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Intro duction

1. Introduction

In November 1997, the National Health Insurance Council agreed to the provision of a grant for the Academic Medical Center in Amsterdam to carry out an applied research project on the *'implications for the course of HIV disease, public health and health care of the introduction of new anti-HIV treatment, the monitoring of that new treatment, as well as the economic costs and benefits of the new treatment'*[1]. The aim of the project was 'to develop, in collaboration with the designated HIV/AIDS centres, a national network in order to systematically collect data on the treatment of HIV-infected patients and the monitoring of those patients'.

The central research question was subdivided into a number of operational questions:

- What are the changes following introduction of new anti-HIV-1 treatment on HIV-1- related morbidity and mortality?
- What are the determinants of therapy failure?
- What are the changes in the quality of life and the functionality of patients treated with new anti-HIV-1 combination therapy (distinguishing patients with and without symptoms of HIV-1 disease) and to what extent do patients adhere to the therapy prescribed and to medical instructions?
- What are the changes, following introduction of new anti-HIV-1 treatment, in the incidence of resistant virus strains?
- Does the measurement of resistance of HIV-1 to antiretroviral drugs and determination of the concentration of drugs in blood contribute to the improvement of HIV-1- related morbidity and mortality?
- What are the long-term implications of the introduction of new anti-HIV-1 drugs for the Dutch healthcare system?
- Is systematic recording of the clinical course of treated HIV-1 infection effective in terms of optimising anti-HIV-1 treatment? If so, what is a suitable way to organise information collection?

In this final report we will present the results of three years of HIV-1 treatment monitoring. In addition the indications of the study in terms of the costs and benefits of highly active antiretroviral therapy (HAART) will be presented. Based on these results recommendations will be made regarding the level and necessity of the monitoring of new HIV-1 infections, and the course and treatment of the infection. An organisational structure for these activities will be proposed at the end.

With respect to the principal aim of the project we can conclude that a network for the collection of patient data and materials is in place. This network has enabled us to include in ATHENA approximately 60% of the HIV-1 infected population of The Netherlands and about 70% of the patients on antiretroviral treatment. The remaining 30% of HIV-1 infected patients on treatment were not included. Inclusion was largely based on the assumptions of the treating physician regarding the ability of patients to participate in ATHENA. In 90% of the recorded but not included patients the reason for non-inclusion as given by the treating physician was the inability to read or understand the informed consent. Another important reason to exclude patients was the valuation of the potential adherence of patients to the new drug regimen. Lastly, some of the patients did not want to participate or were not eligible because they continued a regimen without one of the newly registered drugs.
Data obtained from the patients included in ATHENA, despite being biased to some degree owing to this inclusion selection, have resulted in research into the impact of antiretroviral treatment on the course of infection, public health and health care.

Summary and recommendations

2. Summary and recommendations

Within the framework of the ATHENA project, an observational clinical cohort of HIV- infected patients treated with highly active antiretroviral therapy (HAART) was set up. Inclusion started in 1998 and is ongoing. Through a network of 22 participating HIV/AIDS centres, 12 virology laboratories and 2 pharmacology laboratories in The Netherlands, clinical, epidemiological, socio-demographic, virological and immunological, as well as pharmacological data were collected from these patients. In addition data regarding the costs of treatment were obtained. Co-ordination of the project, collection, management and analysis of the data was organised through a separate ATHENA project organisation within the National AIDS Therapy Evaluation Centre (NATEC) at the Academic Medical Center of the University of Amsterdam. The Dutch Association of AIDS Physicians provided organisational support and a system of consultative working groups and meetings has been developed.

On 1st November 2000, the day chosen for the data-freeze, 3449 patients had been included in the study; 554 of them were participating in the focus group. The focus group was used for the sub-studies on resistance, adherence, quality of life, therapeutic drug monitoring and the costs of HAART. The majority of the individuals were Dutch homosexual men and were infected with HIV-1 subtype B. Owing to the inclusion criteria and procedure there might have been underreporting of individuals infected with non-B subtypes. Guidelines for the start of treatment of HIV were followed closely and most of the patients participating in ATHENA started HAART accordingly.

In general, HIV- infected patients benefited from HAART. The incidence of HIV-related morbidity and mortality declined after the introduction of HAART. The concentration of HIV decreased in 80% of the antiretroviral therapy-naïve patients and in 57% of the experienced patients to less than 500 HIV-1 RNA. copies per ml plasma. $CD4^+$ T cell numbers increased, and the counts at the onset of HAART was one of the determinants of therapy success. Other factors were the drug concentration reached in plasma and the susceptibility of HIV to antiretroviral drugs. Therapy regimens were frequently changed, mainly because of toxicity of the drugs used and therapy failure. Clinical signs and symptoms of toxicity were registered over time in 10% of the treated population. Quality of life improved in symptomatic, but not in asymptomatic patients. In spite of this improvement, quality of life was lower than that of the general Dutch population. Half of the patients took all antiretroviral medication in accordance with time and other prescriptions but asymptomatic patients were more likely to deviate than symptomatic patients. The proportion of therapy naïve patients having resistant HIV at the start of therapy was 0.5 and 1.7% for protease and RT inhibitors, respectively. This indicates that resistant variants of HIV are transmitted. Development of resistance after 6 months of HAART was seen in 24% of the virological failures. Therapeutic drug monitoring in therapy naïve patients improved the virological outcome. Introduction of HAART appeared to be cost saving, mainly because of the reduction of in-patient days, which accumulated to 8000 euros per person year. Moreover, most patients on HAART kept working with only a small loss of efficiency.

Our conclusion is that HAART is beneficial. The costs of HAART are offset by the cost saving in HIV patient care. However, like other chemotherapy, toxicity is a severe and growing problem, as are therapy failure and drug resistance of the virus. The following recommendations are made:

- Retain the infrastructure that has been developed in ATHENA and integrate it into patient care as a system that provides essential information about the epidemiology of HIV, the antiretroviral treatment of HIV and the effect of treatment on the course of HIV infection, including toxicity and resistance.
- Include all HIV infected individuals in the observational cohort and take the necessary measures to secure the benefit of this for all patients.
- Start a registration of the new HIV-1 and HIV-2 infections and consider collaboration with the GGD's and the RIVM.
- Protocolise the data collection, based on the average three-monthly schedule of outpatient clinic visits of the treated population.
- Include monitoring of adherence, HIV resistance monitoring and therapeutic drug monitoring in the care of HIV- infected patients.

Samenvatting en aanbevelingen

3. Samenvatting en aanbevelingen

In het kader van het ATHENA project werd een observationeel klinisch cohort gevormd bestaande uit HIV geïnfecteerde patiënten die met highly active antiretroviral therapy (HAART) werden behandeld. Inclusie startte in 1998 en gaat nog steeds door. Via een netwerk van 22 HIV/AIDS centra, subcentra en geaffilieerde ziekenhuizen, 12 virologische en 2 farmacologische laboratoria werden klinische, epidemiologische, socio-demografische, virologische en immunologische gegevens van deze patiënten verzameld. Bovendien werden financieel-economische gegevens verzameld. Coördinatie van het project en van de verzameling, management en analyse van de gegevens was georganiseerd in een aparte ATHENA projectorganisatie binnen het Nationaal AIDS Therapie Evaluatie Centrum (NATEC) in het Academisch Medisch Centrum bij de Universiteit van Amsterdam. De Nederlandse Vereniging van AIDS Behandelaren (NVAB) was betrokken bij de organisatie van consultatieve werkgroepen en bijeenkomsten. Op de dag van de bevriezing van de gegevens, 1 november 2000, waren 3449 patiënten in de studie opgenomen. Daarvan participeerden er 554 in de focusgroep, die werd gebruikt voor substudies naar resistentie, therapietrouw, kwaliteit van leven, therapeutische geneesmiddelen monitoring en de kosten van HAART. De meerderheid van de patiënten had de Nederlandse nationaliteit en was afkomstig uit de groep homosexuele mannen. HIV-1 subtype B infectie was het meest prevalent in de studiepopulatie. Dit kan het gevolg zijn geweest van onderrapportage van de niet in Nederland geïnfecteerde patiënten. Richtlijnen voor de start van de behandeling van HIV werden opgevolgd bij de meeste patiënten die met HAART begonnen.

