Combination antiretroviral therapy among immigrant and indigenous HIV infected patients: quality of life and treatment adherence

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Summary, Discussion and Concluding Remarks
SUMMARY

The overall aim of this thesis was 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 was to examine to what extent those factors account for levels of adherence and treatment outcome among immigrant patients in comparison to indigenous HIV infected patients.

Chapter 1 gives an introduction to HIV infected patients using cART, quality of life, and the relevance of adherence to treatment in HIV infection. Methods to assess adherence and possible psychosocial factors influencing adherence to treatment and treatment outcome are introduced. Furthermore, we describe the situation of immigrant HIV infected patients in the Netherlands.

In chapter 2, we investigated longitudinally the extent to which patients experience a variety of symptoms in a cohort of HIV infected patients receiving cART, the national AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. Data collection started in 1998 retrospectively of patients who started cART before 1998, and prospectively of patients who started cART thereafter. Data about clinic visits, demographic, epidemiological and clinical outcomes, and laboratory measurements are registered. Patients received a questionnaire asking about symptoms and physical and mental quality of life every six months since study entry. The first aim was to investigate the course of self-reported symptoms over time. We found a high prevalence of self-reported symptoms with many symptoms being reported in more than 30% of the questionnaires of each patient. Reporting of ‘numb feeling in fingers or toes’, ‘pain in legs’, ‘pain when urinating’, ‘sore muscles’, ‘tingling of hands or feet’ and ‘difficulties with seeing’ increased significantly over time. Next, we investigated the relevance of self-reported symptoms for the individual patient by exploring associations between self-reported symptoms and concurrent quality of life and virological failure. All self-reported symptoms were associated with concurrent physical and mental quality of life, even after adjustment for clinical and demographic parameters. Additionally, trouble with sleeping, constipation, pain in legs and numb feeling in fingers or toes were significantly related to a concurrent detectable viral load (plasma HIV RNA >500 copies/ml blood). The finding that most symptoms were related to using particular ARV drugs suggests that these symptoms may be adverse effects of drugs. Because symptoms are frequently reported and are related to lower levels of quality of life and worse treatment outcome, i.e. detectable viral load, identification and management of symptoms among HIV infected patients is highly important. Future studies should investigate strategies to decrease symptoms experienced by HIV infected patients on cART.

In chapter 3, we examined the extent to which baseline quality of life predicted treatment outcome, i.e. survival, among HIV infected patients in the ATHENA cohort. This study added to existing knowledge because of the long follow-up (median of 8.4 years). Physical and mental quality of life were assessed at study entry. Time was censored at the end of follow-up, which was the last contact with the hospital or date of death, whichever happened first. Physical and mental quality of life were divided into quartiles. Lower levels of physical quality
of life at baseline were significantly related with an increased likelihood of death during the follow-up period. However, we did not find this pattern for mental quality of life. Causes of death varied among patients, but there was no clear relation between causes of death and levels of quality of life. We found that higher levels of physical quality of life also independently predicted survival in Cox proportional hazards regression analyses. Our findings suggest that, in combination with demographic and clinical variables, quality of life can be used to assess the prognosis among HIV infected patients. Future research should investigate the predictive value of quality of life on treatment outcome, i.e. survival, in daily clinical practice. Also, the mechanism by which physical quality of life impacts survival remains to be determined.

In chapter 4, we investigated the use of pharmacy refill data for measuring adherence among HIV infected patients in the THETRHA study. In this study, we interviewed 201 immigrant and Dutch indigenous HIV infected patients about psychosocial risk factors for nonadherence. Additionally, we established adherence by self-report and pharmacy refill counts and virological failure. We collected refill data from 132 different pharmacies. By sending a fax to those pharmacies it was feasible to get data of all refills; however, it needed effort and time to collect and manage pharmacy refill data. We investigated how to operationalize refill data to a single measure of adherence. Adherence was calculated over a monitoring period of 90 days preceding a viral load measurement. There was no difference in the prediction of virological failure between a calculation of adherence based on the average of the entire regimen and a calculation based on only a single drug in the regimen. Taking into account leftover medication from previous refills, preferably for the whole period since starting the current cART-regimen, prevented misclassification of adherent patients as nonadherent patients. If adherence was defined as taking <100% of the prescribed pills, 43% of patients would have been misclassified as nonadherent when former refills since starting the current regimen were not taken into account. Instructed treatment interruptions could potentially be misclassified as periods of nonadherence when only looking at pharmacy refill data. Taking into account treatment interruptions prescribed by a patients’ physician did not affect the prediction of virological failure in our study. However, only few patients had instructed treatment interruptions in the 90 day monitoring period. Our main findings suggest that collecting pharmacy refill data from multiple pharmacies is feasible and that it is important to account for previous refills when calculating adherence based on pharmacy refill data. Additionally, we would advise to account for instructed treatment interruptions.

