voor deze extra werkzaamheden die jullie hiervoor hebben moeten doen.

Natuurlijk wil ik ook alle mensen bedanken die bereid waren deel te nemen aan de onderzoeken. Zonder hun medewerkingen zouden deze onderzoeken niet hebben plaatsgevonden.

Als laatste wil ik toch nog even Herman Sprengers noemen, Herman, ook jij hebt gegevens van de FREE studie gebruikt voor je promotie. Ik had niet gedacht dat het je zou lukken om voor mij te eindigen. Proficiat met je promotie en ga nu lekker ontspannen van je pensioen genieten.

Bas, dat je het al vele jaren met mij uithoud, zegt al genoeg. We zeggen het niet vaak tegen elkaar, maar ik hou van je!

Als laatste wil ik mijn ouders herdenken. Helaas hebben jullie deze promotie niet meer mee mogen maken, maar wat zouden jullie trots zijn geweest.
Ik mis jullie!

Curriculum Vitae

Nienke Langebeek was born on the 16th of October 1957 in Utrecht. She grew up in Roden, a little village in the north of the Netherlands. After her graduation at the Scholengemeenschap Noordenveld-Westerkwartier in Leek, she started her nursing career in the Academic Hospital in Utrecht and the Academic Hospital Dijkzigt in Rotterdam. In 1986 she became a consultant nurse in aids care. After graduation as clinical nurse specialist she started with the Master of Science in Nursing at the Hogeschool Utrecht in corporation with the University of Wales and graduated in 1998.

She moved to Arnhem and start working in the Rijnstate Hospital in 1997. After graduating the Master in Advanced Nursing Practice at the Hogeschool Utrecht, she is registered as Nurse Practitioner (Verpleegkundig Specialist Intensieve zorg bij somatische aandoeningen). From 2003 till 2009 she was sub investigator in the Free study which was the beginning of her PhD program.