Over het algemeen hadden patiënten voordeel bij behandeling met HAART. De incidentie van aan HIV gerelateerde morbiditeit en mortaliteit daalde na de introductie van HAART. De HIV concentratie daalde in 80% van de therapie naïeve en 57% van de eerder met andere antiretrovirale middelen behandelde patiënten tot waarde beneden 500 HIV-1 RNA kopieën per ml plasma. $CD4^+$ T cellen stegen en het aantal cellen bij de start van HAART was een van de determinanten van therapiesucces. Andere factoren waren de geneesmiddelenconcentratie die werd bereikt in plasma en de gevoeligheid van HIV voor antiretrovirale middelen. Therapieregiems werden vaak veranderd, vooral door toxiciteit en door therapiefalen. Gedurende de studieperiode had 10% van de behandelde populatie klinische symptomen van toxiciteit. Met name in symptomatische, maar niet in de asymptomatische patiënten verbeterde de kwaliteit van leven. Het niveau van de gemiddelde Nederlandse bevolking werd echter niet gehaald. Slechts de helft van de patiënten gebruikte alle medicatie op tijd en volgens de voorschriften. Asymptomatische patiënten bleken in dit verband minder trouw aan de voorschriften dan symptomatische. HIV dat resistent bleek voor protease en RT remmers werd gevonden bij 0.5%, respectievelijk 1.7% van de naïeve patiënten, hetgeen erop duidt dat resistente HIV stammen worden overgedragen. Bij 24% van de patiënten die na 6 maanden virologisch faalden op HAART werd HIV resistentie aangetoond. Therapeutische geneesmiddelen monitoring verbeterde de virologische uitkomst van de behandeling. HAART bleek kosten besparend, vooral omdat het aantal ziekenhuisopnames verminderde, hetgeen 8000 euro's per persoonsjaar opleverde. Bovendien bleven de meeste met HAART behandelde patiënten gewoon werken.

In conclusie: HAART bleek gunstig te werken en bleek voor de patiëntenzorg van HIV kosten besparend te zijn. Maar, net als bij andere chemotherapie is de toxiciteit een ernstig en groeiend probleem, evenals het falen van de therapie en de resistentie van het virus tegen de geneesmiddelen. De volgende aanbevelingen worden gedaan:

- Hou de opgebouwde ATHENA infrastructuur in stand en integreer deze in de patiëntenzorg als een systeem dat essentiële informatie levert over de epidemiologie van HIV, de antiretrovirale behandeling van HIV en het effect van de behandeling op het beloop van de infectie, inclusief toxiciteit en resistentie.
- Neem alle HIV geïnfecteerde patiënten op in het observationele cohort en neem de nodige maatregelen om te verzekeren dat alle patiënten ervan kunnen profiteren.
- Start een registratie van de nieuwe HIV-1 en HIV-2 infecties en overweeg daarvoor samenwerking met de GGD's en het RIVM.
- Protocoliseer de verzameling van gegevens op basis van de gemiddelde polikliniek bezoekfrequentie van de behandelde populatie
- Voeg de monitoring van therapietrouw, de HIV resistentie monitoring en de therapeutische geneesmiddelen monitoring toe aan de zorg voor HIV geïnfecteerde patiënten.

Monitoring of HIV-1

4. Monitoring of HIV-1 in The Netherlands

4. Monitoring of HIV-1 in The Netherlands

4.1. Organisation of ATHENA

Essentially, the collection of data on the course of treated HIV-1 infection in each individual patient who has entered ATHENA after signing an informed consent is decentralised, that is to say, data are collected on case report forms and entered into the database on site. Data are sent to the central database on floppy discs. A procedure by which data can be put into the central database by email is in progress.

In total 10%, and in case of the focus group (see par.5.2.2.) 50% of the data are monitored and data are changed in case of mistakes. Per site, results of monitoring are reported and data are corrected or complemented in case of missing data. Subsequently data consistency checks are performed. After correcting for inconsistencies if necessary, data are sent back to the hospital from where they were obtained.

Hospital	N patients in ATHENA	
	Total	focus group
AMC-UvA, Amsterdam	609	95
Slotervaart Ziekenhuis, Amsterdam	343	37
AZR-Dijkzigt, Rotterdam	314	56
OLVG (Prinsengracht), Amsterdam	260	64
UMCU, Utrecht	241	47
OLVG (Oosterpark), Amsterdam	215	35
St Elisabeth Ziekenhuis, Tilburg	192	19
AZM, Maastricht	162	33
Stichting Medisch Centrum Jan van Goyen, Amsterdam	151	20
AZG, Groningen	146	34
Ziekenhuis Leyenburg, Den Haag	129	27
UMC-St. Radboud, Nijmegen	129	15
Medisch Centrum Haaglanden, locatie Westeinde, Den Haag	125	29
AZVU, Amsterdam	119	15
LUMC, Leiden	101	14
Kennemer Gasthuis, locatie EG, Haarlem	100	17
Ziekenhuis Rijnstate, Arnhem	99	11
MST, Enschede	82	8
MCL, Leeuwarden	43	7
Catharina Ziekenhuis, Eindhoven	34	1
Ziekenhuis Walcheren, Vlissingen	31	1
MCA, Alkmaar	26	9
Total	**3651**	**594**

Table 4.1.1: *Overview of hospitals participating in the ATHENA project: presented are the total number of HIV/AIDS patients included in ATHENA as of 3 March 2001 and the number of patients included in the focus group.*

In this process, the local data-entry clerks and the data monitors play a crucial role, together with the data manager and the co-ordinator of data logistics within the central ATHENA bureau in NATEC. In total 22 hospitals are participating in the monitoring project (Table 4.1.1): The AMC-UvA in Amsterdam as the leading reference centre for HIV and AIDS plus eleven HIV/AIDS centres and 10 associated centres.

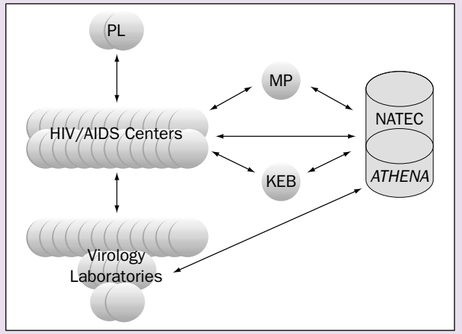

Figure 4.1.1: *Schematic overview of the data communication in ATHENA. Central to the collection of data are the 22 HIV/AIDS centres. Twelve medical microbiology (virology) laboratories are involved in the measurement of HIV-1 RNA levels in plasma, four of which are genotypically measuring resistance. Of those four, two perform phenotypic resistance measurements. Two pharmacological laboratories (PL) at the St Radbout Ziekenhuis in Nijmegen and the Slotervaart Ziekenhuis in Amsterdam are measuring antiviral drug levels. MP, the department of Medical Psychology, AMC-UvA is responsible for the adherence and quality of life studies and KEB, the department of Clinical Epidemiology and Biostatistics, AMC-UvA is performing the study on cost-effectiveness. The ATHENA project bureau within the organisational framework of NATEC, the National AIDS Therapy Evaluation Centre, provides data logistics and databasing.*

Twelve virology laboratories are involved in the measurement of viral RNA levels. The virology laboratories at the AMC-UvA in Amsterdam, the UMCU in Utrecht, the LUMC in Leiden and the AZR-Dijkzigt in Rotterdam measure correlates of resistance of HIV-1 to antiretroviral drugs by genotyping HIV-1 RT and protease. HIV-1 RT and protease are phenotyped in the laboratories at the AMC-UvA in Amsterdam and the UMCU in Utrecht. As well as the virology laboratories, two pharmacology laboratories at the UMC-St Radboud in Nijmegen and the Slotervaart Ziekenhuis in Amsterdam contribute by measuring antiretroviral drug concentrations in plasma.

The 22 hospitals are the key-institutes in the ATHENA network, and most of the patient data are collected here. The data communication is patient oriented and directed to these hospitals (see Figure 4.1.1).

The pharmacological data are sent back directly to the requesting physician and are then added on site to the locally stored patient data. Subsequently these data are communicated to the central ATHENA database alongside the other clinical data. The same is the case for the data on HIV-1 RNA plasma concentrations. Each of the 12 virological laboratories involved report back to the physician. Reported data are an integral part of the patient data set sent to the central database. Only the data concerning genotypic and phenotypic resistance are handled centrally. These data are sent directly from the virological laboratories involved to the department of Human Virology at the AMC-UvA, and are added to a specific resistance database after a quality control procedure. In order to limit time loss, genotypes obtained de-centrally by the laboratory involved are reported directly to the requesting physician by the laboratory.

4.2. Data collection

Within the ATHENA framework data were collected from patients who started antiretroviral combination therapy including at least one of the antiretroviral drugs that were officially approved on or after 1 July 1996. At that time a number of new antiretroviral drugs, i.e. protease inhibitors, non-nucleoside RT inhibitors

and a few nucleoside RT inhibitors were registered in the Netherlands. In this report we will refer to these new combinations as highly active antiretroviral therapy or HAART.

A system to monitor patients who were treated with such a new combination was in place from May 1998. Data from patients starting new therapy before 1998 were systematically collected retrospectively using patient files and data sets obtained from participating laboratories. Essentially, data from all patients who were on therapy were included, including those patients who died before May 1998. From 1998 onwards data were collected prospectively.

Patients included in the study were older than 18 years and participation was possible only after signing an informed consent. Follow-up schemes were not protocolised. Demographic data were collected at entry. Clinical data focused on HIV-1 infection-related events according to the classification of the Centers for Disease Control[2], the therapeutic and prophylactic drugs used in case of opportunistic infections, the combination and dose of the antiretroviral drugs used, as well as the signs and symptoms (including the chemical and haematological laboratory results) of toxicity and side effects of the antiretroviral drugs used. Clinical data were collected at each outpatient clinic visit. In addition data on the HIV-1 RNA plasma concentration and the number of $CD4^+$ and $CD8^+$ T cells were collected[3].