Chapter 5 describes a study investigating the influence of social desirability on self-reported adherence. We examined whether the relation between nonadherence and virological failure was stronger among patients in the ATHENA cohort with a lower tendency towards providing socially desirable answers in comparison to patients with a higher tendency to give socially desirable answers. We measured socially desirable responding with the 5-item social desirability response set. Adherence to treatment was assessed using four self-report questions. Odds ratios for the prediction of HIV RNA >50 copies/ml blood by non-adherence were significant among patients with low social desirability scores, while not significant among patients with high social desirability scores. In conclusion, social desirability influences the validity of self-reported adherence. Further research is needed to investigate ways to reduce social desirability bias on self-report measures of adherence to cART.

Beliefs about medication play a major role in adherence to treatment. Doubts about the necessity of cART and concerns about the adverse effects of cART may reduce adherence to treatment. In chapter 6, we investigated the extent to which perceived necessities of cART and concerns about adverse effects of cART are predictive for adherence to treatment and virological treatment response in the ATHENA cohort. Patients completed a questionnaire on beliefs about medication and adherence to cART. Reporting lower necessity of cART predicted lower adherence to cART and predicted a higher chance of a detectable viral load. In addition, we found that necessity scores were not associated with a patient’s sex, age, country of origin, transmission category, former ARV treatment and number of years on cART. However, necessity scores were related to CD4 cell count at study entry. We could not find a relation between concerns about adverse effects of cART and adherence or virological failure. Our data suggest that asking patients about their perceived personal need for cART could be helpful in identifying patients at risk for poor treatment adherence and detectable viral load. In future studies, the value of the necessity-concern framework in designing adherence-enhancing interventions might be examined. Intervention studies may examine to what extent talking about the patient’s view about his/her personal need for cART would result in improved adherence.

HIV stigma may influence treatment adherence. Immigrant HIV infected patients might experience or perceive more HIV stigma and therefore in chapter 7, we investigated whether HIV stigma is reported more often among immigrant HIV infected patients (THETRHA study). For this study, we used the Berger HIV stigma scale. Because this scale has never been investigated among immigrants in Western Europe, we first explored its feasibility among HIV infected immigrant patients. The Berger HIV stigma scale was administered in an interview format. Although immigrant patients more often needed explanation of items, the measure yielded adequate internal consistency. An important finding was the relatively high percentage of patients with one or more missing items. It seemed that this was the result of particular items in the HIV stigma scale, for which patients had to imagine how they would perceive certain situations while they never had been in such situations. During interviewing we observed that patients had difficulties with imagining unknown situations. As expected, personalized stigma was significantly higher among immigrant patients in comparison to indigenous patients. Furthermore, disclosure concerns were significantly predicted by having a HIV transmission route other than homosexual. This study shows that the type of HIV stigma may vary for different groups. Future studies may try to elucidate mechanisms underlying HIV stigma in the different subgroups, so that interventions can be developed that are targeted at different subgroups.

In chapter 8 we describe the extent to which quality of life, depression, HIV stigma and beliefs about medication influence adherence to cART and treatment outcome among immigrant and indigenous HIV infected patients (THETRHA). We anticipated that immigrant HIV infected patients have lower levels of quality of life and more HIV stigma, depression, doubts about the necessity of cART and concerns about adverse effects of cART. Further, we anticipated that these factors may explain poor adherence and worse treatment outcome.
among immigrant HIV infected patients. Adherence was measured using both self-report and pharmacy refill data. Quality of life, depression, HIV stigma and beliefs about medication were measured using standard questionnaires. Plasma viral load was considered detectable when >40 copies/ml blood. Immigrant patients had lower levels of adherence and more often had a detectable viral load. Additionally, levels of HIV stigma and depression were higher among immigrant patients. HIV stigma significantly predicted nonadherence. Depression significantly predicted having a detectable viral load, independently of nonadherence. Our study shows that HIV stigma and depression might be important targets for interventions among immigrant patients. Clearly, future studies are needed that evaluate such interventions in terms of risk reduction for nonadherence and virological failure.

