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INTRODUCTION

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HIV infected patients treated with cART

The management of human immunodeficiency virus (HIV) infection has changed considerably since the discovery in the mid-nineties that combination antiretroviral therapy (cART) can suppress HIV replication, resulting in subsequent immune recovery. Wide-scale introduction of cART in the Western world has resulted in a substantial increase in survival of HIV infected patients. HIV infected patients treated with cART experience less disease-related symptoms, resulting in higher levels of quality of life.[1] However, survival and quality of life of HIV infected patients are still impaired in comparison with the general population.[2] Quality of life may be influenced by the disease, cART and the need to adhere to lifelong treatment. Furthermore, quality of life and adherence to treatment may be impaired due to several psychosocial factors that may be present among HIV infected patients such as experience of HIV stigma and depression.

Quality of life

Quality of life can be defined in many ways. It is a multidimensional concept including the three large areas of physical, psychological, and social functioning, which may be affected by disease and treatment.[3] A key purpose of treatment with cART is to increase the level of quality of life of HIV infected patients.[4] Quality of life may be impaired by disease-related factors which may result from a deteriorated immune system, resulting for instance in opportunistic infections. Additionally, quality of life may be affected by cART due to adverse effects of varying severity.[5-10] Former studies have shown that poor physical or mental quality of life and self-reported symptoms are related to nonadherence and worse treatment outcome.[11-14] Also, poor quality of life negatively influences survival of HIV infected patients receiving cART, independently of socio-demographic and clinical variables.[13, 14] There is little knowledge about the course of symptoms and quality of life among HIV infected patients on cART over a long time. Moreover, the impact of symptoms and quality of life on treatment outcome (i.e. virological failure and survival) has only been investigated in studies with a short follow-up time.[13-15]

Treatment adherence

The main purpose of cART is to suppress viral replication. Virological treatment failure arises when replication is insufficiently suppressed and may ultimately lead to resistant virus strains development. To prevent treatment failure and development of resistant virus, high levels of adherence to treatment are needed.[16] The definition of adherence to HIV treatment is the
extent to which a patient takes his or her medication according to the prescription of the clinician.\[17\] Several studies have shown that higher levels of adherence to cART lead to fewer virological failures and improved survival.\[18-27\]

In recent years, convenience of taking cART has improved significantly, because patients may need to take fewer pills and doses of cART per day. Moreover, the toxicity of regimens has been substantially reduced. Still, HIV infected patients have difficulties with achieving the required high levels of adherence.\[28,29\] Suboptimal adherence may be influenced by several factors such as characteristics of the patient, the HIV disease itself and by different cART-regimens.\[30\]

Adherence to treatment can be investigated using several methods, such as self-reports, (un)announced pill counts, electronic drug monitoring systems, plasma drug level measurement and counting of pharmacy refill data.\[31\] The most widely used measures of adherence are self-reports and pharmacy refill data, which have been shown to correlate well.\[31-33\]

Although self-reported adherence may be subject to social desirability bias and recall bias, it is a simple and inexpensive way to measure adherence. Several studies found a relation between self-reported nonadherence and virological failure.\[25,33,34\] Up till now there have been few studies investigating the influence of social desirability bias on the relation between self-reported adherence and virological response.\[35-38\]

Pharmacy refill data are often used as adherence assessment method and they are also convenient and inexpensive as not much effort from patients is needed.\[21,39,40\] However, some challenges remain, such as the feasibility of obtaining pharmacy refill data from multiple pharmacies and the optimal way to calculate a comprehensive adherence measure from these data.\[31\] Adherence can be calculated by averaging adherence of each antiretroviral drug taken by the patient or by using the adherence to one drug only. Additionally, when calculating adherence, it may be important to account for leftover medication from previous refills and instructed treatment interruptions. To the best of our knowledge, these different calculations of adherence and their prediction of virological failure have never been investigated in a single study.

HIV stigma, depression and beliefs about medication

Several psychosocial factors are known to be associated with adherence. First, HIV stigma may result in lower adherence.\[41-44\] HIV stigma refers to the social notion that someone, in this case the HIV infected patient, is considered to hold a shameful characteristic and consequently is blemished by other persons.\[45,46\] In general, heterosexualy infected HIV patients, and especially women, are known to experience or perceive more HIV stigma than white men having sex with men (MSM), as they lack the supportive networks and the relative HIV/AIDS tolerant mind-set commonly experienced within the MSM population.\[47\] Previous studies have shown that HIV stigma is associated with poor quality of life and depression.\[41,48\]

Second, depression might lead to suboptimal adherence through different mechanisms. \[11,34,49-51\] Spire at al. found that the development of depression during the course of treatment rather than depression at the start of cART affects adherence.\[49\] However, a review on predictors of adherence showed that the relation between depression and/or quality of life and adherence was inconsistent. Some studies found that depression affects adherence while others did not find such relation.\[52\]

Third, beliefs about medication might play a role in taking medication. Doubts about the necessity of cART and concerns about adverse effects of cART predict lower levels of adherence to cART.\[53-57\] All these psychosocial factors may relate to each other and predict nonadherence and virological failure. However, there is little and inconsistent knowledge about the exact mechanism of the prediction of nonadherence and virological failure by these psychosocial factors.