In a focus group of randomly chosen patients, data on genotypic and phenotypic resistance of HIV-1 to antiretroviral drugs and on plasma concentrations of antiretroviral drugs were collected (see paragraph 5.8). Patients in this specific subgroup were asked to fill in questionnaires on compliance and adherence to the drugs used (see paragraph 5.6), as well as on (changes in) their quality of life since the start of therapy with the new antiretroviral drug combinations.

At the moment, data are stored in a custom made Microsoft ACCESS database with facilities to enter data locally. This database has been in use since the beginning of 2000 when on-site data entry started in a few HIV/AIDS hospitals. By the end of 2000, almost all sites were able to enter their own data. The speed at which this de-centralisation process has been performed has resulted in a number of significant problems that are currently being solved. One of these problems is the merging of centrally stored historical ATHENA data and the de-centrally entered data, caused by subtle differences between the databases. The other is the request to connect existing patient registration systems (patient management systems, laboratory systems) at different sites to the ATHENA database in order to reduce the workload of data-collection and entry clerks. Lastly, the growth of the amount of data requires a more sophisticated database system as well as data communication system. In collaboration with the AMC, necessary steps are being made to change the database and data communication systems.

4.3. Research

In the third and last year of the ATHENA project, data from a sufficiently large group of patients followed for a sufficient amount of time were available for analysis. A first report, in combination with results obtained in a number of observational clinical cohorts, emphasised the change in prophylactic treatment strategies for Pneumocystis carinii pneumonia[4]. A second report on the importance of not only the right number of pills, but also the right scheme at the right time, meals and diet based on adherence and pharmacological data has been accepted for publication[5], as well as a descriptive analysis of antiretroviral treatment success and failure[3]. A separate study on the importance of plasma drug concentrations is submitted[6]. Apart from these full papers, several abstracts and short reports based on the data obtained in ATHENA have been presented.

The above-mentioned publications together with several papers 'in progress' dealing with various issues that are relevant for the treatment of HIV-1 show the potency of the ATHENA observational clinical cohort for applied and health care policy oriented research. These publications, however, are the spin-off of the research performed for the present report on the implications for the course of HIV-1 disease, public health and health care of the introduction of new anti-HIV-1 treatment, the monitoring of as well as the economic costs and benefits of the new treatment.

4.4. Conclusions and recommendations

A network for monitoring the effect on HIV-1 infection of (new) antiretroviral treatment was set-up within the granting period 1998-2001 with the enthusiastic help and effort of treating physicians in 22 hospitals, medical microbiologists in 12 laboratories and pharmacologists in two laboratories. A co-ordinating bureau is in place and is able to collect and store the relevant data and to maintain a database and data communication infrastructure. With the help of the Dutch Association of AIDS Physicians (Nederlandse Vereniging van AIDS Behandelaren –NVAB) a system of regular consultative and consensus meetings has been developed. A set of standard data is collected from the whole group of patients included and additional data is collected within a focus group. These data enabled participants in the ATHENA project to perform applied clinical research as well as to answer the research questions as stated in the grant application.

Essentially, the structure of ATHENA could continue, provided the decision is taken to continue the monitoring of HIV. The organisational structure including workshops and local and central facilities functions quite well. However, for the sake of continuity it is important to transform ATHENA into a more structural organisation that would acknowledge the existing local structure better and in turn emphasize the supportive nature of the organisation for applied research and policy consultancy. A proposal for a 'Foundation for HIV Monitoring', embedded in the financial structure of patient care, is therefore part of this report.

A continuous monitoring of HIV will heavily depend on the database and data communication facilities. Also important in this regard is a more structural solution for the long-term de-centralised collection of data.

The ATHENA Cohort Study

5. The ATHENA cohort study: Implications of the introduction of HAART for the course of HIV-1 disease, public health and health care as well as the economic costs and benefits.

5. The ATHENA cohort study

5.1. Introduction

At present three groups or classes of antiretroviral drugs are available for the treatment of HIV-1 infected patients[7]: a) nucleoside analogue HIV-1 reverse transcriptase inhibitors (nRTI's)[8-13], b) non-nucleoside HIV-1 RT inhibitors (NNRTI's)[14] and c) HIV-1 protease inhibitors (PI's)[15-18]. RT is necessary for the translation of HIV-1 RNA into DNA that will be incorporated in the cellular DNA, an early step in the replication cycle of the virus[19]. Protease is needed for the production of infectious viral particles at the end of the replication cycle of HIV-1[20]. Combining two nRTI's with one or more PI's[21,22], two nRTI's plus one NNRTI or triple nRTI results in a strong suppression of HIV-1, although total eradication of HIV-1 from the body is not achieved[23-26]. The concentration of HIV-1 in plasma, important for the course of the infection[27-29], declines rapidly after starting combination therapy[21,22], but the slope of the decline may differ between regimens[24]. $CD4^+$ T cell counts increase after starting combination therapy[30,31]. Altogether these effects of antiretroviral combination therapy are positive for the patient and this is reflected in the impressive decrease of HIV-1 related morbidity and mortality rates[32-34].

The disadvantages of current antiretroviral combination therapy of HIV-1 include the complicated medication schemes[5], as well as the intolerance and toxicity of the drugs. In particular, intolerance and toxicity are increasingly observed and can sometimes develop into life threatening problems. Serious complications of treatment with antiretroviral drugs are peripheral neuropathy, lactic acidosis, hepatic steatosis, pancreatitis, nephrolithiasis, lipodystrophy, loss of libido, and diabetes mellitus[35-37]. In the case of lipodystrophy, blood lipid profile changes may result in a higher chance of developing cardiovascular diseases. Inaccurate interpretation of instructions, reduced tolerance and toxicity may result in sub-optimal drug levels in plasma and insufficient suppression of virus replication. Selection of viruses less sensitive to the drugs used may be the result[38,39].

Since July 1996, a combination of antiretroviral drugs from at least two different classes has been the standard treatment for HIV-1 infection[40,41]. Guidelines for the treatment of HIV-1 and the monitoring of antiretroviral therapy are available[42,43] and have been updated recently[44]. To evaluate the implications for the course of HIV-1 disease, public health and health care of the introduction of these new anti-HIV-1 drug regimens a clinical observational cohort study was developed. Results from this cohort, obtained within the ATHENA framework and related to the more specific research questions, are presented in this final report.

5.2. Materials and methods

5.2.1. Study population

Patients were included in the observational cohort after giving informed consent. At each (outpatient clinic) visit data were collected regarding the HIV-1 infection status of the patients[2], current and previous antiretroviral therapy regimens, the effect of antiretroviral treatment on plasma HIV-1 RNA levels and the T cell subsets in peripheral blood. Adverse events and toxicity were also registered. Data collection was performed using standard case report forms. The treating physician and a (research) nurse or an AIDS consultant filled out other, specific forms. Until January 2000, forms were sent to the ATHENA project bureau at the National AIDS Therapy Evaluation Centre (NATEC) in the AMC in Amsterdam and data were entered in the ATHENA database. From the beginning of 2000, decentralised data-entry facilities were successively installed and local data entry is now taking place at almost all sites.

At the start of the ATHENA project in January 1998 a total number of approximately 3000 patients was anticipated to participate in the study. Inclusion over time is depicted in Figure 5.2.1.1. It shows an intake over time slightly behind the estimates for the first 18 to 24 months. However, by December 2000, numbers exceeded the target by more than 500.

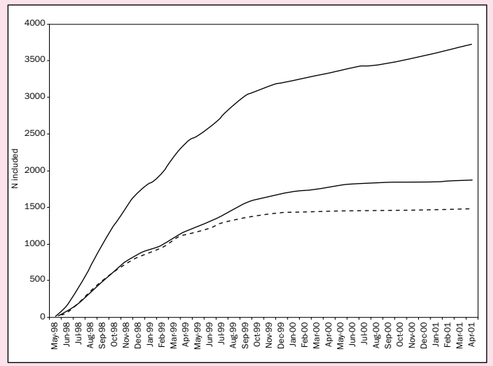

Figure 5.2.1.1: *Inclusion of patients in ATHENA. The lower two lines depict the inclusion of antiretroviral therapy naïve (continuous line) and experienced (dotted line), respectively.*

Assuming a total HIV/AIDS patient population on treatment of approximately 6000, 60% of them were included in ATHENA. Although there were differences between hospitals, important reasons for non-inclusion were language difficulties and the physician's evaluation of the patient's ability to participate.

For this report, the data collection was frozen on the first of November 2000. At that time a total of 3449 patients had been included. For 101 of these patients, the ones most recently included, the start date of HAART had not yet been recorded or entered into the database. Thus for the present analysis, data obtained from a study population of 3348 patients were used. These patients were treated with an antiretroviral drug combination encompassing at least one of the new (that is registered since July 1996) antiretroviral drugs.

5.2.2. Focus group

For the study items on resistance, antiviral drug concentrations in plasma, adherence and compliance to antiretroviral drugs, changes in quality of life and (partly) on the cost effectiveness of antiretroviral treatment, from the start of the ATHENA project in 1998 a subgroup was formed that was more intensively monitored. This so-called focus group was geographically balanced, and treating physicians were asked to enrol incoming naïve and pre-treated patients on a consecutive basis until target numbers were reached. Patients had to sign an informed consent form specifically for their participation in this group. Inclusion in the focus group is depicted in figure 5.2.2.1 and in the present report, data from 554 patients included as of November 1, 2000, were used.