DISCUSSION AND CONCLUDING REMARKS

Measuring adherence to combination antiretroviral therapy

To date, none of the existing adherence assessment methods is considered the gold standard. Self-report and pharmacy refill data are currently the most widely used measures. Self-reported adherence is inexpensive and convenient. However, it is subject to social desirability and recall bias. The role of social desirability was shown in the ATHENA cohort where a relationship between self-reported adherence and virological response was absent among patients who tended to give socially desirable answers (chapter 5). Moreover, in the THETRHA study we found that pharmacy refill nonadherence predicts a detectable viral load more accurately than self-reported nonadherence did (chapter 8). Although collecting and managing pharmacy data is more labour-intensive, pharmacy refill adherence is a more robust measure of adherence than self-report.

Collecting pharmacy refill data for measuring adherence among patients using multiple pharmacies was found to be feasible (chapter 4). We showed that it is important to account for leftover medication of previous refills. Unfortunately, we were not able to draw definite conclusions about the length of the period needed to account for previous refills. We would suggest to account for all refills since starting the current regimen to obtain a complete picture. The optimal monitoring interval, including the optimal period to account for previous refills, remains to be determined. One study found that there was no difference in prediction of viral load between adherence in the 90-day monitoring period preceding the viral load measure and adherence in the first 30 days of that 90-day episode.[1] In conclusion, future studies are needed with adequate power (i.e. large samples and sufficient patients with virological failure) to investigate the optimal period preceding the viral load measure, and the optimal period of accounting for leftover medication.

Factors influencing treatment adherence and outcome

HIV infected patients still have a shorter duration of survival.[2] Many factors may contribute to a shorter duration of survival. An important factor is lower levels of treatment adherence for its effect on treatment outcome. We found that adherence predicts treatment outcome, i.e. virological failure (Chapter 8). This was also found in other studies.[3-9] Therefore, lower levels of adherence are a major problem to address in the HIV infected population. However, nonadherence may be caused by many factors.

We found that immigrant patients had lower levels of adherence than indigenous patients (chapter 8). This is consistent with findings from other studies.[10-14] Additionally, virological response is worse among immigrant patients. This was also found in other studies.[15-17] Being immigrant is thus playing a major role in treatment adherence and outcome. However, immigrant origin is not the predicting factor per use. Previously, it was thought that insufficient knowledge about the cART regimen was the explanation for lower levels of
treatment adherence and outcome among immigrants. However, Nellen et al. [17,18] showed that HIV infected immigrant patients do not have insufficient knowledge about the disease and its treatment. Remarkably, in a qualitative study Nellen et al. found low levels of quality of life among immigrant HIV infected patients. [18] We quantitatively confirmed this finding in our THETRHA study (chapter 8). Additionally, we found that baseline quality of life is an independent predictor of survival among HIV infected patients in the ATHENA cohort (chapter 3). Quality of life may thus be one of the factors influencing treatment outcome, in part, directly.

Nellen et al. also found high levels of HIV stigma and depression among immigrant HIV infected patients. [18] We quantitatively confirmed these higher levels of HIV stigma and depression among immigrant HIV infected patients in comparison to indigenous patients (chapter 8). Interestingly, different groups of HIV infected patients report different types of HIV stigma (chapter 7). In our study, we showed that a higher level of experienced HIV stigma is related to lower levels of adherence. The relation between HIV stigma and lower levels of adherence was found in other studies as well.[19,20] Other studies also found a relation between higher levels of depression and lower levels of adherence.[21-25] However, we did not find such a direct relation between depression and adherence, probably, because we used a different way of measuring adherence. We found that depression predicted virological failure independent of adherence (chapter 8). Other studies also found that depressive symptoms are related to virological failure independent of treatment adherence. [26-28] According to Ickovics et al. [27] immunological and neuroendocrine factors may mediate the relation between depression and HIV disease progression. Additionally, they mention behavioural factors related to depression, such as smoking, alcohol and the mere use of health care, as possible confounders in the relationship between depression and treatment outcome, independent of treatment adherence. [27] Studies are needed to investigate the role of these biological and behavioural factors as intermediating variables between depression and virological failure.