Immigrant HIV infected patients in the Netherlands

The HIV infected population in the Netherlands has evolved from a population mainly consisting of Dutch MSM to a population with an increasing percentage of HIV patients being infected heterosexually and of immigrants. Patients born in Sub Saharan Africa, and Surinam and the Netherlands Antilles form the largest group of immigrants.\[58\] CART was found to be less effective among immigrant HIV infected patients in the Netherlands, as demonstrated by a lower incidence of suppression of HIV RNA to levels below 50 copies/ml blood among immigrants in comparison to Dutch indigenous patients.\[59\] In another Dutch cohort, non-European patients more often failed on cART than European patients.\[60\] Worse treatment outcome among immigrants might be due to lower adherence to cART. In the Americas, studies have found worse adherence among non-whites.\[23,6\] Additionally, the clinical impression of poorer adherence among immigrant HIV infected patients was confirmed in studies in the Netherlands, which showed more unstructured treatment interruptions among immigrant patients\[62\] and more self-reported nonadherence.\[63\]

It is often thought that immigrant patients do not take their medication correctly, because they have more difficulties understanding the disease and treatment instructions. However, HIV infected immigrants in the Netherlands who originated from Sub Saharan Africa, Surinam or the Dutch Antilles were found to have adequate knowledge of HIV infection and treatment.\[64,65\] Consequently, the difference in adherence to cART and treatment outcomes between immigrant and indigenous Dutch patients cannot be explained by a difference in HIV related knowledge. Remarkably, a qualitative study showed that immigrant HIV infected patients reported lower levels of quality of life. Also, immigrant patients reported considerable levels of depression and HIV stigma concerns, especially fear of social exclusion.\[64\] As mentioned above, HIV stigma and depression are known risk factors for nonadherence. Additionally, HIV stigma associated with taking medication was shown to influence adherence directly in ethnic minority groups.\[66\] The finding that patients in ethnic minority groups experience more depression than indigenous patients confirms findings from earlier studies.\[47\] Moreover, beliefs about medication are influenced by ethnic background.\[67\] Therefore, poorer
adherence and worse treatment outcome among immigrant patients may be caused by poorer levels of quality of life, more HIV stigma and depression, more doubts about the necessity of cART and more concerns about adverse effects of cART in comparison to indigenous patients. These factors have never been investigated simultaneously in a single multivariate model.

Outline of thesis

The overall aim of this thesis is to investigate the extent to which quality of life, HIV stigma, depression and beliefs about medication influence adherence to cART and treatment outcome among HIV infected patients in the Netherlands. An additional aim is to examine the extent to which these factors account for differences in levels of adherence and treatment outcome between immigrant patients and Dutch indigenous HIV infected patients.

In this thesis, several terms are used to indicate HIV medication in the different chapters and they are used as synonyms. These are combination Antiretroviral Therapy (cART), Highly Active Antiretroviral Therapy (HAART) and Antiretroviral (ARV) drugs. The term ‘ARV’ is mostly used when referring to particular drugs. Additionally, another term for quality of life is used in chapter 3, namely Health-Related Quality of Life (HRQL).

The first two chapters focus on quality of life. Improvement of quality of life is one of the main goals of cART and quality of life might influence adherence to treatment and treatment outcome. Symptoms experienced by patients may affect quality of life. In chapter 2 we describe a longitudinal study that examines the course of self-reported symptoms and their relation with concurrent quality of life, particular ARV drugs and concurrent virological failure. This was investigated in HIV infected patients who participated in the Netherlands in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort.

Former studies have shown that quality of life predicts survival; however these studies were limited due to a small sample size or a short follow-up time. To examine the effect of quality of life on treatment outcome in terms of survival, we conducted a longitudinal study, which is described in chapter 3. In this study we investigated the influence of quality of life at baseline on survival of HIV infected patients on cART in the ATHENA cohort.

The following two chapters target primarily on the measurement of adherence. Because the optimal way to calculate pharmacy refill adherence is largely unknown, we investigated different calculations of pharmacy refill adherence in their ability to predict virological failure in chapter 4. This study was part of the larger THETRHA (THerapieTRouw HAart which can be translated into Adherence to cART) study in which pharmacy refill data were collected from multiple pharmacies. We were therefore able to investigate the feasibility of conducting such a study when multiple pharmacies are involved. Considering the calculation, we first investigated the extent to which taking into account leftover medication in pharmacy refill adherence impacts the prediction of virological failure. Second, we investigated the effect of accounting for instructed treatment interruptions on the prediction of virological failure.

Another method to assess adherence to cART is self-report. This way of measuring adherence may however be subject to social desirability bias. In chapter 5, we investigated the relationships between self-reported adherence and virological response for HIV infected patients who are more prone to respond in a socially desirable way compared with HIV infected patients who are not. Patients participated in the ATHENA cohort.

The remaining chapters focus on the explanation of nonadherence by psychosocial factors. One factor determining treatment adherence is beliefs about medication. In chapter 6, we studied the influence of doubts about the necessity of cART and concerns about its adverse effects on adherence to cART among HIV infected patients in the ATHENA cohort.

HIV stigma might be another important predictor of nonadherence to cART. To ensure the use of an adequate measure for HIV stigma, we first evaluated the use of the Berger HIV stigma scale [48] in a population of Dutch indigenous and immigrant HIV infected patients using an interview format. This study is part of the THETRHA study and is described in chapter 7.

In chapter 8 we examined the extent to which adherence to cART and treatment outcome are explained by a model in which immigrant origin influences treatment adherence and outcome via HIV stigma, depression, quality of life, and beliefs about medication. We investigated this in the THETRHA population.

A summary of our findings is given in chapter 9. Recent developments and suggestions for further research are also provided and discussed.