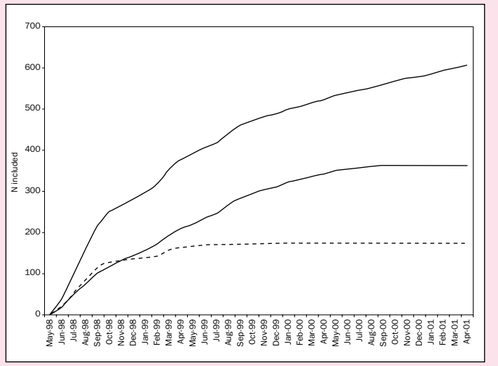

Figure 5.2.2.1: *Inclusion of the focus group. The lower two lines depict the inclusion of the antiretroviral therapy naïve (continuous line) and experienced (dotted line) patients, respectively.*

5.2.3. Retrospective and prospective data collection

Clinical, epidemiological and laboratory data were collected from each patient from the start of HAART onwards. Most patients started new combination therapy from July 1996 onwards. However, 620 patients had already started by this time through their participation in trials or compassionate use programmes. From May 1998, all data were collected prospectively. When available, data from patients obtained before the start of HAART were also added to the ATHENA data set.

5.2.4. Laboratory measurements

HIV-1 RNA

The HIV-1 RNA concentration in plasma, representative of the amount of virus produced, was measured by using one of the three commercially available quantitative tests: Amplicor (Roche Diagnostics, Branchburg, NJ, USA), NucliSens (Organon Teknika, Boxtel, The Netherlands) or Quantiplex (Chiron Diagnostics Corporation, East Walpole, MA, USA). The test was performed in the twelve virological laboratories participating in ATHENA throughout the country (see page 66). The quantification limit of these assays was at least 500 HIV-1 RNA copies/ml. Standard controls showed that results from different tests were comparable. Retrospectively obtained HIV-1 RNA results as measured by using the NASBA (Organon Teknika, Boxtel, The Netherlands) below 1000 copies/ml (the detection limit of this first generation quantitative HIV-1 RNA assay) were considered as below 500 copies/ml in all analyses.

T-cell subset

Absolute numbers of $CD4^+$ and $CD8^+$ T cells were determined by using immune fluorescence techniques and flow cytometry.

5.3. Baseline characteristics

5.3.1.1. Total study population

Baseline was defined as the start of HAART. The composition of the study population is depicted in figure 5.3.1.1.1 in terms of start date of HAART, showing that part of the data had to be collected retrospectively and that 620 patients were on HAART before July 1996.

Socio-demographic, epidemiological, virological and immunological characteristics are summarised in Table 5.3.1.1.1.

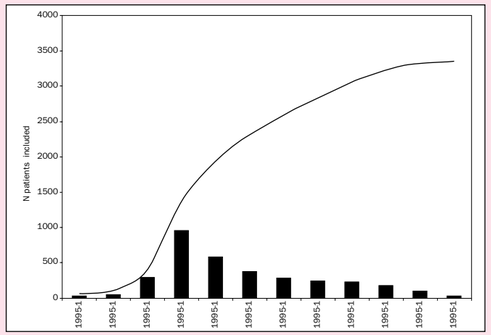

Figure 5.3.1.1.1: *The inclusion of patients in the ATHENA study according to their HAART start date. The ATHENA project started with the inclusion of patients in May 1998. Line represents the cumulative number and bars show the number of inclusion per half year.*

Of the 3348 patients, 1904 (57%) did not have any antiretroviral treatment before starting the new combination therapy (the so-called therapy naïve patients) and 1444 (43%) did (the therapy experienced or pre-treated patients). The median age of patients was 38 years (IQR 33-45), the naïve patients being younger as compared with the pre-treated ones. In total 86% of the group was male and no difference in gender was found between naïve and pre-treated patients. The proportion of women in the clinical cohort increased slowly over time from 11% in 1996 to 17% in 1999 in the naïve group and from 13% to 17% in the pre-treated group. Men having sex with men was the main risk factor in both the naïve and pre-treated patients, although the proportion of infections acquired heterosexually was higher in the naïve patients. Over time the proportion of infections acquired heterosexually increased from 17% in 1996 to 28% in 1999 in the treatment naïve group. This proportion remained relatively stable in the pre-treated group (approximately 15%).

The majority of the patients (81%) were of Dutch nationality with no difference found between naïve and pre-treated patients. Although some overlap may exist, it is of interest to note that of the naïve patients, 2% were of Southeast Asian and 8% of African origin. These percentages were 2 and 5, respectively, for the pre-treated group.

The plasma HIV-1 RNA concentration at the start was 5.0 log copies/ml (IQR 4.5-5.4) in the naïve patients, significantly higher than that in the pre-treated patients (4.5 log copies/ml; IQR 3.5-5.1). Plasma levels at the start of HAART remained relatively stable over time (Figure 5.3.1.1.2.) and the fraction of patients with plasma levels <500 copies/ml ranged from 0.01 to 0.03 in the naïve and from 0.03 to 0.18 in the pre-treated patients.

$CD4^+$ T cell counts at the start were lower in the pre-treated group compared to the un-treated group (150 and 220 cells/mm^3, respectively). In the naïve group, this number remained stable over time. Interestingly, the $CD4^+$ T cell count at start of HAART increased over time in the pre-treated group from 60 cells/mm^3 in 1996 to 360 cell/mm^3 in 1999 (data not shown).

These baseline characteristics indicate that the pre-treated patients in general were in a more advanced stage of HIV-1 infection, especially those included early in the ATHENA cohort. The proportion of patients that were infected through heterosexual contact increased over time, especially in the treatment naïve group. Also the proportion of women increased. Furthermore there appeared to be a relatively stable proportion of patients with a non-Dutch nationality, however, under-reporting may impact here owing to the inclusion criteria and procedure.

	Number of patients		Naïve		Pre-treated		P-value
	N	%	N	%	N	%	
All patients	3348	100	1904	57	1444	43	
Gender, male	2871	86	1618	85	1253	87	NS
Risk group (N=3104)							<0.001
- MSM	2133	69	1149	66	984	72	
- Heterosexual	661	21	434	25	227	16	
- IVDU	221	7	101	6	120	9	
- Other	89	3	48	3	41	3	
Dutch Nationality	2726	81	1530	80	1196	83	NS
Year start HAART <1998	2325	69	1167	61	1158	80	<0.001
AIDS at start	898	38	286	15	612	42	<0.001
	Median	IQR	Median	IQR	Median	IQR	
Median age (IQR)	38	33-45	37	32-45	39	34-46	<0.001
CD4 cell count at start (N=2949)	70	190-330	220	80-365	150	53-280	<0.001
Log HIV-1 RNA at start (N=2353)	4.8	4.2-5.3	5.0	4.5-5.4	4.5	3.5-5.1	<0.001

Table 5.3.1.1.1: *Baseline characteristics of the population included in ATHENA as of 1 November 2000 and having a recorded HAART start date. MSM= men having sex with men; IVDU=intravenous drug users.*

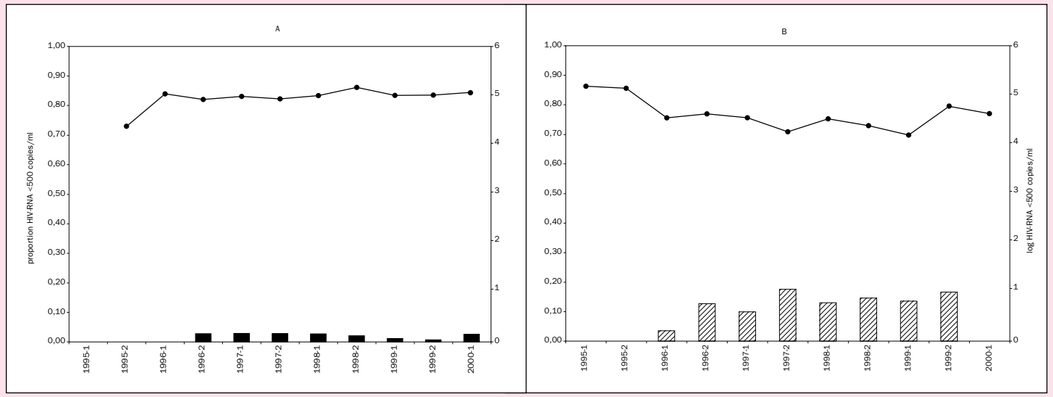

Figure 5.3.1.1.2: *HIV-RNA at baseline: Proportion <500 copies/ml and median concentration in naïve (upper graph) and pre-treated (lower graph) patients with detectable plasma levels.*

5.3.1.2. Molecular epidemiology

As spin-off from the HIV-1 RT and protease genotyping for the detection of resistance associated mutations (see paragraph 5.7), we were able to determine the HIV-1 subtype in 322 patients, using the nucleotide sequence of RT. One sequence per patient was used for analysis and most of the sequences were obtained at the start of HAART. Sequences were compared pair-wise using the Kimura two- parameter model for distances between nucleotide sequences. Of the 322 patients, 294 or 91.3% was infected with a subtype B virus. In total 28 patients or 8.7% appeared to be infected with another subtype than B (Figure 5.3.1.2.1). Subtypes C and E were most frequently found among the patients with a non-B HIV-1 infection.