**Improving adherence and virological response by influencing psychosocial factors**

Until now, a number of studies have been conducted to evaluate the effectiveness of interventions aimed at enhancing adherence to treatment. For example, interventions may give additional information about the need for adherence, may use reminders such as pagers or mobile phones, may teach self-monitoring of adherence, may entail intensive counselling or motivational interviewing and may engage the family. Such interventions were found to vary in their effectiveness.[29-31] Because a range of factors might influence adherence, such as psychosocial factors or healthcare related factors, no single intervention is adequate to improve adherence and treatment outcomes. Interventions that combine different strategies are therefore needed.[30] We recommend that interventions also specifically target quality of life, HIV stigma and depression.

As we found that quality of life is a predictor of survival (chapter 3) and is a factor that might impact adherence, low levels of quality of life might be an important target for interventions. [13,32] First, identification and management of symptoms is important because symptoms are related to quality of life and worse treatment outcome as shown by our study (chapter 2.3) and other investigations.[33,34] One way to increase levels of quality of life is to switch to other regimens with different profiles of side effects. For example, Potard et al. found higher levels of quality of life and less symptoms after switching from a PI-regimen to a NNRTI-regimen among HIV infected patients with controlled viral replication.[35] It is thus important to alleviate symptoms for which specific interventions are needed and to investigate whether such interventions indeed improve treatment adherence and outcome.

Because we showed that immigrant HIV infected patients reported higher levels of depression and HIV stigma, interventions targeting these factors can be expected to improve adherence levels and virological response. First, HIV stigma should be reduced. HIV stigma as experienced by HIV infected patients in the Netherlands was also investigated by Stutterheim et al. They showed that HIV infected patients frequently report HIV stigma and that HIV stigma impacts psychological well-being in different ways dependent on different social settings, such as family or health care.[36] There are basically two types of interventions to reduce HIV stigma: interventions targeted at HIV infected patients themselves and interventions targeted at the general population to increase the tolerance towards HIV infected patients. To our best knowledge, no studies have been conducted to reduce HIV stigma in HIV infected patients in the Netherlands, such as in immigrants. Most recent studies investigating concrete interventions to reduce HIV stigma have been carried out in non-Western countries. An example of a study targeted at HIV infected patients was an evaluation of a group intervention for patients starting cART in Tanzania using interactive sessions on HIV, cART, care giving, HIV stigma and disclosure to empower patients to tackle HIV stigma.[37] Some studies have addressed the general populations and have shown that interventions in the community are effective in reducing HIV stigmatisation. An example is an intervention that was aimed to increase the knowledge about HIV/AIDS in the community by HIV prevention strategies through for example publicly available media.[38,39] Another example of an intervention targeted at increasing the tolerance of the community towards HIV infected patients is the use of a HIV story line in a television drama in Botswana, which resulted in lower HIV stigmatisation by viewers of the television drama.[40] Some general recommendations to reduce HIV stigma exist. The 2007 declaration of commitment on HIV/AIDS of UNAIDS recommends larger participation of HIV infected patients in the development of HIV-stigma reducing interventions and policies, the so-called GIPA- (Greater Involvement of People Living with HIV/AIDS) principle.[41] Furthermore, Mahajan et al. recommend adapting laws and policies so that HIV stigma and discrimination of risk groups such as immigrants may diminish.[42] Second, interventions need to be developed to reduce depression. Such interventions are expected to reduce the risk of nonadherence and virological failure, but this should be investigated in daily clinical practice and specifically among immigrant HIV infected patients. [43] One study in the Netherlands showed that HIV nursing consultants might play a major
role in assessing depression among HIV infected patients, which is needed to identify patients at risk.\[44\] Pharmaceutical therapy, such as anti-depressants, and psychological therapy, such as cognitive behavioural therapy, were both found to be effective in reducing depression among HIV infected patients.\[26\]

In conclusion, future studies should investigate whether interventions aiming to decrease self-reported symptoms, to reduce HIV stigma, and/or depression actually improve adherence and reduce the risk of virological failure. As these factors are highly prevalent among HIV infected immigrants, interventions should be specifically targeted at this group of patients.

Reference List


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