In 4 cases sequences were recombinants for which we were unable to determine a specific subtype.

These results indicate that the introduction of HIV-1 subtypes other than B has occurred. The non-representative composition of the focus group (see chapter 5.3.2) may underestimate the proportion of non-B viruses. To monitor the introduction of the various subtypes of HIV-1 and the impact on the results of antiretroviral treatment it is recommended to at least analyse the RT and protease sequences obtained for genotypic resistance measurements for molecular epidemiological purposes, in addition to the sub-typing of new HIV-1 infections.

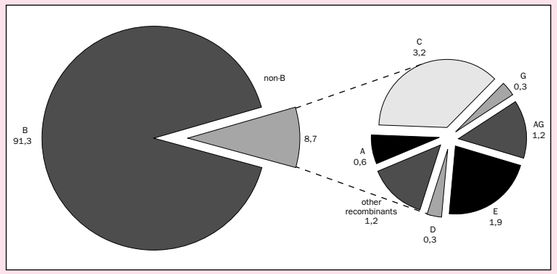

Figure 5.3.1.2.1: *HIV-1 subtypes, based on RT sequences, found in 322 participants in the focus group of ATHENA. One sequence per patient, preferably obtained at baseline, was used.*

5.3.2. Representativeness of the focus group

The proportion of therapy naïve patients among the 554 participants in the focus group was significantly higher than the proportion among the remaining 2794 patients (p=0.001; Table 5.3.2.1). This was the result of the inclusion procedure. At inclusion, patients were divided according to their treatment status, i.e. on treatment at the time of inclusion in ATHENA versus starting antiretroviral therapy for the first time. At the start of the ATHENA project in the first half of 1998, 281 patients were included, most of them as being therapy experienced at inclusion in the study. However, from 115 of these experienced patients, the start date of their first HAART regimen was known. Correcting for this resulted in a shift from pre-treated to naïve patients.

	Focus group	Regular group
N	554	2794
% Naïve	68.4	53.3
% Pre-treated	31.6	47.7

Table 5.3.2.1: *Comparison of the focus group with the regular group in terms of treatment history: significantly (p=0.001) more naïve patients were included in the focus group*

The composition of the focus group in terms of the HAART start date is summarised in figure 5.3.2.1, again showing that HAART was administered to patients from late 1995 or early 1996 onwards.

When comparing the naïve patients in the focus group with those in the regular group as well as the pre-treated patients of both groups, some differences were found (Table 5.3.2.2). The proportion of male patients in the naïve group was somewhat higher in the naïve focus group compared to the naïve regular group (p=0.03). In addition, the proportion of homosexual men in the naïve as well as the pre-treated focus group was somewhat higher compared to the naïve and pre-treated regular group. Of interest is the difference with respect to the drug users, where the proportion of drug users in the focus group was lower com-

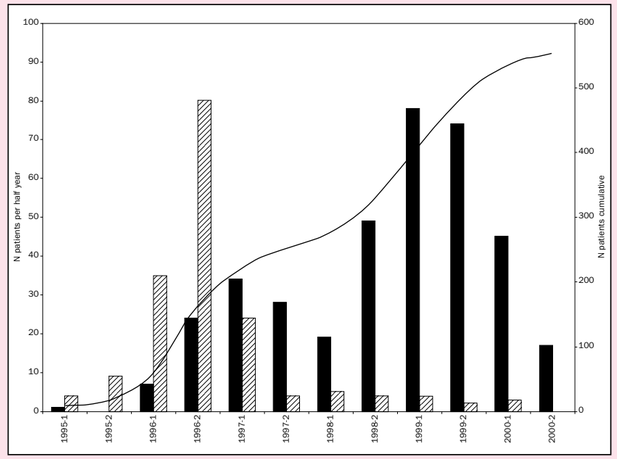

Figure 5.3.2.1: *Inclusion in the focus group, according to the start date of HAART: pre-treated (ruled) and naïve (closed) patients per half year of start of HAART and the group cumulatively (line). Note that the inclusion into ATHENA started in May 1998 and that patients already on HAART were recorded as pre-treated. The closed bars prior to the second half of 1998 show the 115 patients for whom the HAART start date was known and who were re-recorded as therapy naïve.*

pared to the regular group, irrespective of treatment history. The median HIV-1 RNA concentration in plasma at the start of HAART appeared not to be different between naives in the focus or regular group or the pre-treated patients in the focus or regular group, however CD4+ T cells on average tended to be higher in the naïve groups.

	Focus group		Regular group	
	Naïve	Pre-treated	Naïve	Pre-treated
% Male	88.9	90.3	84.4	86.1
Average age	40	40.9	39	40
% HIV-1 transmission risk group				
- Homosexual:	79	79.4	64.4	69.7
- Heterosexual:	17.3	14.1	26.8	17.4
- (I)VD	2.5	2.9	5.9	9.7
- Other	1.1	3.5	0.3	3.2
Median log HIV-1 RNA at start	5.0	4.35	4.98	4.49
Average CD4+ T cells x109/l at start	0.27	0.20	0.25	0.19

Table 5.3.2.2: *Comparison between the focus group and the regular group separated for therapy naïve and pre-treated patients*

Alltogether, this indicates that the focus group was selected from the regular group based on how 'suitable' patients were: A preference for non-drug users for example leads to a higher inclusion of male homosexuals. Moreover, because the intake in the focus group started from the moment the ATHENA project was implemented in 1998, the immunological status of the focus group was inevitably better as compared with the regular group, the latter influenced by the results of the 1995-1998 population.

5.4. Morbidity and mortality

All data from the start date of the first HAART regimen until the last follow-up visit before the end of the follow-up period (1 November 2000) were used. Morbidity and mortality rates per calendar year were calculated by person-year analysis. Kaplan Meier survival curves were used to study the time to death and CDC-B or C events from the start of therapy onwards.

A dramatic change in both the absolute number as well as the incidence per person year of CDC-B events occurred after

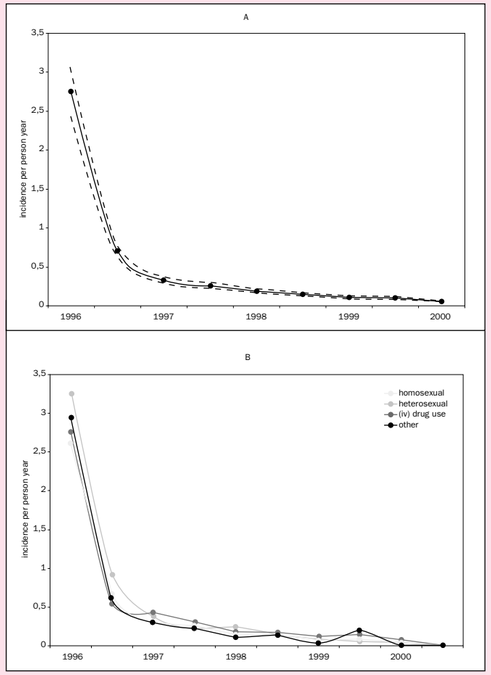

Figure 5.4.1: *Incidence per person year of CDC-B events diagnosed in each half year since 1996 in A) the whole group and B) per transmission risk group (dotted line is 95% CI).*

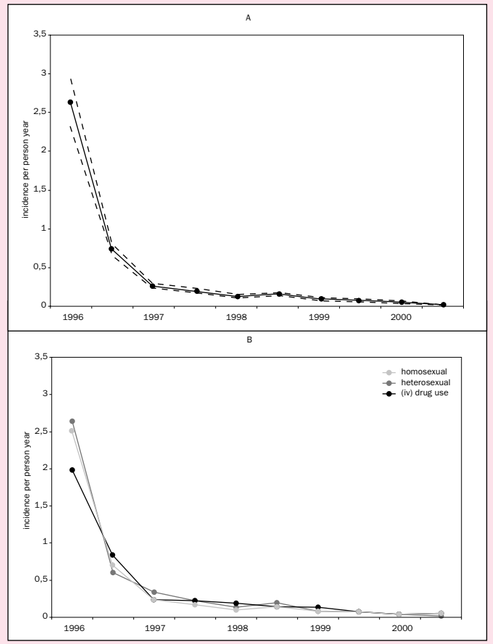

Figure 5.4.2: *Incidence per person year of CDC-C events diagnosed in each half year since 1996 in A) the whole group and B) per transmission risk group (dotted line is 95% CI).*

the introduction of HAART in July 1996. The total number of CDC-B events registered in 1996 was 614 and this number decreased to 98 in 2000. Per person year, the incidence of CDC-B events declined from 2,74 in the first half of 1996 to 0.05 in the first half of 2000 (Figure 5.4.1.). There were no significant differences between the HIV-1 risk groups. Among homosexual men the CDC-B incidence declined from 2.62 to 0.05, among the heterosexual HIV-1 positive patients incidence declined from 3.25 to 0.05 and among the (intravenous) drug users from 2.76 to 0.08 per person year.

Comparable figures were found for CDC-C or AIDS defining events. After the introduction of HAART the CDC-C incidence declined from 2.63 in the first half of 1996 to 0.25 in the first half of 1997 and subsequently to 0.04 in the first half of 2000 (Figure 5.4.2). Again, no differences were found between risk groups. Incidences in the first six months of 1996 were 2.53, 2.64 and 1.98 for HIV-1 positive homosexual men, heterosexuals and (intravenous) drug users, respectively. In the first half-year of 2000, figures were 0.06, 0.09 and 0.07, respectively.

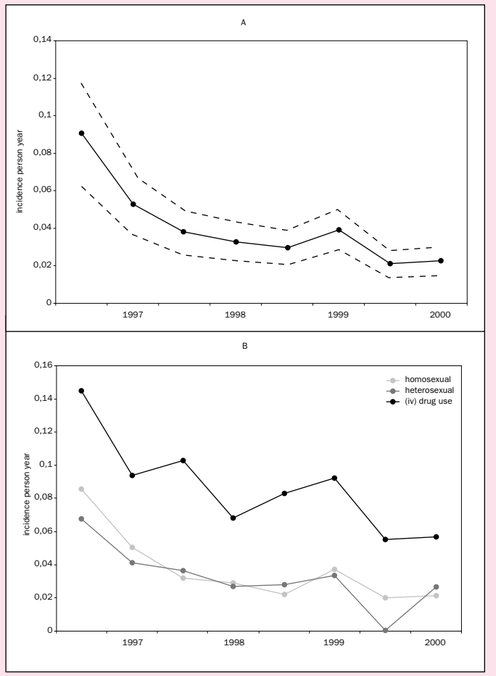

Figure 5.4.3: *Mortality per person year in each half year since the second half year of 1996 for A) the whole group and B) per HIV-transmission group (dotted line is 95% CI).*

Finally, mortality rates declined as well. Half-year incidence figures for the whole group declined from 0.09 in the second half of 1996 to 0.02 per person year in the first half of 2000 (Figure 5.4.3). The decline in mortality was similar for each of the HIV-1 transmission risk groups, however, in the group of (intravenous) drug users, incidences were higher compared to those found in homosexual men or the heterosexual group. Preliminary data from a further study on these mortality figures indicate that the proportion of non-HIV-1- related deaths increased over time[45].

In conclusion, the data obtained from the monitoring of the ATHENA cohort show a dramatic improvement in the morbidity and mortality figures in the HIV-1-infected population after the introduction of HAART in July 1996. Preliminary results discerning HIV-1-related mortality from non-HIV-1-related mortality indicate a steady increase of the latter relative the first. It is strongly recommended that registration of the cause of death is improved in order to better distinguish between death causes directly linked to HIV-1 and those related to the non-HIV-1-infected population. This distinction should give more insight in causes of death that might be related to the toxicity of antiretroviral drugs used.

5.5. Therapy success and failure

5.5.1. Changes in viral load

An important end-point in monitoring antiretroviral therapy is the level of suppression of the virus production, measured by the effect of antiretroviral therapy on the concentration of HIV-1 RNA in plasma. In the ATHENA observational cohort, therapy success was defined as a plasma HIV-1 RNA level <500 copies/ml after 24 weeks of new antiretroviral combination treatment.

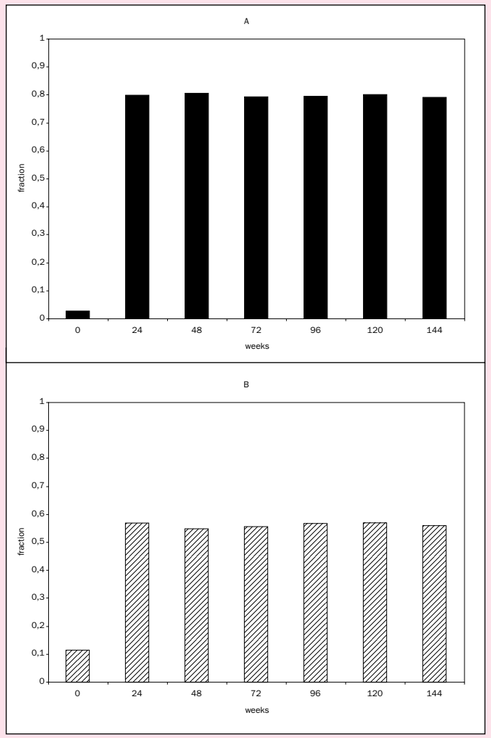

Figure 5.5.1.1: *Proportion of patients with HIV-RNA <500 copies/ml until 144 weeks after start of new antiretroviral combination treatment. (A) represents the naïve and (B) the pre-treated patient groups.*

The effect of HAART on HIV-1 RNA levels in plasma is shown in Figure 5.5.1.1. At 24 weeks of new therapy, 79.8% of the naïve patients had HIV-1 RNA levels <500 copies per ml in plasma and this percentage remained stable over time until 144 weeks after the start of therapy. Proportions with HIV-1 RNA levels <500 copies/ml plasma in the pre-treated group were lower: 56.6% at week 24 and similar percentages in the further follow-ups. In other words, the percentages of HAART successes were relatively high, but were however limited to approximately half of the pre-treated population. For those naïve and pre-treated patients who had HIV-1 RNA concentrations in plasma of more than 500 copies per ml after the start of HAART, the median concentration over time until 144 weeks of therapy is depicted

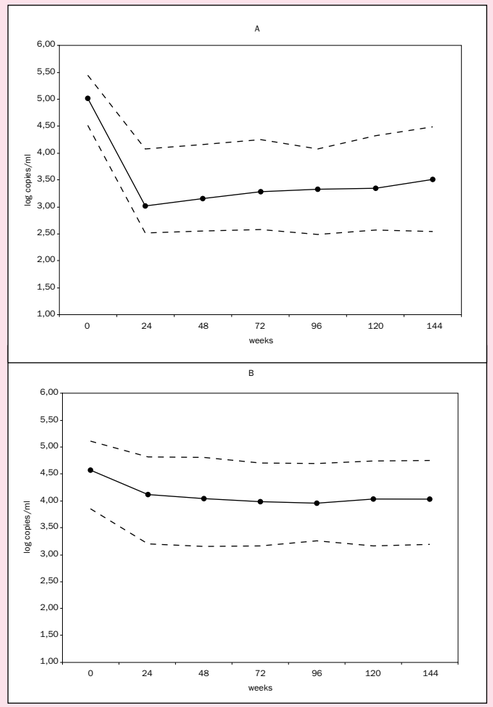

Figure 5.5.1.2: *Median HIV-RNA concentration in plasma after starting HAART in A) naïve and B) pre-treated patients who had plasma concentrations >500 copies/ml (dotted lines are inter-quartile ranges).*

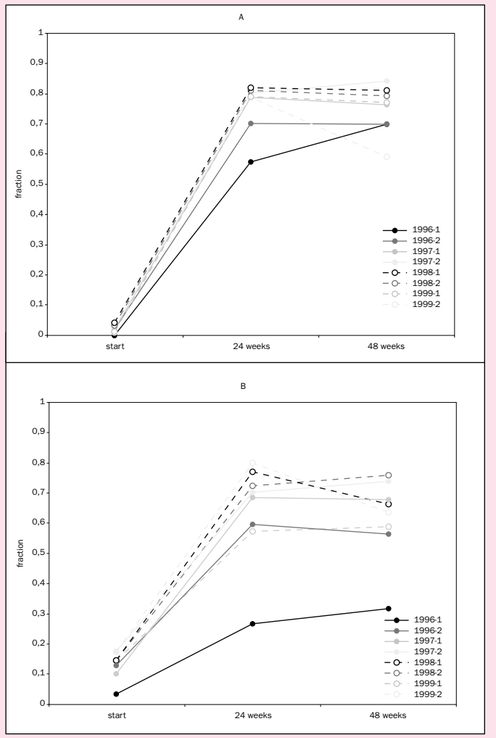

Figure 5.5.1.3: *Proportion of naïve (A) and pre-treated (B) patients with HIV-RNA levels <500 copies/ml during 48 weeks of new antiretroviral combination treatment.*

in Figure 5.5.1.2. Remarkably, the median HIV-1 RNA level in the naïve population declined from 5.0 log copies per ml at the start to 3.0 log after 24 weeks of new therapy and subsequently increased slowly to 3.5 log at week 144. Among the pre-treated patients the picture was different. Median HIV-1 RNA levels declined, however with only 0.5log copies per ml to approximately 4.0 log at week 24 and the weeks thereafter. Thus, between the naïve and pre-treated patients that had failed on HAART a difference similar to the successfully treated patients was found. Naïve patients showed a response of 1.5 to 2 log HIV-1 RNA copies/ml, although without a decline to levels <500 copies/ml. Pre-treated patients showed a lesser response of 0.5 log.

Of general importance is the finding that at a population level after start of HAART the amount of virus produced substantially declines. Moreover, this decline appeared to be stable over a period of 144 weeks. Of note, however, is the 20 to 50% of treated individuals that still produce virus at relatively high levels. In addition, one has to keep in mind that HIV-1 RNA concentrations in plasma <500 copies per ml still implicates virus production. This low level production may be of importance in maintaining the viral reservoir in an individual patient and presents a risk for the development of resistance[25,46,47].

The effect of HAART is also reflected in the proportion of patients declining to plasma HIV-1 RNA levels <500 copies per ml per half-year of start of new therapy. Between the half-year groups no significant differences were found with respect to the proportion <500 after 24 or 48 weeks (Figure 5.5.1.3), indicating that the effect of antiretroviral drug combinations used in 1996 is not that different from the effect of those used later.

5.5.2. Changes in CD4⁺ T cells numbers

The proportion of patients with CD4⁺ T cell counts <200 per mm³ blood decreased in both the naïve and pre-treated patient populations after the start of HAART (Figures 5.5.2.1). Of the naïve patients 44.8% had counts <200 per mm³ at start of therapy, changing to 22.8% at 24 and 7% after 144 weeks of HAART. Percentages of naïve patients with >500 CD4⁺ T cells per mm³ increased rapidly from 10.4% at start to 29.7% at 24 and 52.3%

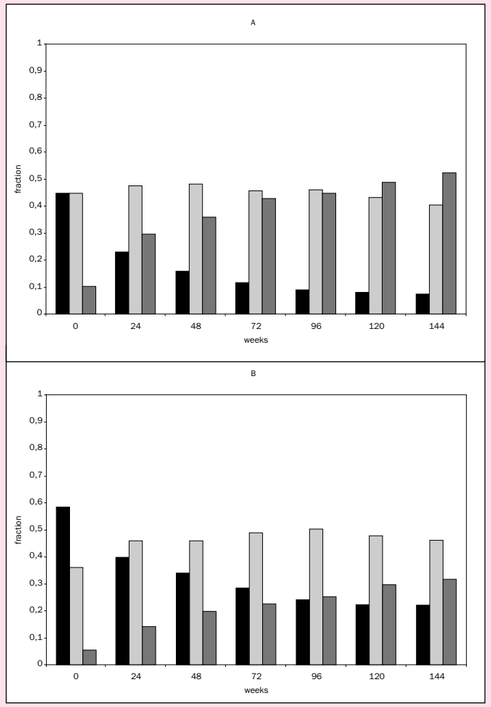

Figure 5.5.2.1: *Proportion of patients with <200 (first bar), 200-500 (second bar) and >500 (third bar) CD4⁺ T cells per mm³ after the start of HAART in A) naïve and B) pre-treated populations.*

at 144 weeks of treatment.

Immunological improvements were less in the pre-treated as compared with the naïve patients. The proportion of patients with CD4⁺ T cell counts <200 per mm³ decreased from 58.5% at start to 39.8% at 24 and 22.2% at 144 weeks of HAART. The proportion pre-treated patients with CD4⁺ T cell counts >500 increased from 5.6% at start to 14.2% at week 24 and 31.6% at week 144. Thus, in both the naïve and pre-treated patients an increase in the median CD4⁺ T cell number was found after the start of HAART (Figure 5.5.2.2). However, the

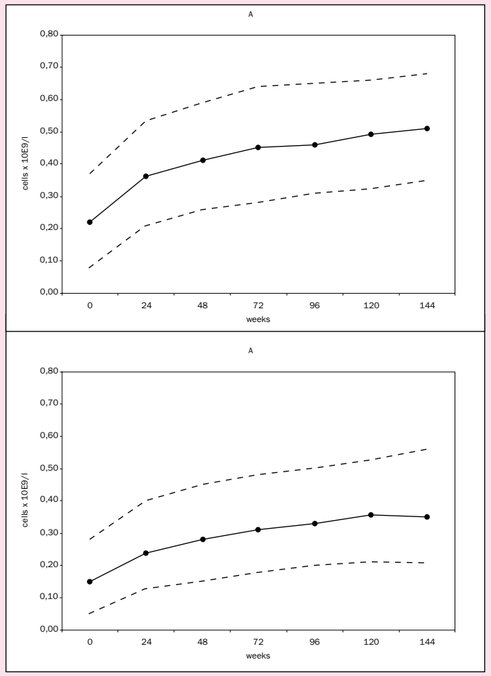

Figure 5.5.2.2: *Median CD4⁺ T cell number after start of HAART in A) naïve and B) pre-treated patients (dotted lines are inter quartile ranges).*

increase was more substantial in the naïve as compared with the pre-treated population.

5.5.3. Determinants of success

Variables, such as therapy history, immunological status and viral load, were used in Cox proportional hazard models to determine the predictive value for therapy success. Therapy success was defined as HIV-1 RNA levels <500 copies per ml plasma in response to 24 weeks of HAART. The first, and most influential determinant of therapy success was the antiretroviral therapy history of patients3. Therapy naïve patients had an almost twice-higher chance of therapy success compared to the pre-treated patients. Failures after initial success at week 24 were lower in the naïve patient group. The number of CD4⁺ T cells at start of new therapy is the main other factor that predicts therapy success.

In conclusion, therapy naïve patients with relative high CD4⁺ T cell numbers at baseline do respond better to HAART in terms of a decline of HIV-1 RNA plasma levels to below 500 copies per ml. The baseline concentration of HIV-1 RNA in plasma appeared to be of lesser importance. These results confirm those of other studies[34]. Interestingly, there is an immunological response to HAART irrespective of the virological response. Other important factors determining therapy outcome are the antiretroviral drug concentrations reached in plasma and the (pre-) existence of resistance to antiretroviral drugs. In the ATHENA cohort we were able to study the effect of therapeutic drug monitoring and at least for indinavir and nelfinavir it was shown that results of treatment of naïve patients improved when drug levels were known (see chapter 5.6). The results from genotypic resistance measurements indicate that, especially among the pre-treated patients, a relationship exists between therapy outcome and resistance at baseline. For both the naïve and pre-treated patients development of resistance when on HAART is of importance for the outcome of therapy (see chapter 5.8).

5.5.4. Changes of therapy regimen

Antiretroviral therapy regimens used are depicted in Figure 5.5.4.1. Interestingly, a constant fraction of approximately 10% of the population was not on antiretroviral therapy. Mono therapy with one RT inhibitor declined rapidly from 23.4% in the first half of 1996 to less than 1 in the second half of 1997. The use of a combination of 2 nRTI's decreased, as well, from 50% in 1996 to 3.8% in 2000. At the same time, the combination of 2 nRTI's plus 1 PI increases to a peak in 1997 and the first half of 1998, almost 70% at the highest.

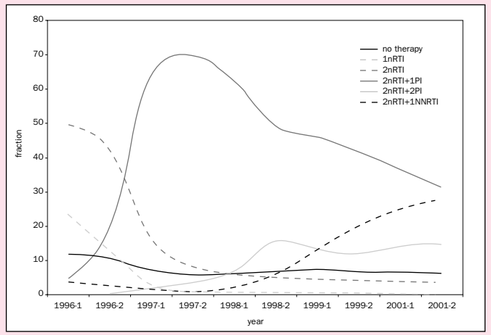

Figure 5.5.4.1: *Changes in the antiretroviral drug regimens used since 1996: Percentage of patients per half year on the various antiretroviral drug regimens.*

The usage of this combination then slowly declines with the rise of the combination of 2nRTI's plus one NNRTI. In 2000 an equal proportion of patients of about 30% uses 2 nRTI's plus 1 PI or 1 NNRTI. In addition, the percentage of patients having a combination of 2nRTI's plus 2 PI's increased as well, most probably because of the pharmacological boosting of one PI by another (especially ritonavir) resulting in a better virus suppression without an increasing toxicity and side effects. Usage of 3 nRTI's was extremely limited.

Over the follow-up period, antiretroviral therapy regimens were changed at least once in 76% of the patients[3]. The first HAART regimen was changed median 36 (IQR: 11-71) weeks after the start. Changing of therapy happened more frequently in the pre-treated group. Side effects, toxicity and therapy failure were the most important reasons for therapy change.

Clearly success of treatment of patients with HIV-1 infection is not only determined by the antiviral efficacy of treatment regimens, but also by the degree to which these treatments are tolerated by the patients. Within one year after the start of new treatment, 58% of the total population has had their regimen changed (Figure 5.5.4.2).

With some variation, most showed a trend towards decline over the years from 1996 onwards, however, at the end of 1999 the percentage was still 47% (Figure 5.5.4.3). A significant difference was found between naïve and pre-treated patients: 50% of the naïve and 68% of the pre-treated patients changed therapy regimens within one year of starting their first new regimen (Figure 5.5.4.2). No difference was found between HIV-1 transmission risk groups.

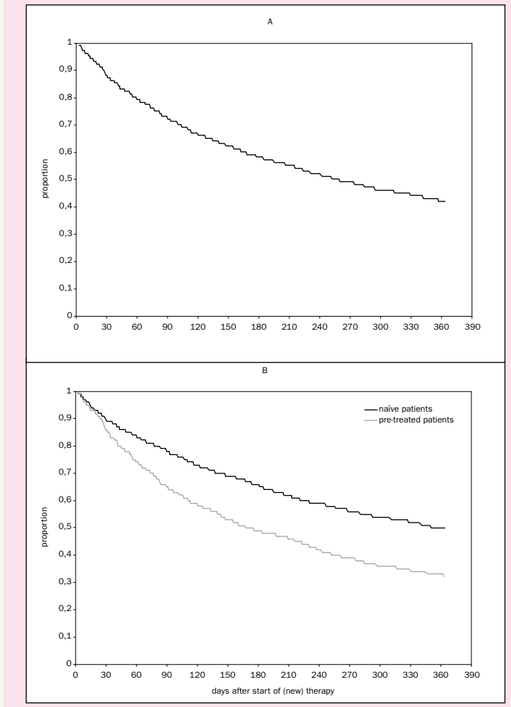

Figure 5.5.4.2: *Change of regimen over time after start of HAART in (A) the whole group of patients and (B) sub-divided for naïve and pre-treated patients.*

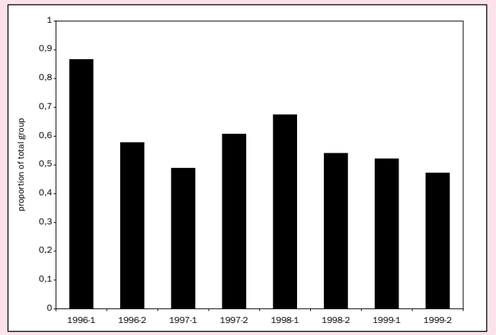

Figure 5.5.4.3: *Proportion of patients per half year since the start of HAART that had had their drug regimen changed within a year of starting.*

5.5.5. Toxicity of the drugs used

Toxicity of the drug combination used was an important reason for changing regimen. Toxicity was registered as the reason for changing in 35% of cases, having increased from 21% in 1996 to 43% by the end of 1999 (Figure 5.5.5.1). Therapy failure appeared to be less important and actually decreased from 13% in 1996 to 4% in the second half of 1999.

These figures confirm that, unfortunately, most of the anti-retroviral drugs are associated with one or several toxicities and that, depending on the severity of such toxicities, they can lead to premature discontinuation of treatment. In addition to the recording of treatment-associated toxicity, at each visit physicians are asked to indicate whether any of a number of specific clinical signs or symptoms has occurred since the previous assessment. These signs and symptoms include a diverse range of clinical entities.

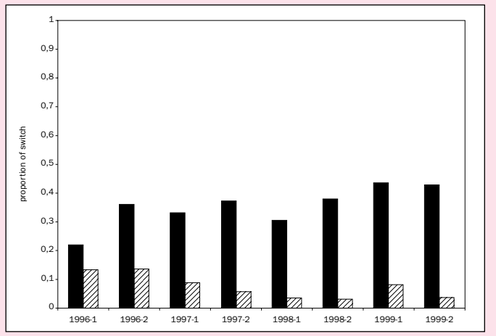

Figure 5.5.5.1: *Proportion of patients per half year since the start of HAART that had had their regimen changed within one year of starting because of toxicity (closed bars) and therapy failure (ruled bars).*

Specified toxicities recorded most frequently during each calendar period are summarised in Table 5.5.5.1. Absolute numbers and proportions of patients diagnosed with neuropathy, loss of libido, lipodystrophy, pancreatitis, diabetes mellitus, hepatic steatosis and nephrolithiasis are shown. Interestingly, neuropathy was most frequent in 1996/1997 and subsequently the frequency declined, at the same time the frequency of lipodystrophy increased. The decreasing proportion of neuropathy may reflect the direct effect of antiretroviral drugs on the incidence of HIV-1-related neuropathy. The remaining proportion could then be assumed to be drug related. The increasing proportion of lipodystrophy results from the introduction of HAART and the time-delay between the start of HAART and the onset of symptoms.

Half year	N	Toxicity, signs and symptoms N	Toxicity, signs and symptoms %	Neuropathy %	Loss of libido %	Lipodystrophy %	Pancreatitis %	Diabetes %	Hepatic steatosis %	Nephrolithiasis %
1996	403	46	11	63	9	0	11	0	13	4
	1342	72	5	67	11	0	8	4	4	6
1997	1899	109	6	56	14	5	2	3	2	18
	2240	208	9	38	11	22	5	7	3	14
1998	2487	232	9	29	9	40	5	3	2	12
	2689	332	12	18	8	57	2	3	4	8
1999	2860	243	8	18	6	61	2	4	2	6
	2965	218	7	18	13	50	4	4	1	9

Table 5.5.5.1: *Signs and symptoms of toxicity after starting HAART.*

Overall clinical signs and symptoms of toxicity were reported in a continuous 10% of the treated population. This may be an underestimate due to the limitations in the collection of toxicity data and the rapidly changing insights in the relationship between the drug combination used and the signs and symptoms of toxicity. Moreover, the combination of long-term toxicity is still unknown and might add to an increasing problem.

These results confirm earlier reports that adverse effects of drugs are an extremely significant problem with the currently available treatment regimens for HIV-1 infection[35-37,48]. Diminished tolerance for the use of these drugs is expected to lead to lesser degrees of treatment adherence, thereby jeopardising the likelihood of maintaining sustained suppression of HIV-1 replication and limiting overall treatment success. Furthermore, certain drug toxicities may result in marked increases in morbidity and result in reduced quality of life. Examples are chronic pain resulting from peripheral neuropathy, and the outward characteristics of lipodystrophy that may adversely influence a patient's sense of psychological well being. Moreover, there may be increased mortality from a number of adverse effects, including the hepatic steatosis/lactic acidosis syndrome and the possibly elevated risk of myocardial infarction and stroke in the case of hyperlipidemia, often present as part of lipodystrophy.

Given the above, continued surveillance and recording of already known, as well as potentially novel adverse effects of both current and future treatment regimens for HIV-1 infection, will be of the utmost importance. In that respect a more detailed monitoring of the toxicity of antiretroviral treatment of patients is highly recommended.

5.6. Quality of life and adherence

5.6.1. Quality of life

Most HAART regimens are far from convenient for patients. Short- and long-term toxicities frequently occur which may have a negative impact on patients' quality of life (QoL). In addition, the need for strict adherence to a substantial number of pills, rigid time schedules, and dietary prescriptions may interfere with the patients' daily activities. In patients with symptomatic HIV-1 infection or AIDS, these negative effects of HAART may be offset by any noticeable clinical benefit[49,50]. In contrast, HAART may have a negative impact on the QoL of patients who are asymptomatic at the outset[51]. This potential difference in the impact on QoL led to the question: *What are the changes in QoL of asymptomatic and symptomatic patients who are treated with HAART?*

To be able to answer this question, we asked patients in the focus group to complete a self-report questionnaire on QoL at inclusion in ATHENA and every six months thereafter. The QoL questionnaire comprised the Medical Outcomes Study Health Survey for HIV (MOS-HIV)[52]. Patients with a CDC class A at initiation of HAART were categorised as asymptomatic and, with a CDC class B or C, as symptomatic[2]. At inclusion in the focus group from 1998 onwards, patients were either initiating- or already receiving a HAART regimen. From patients who started HAART at the time of inclusion into the focus group, QoL-scores at initiation (baseline measurements) were subtracted from those collected at six-month time intervals after initiation. Repeated measures analysis of variance was performed on these change-scores to investigate differences between asymptomatic and symptomatic patients, and change over time. The same procedure was repeated for patients already receiving a HAART regimen at the time of inclusion into the focus group, but QoL-scores at inclusion were not subtracted from those collected later. In addition we compared QoL to Dutch population norms, which are available for four out of ten MOS HIV subscales[53] Age and gender matched mean population scores were subtracted from the observed scores and divided by the standard deviation of the reference population. 'Effect sizes' of 0.20, 0.50 and 0.80 were considered to indicate small, moderate and large effects, respectively.

Of the patients who initiated HAART at the time of inclusion into the focus group, 59% were asymptomatic. The majority had started a HAART regimen in 1999 and/or 1998. Patients were predominantly male (94%), and had a mean age of 40 years (SD± 8). Asymptomatic patients had a significantly better QoL at the start of HAART compared to symptomatic patients. Improvements in QoL relative to the start of HAART were found in the symptomatic but not in the asymptomatic patients. Mean changes in QoL over 18 months are shown in Figure 5.6.1.1.

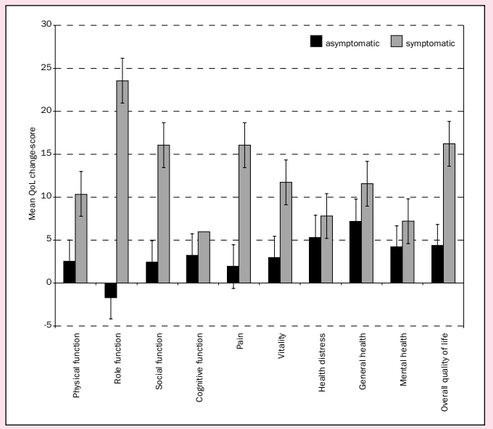

Figure 5.6.1.1: *Changes in QoL from initiation of HAART over 18 months in naive asymptomatic (black bars) and symptomatic (gray bars) patients enrolled in the focus group. Values are means (standard errors). Bars above the zero line indicate improvement in QoL relative to that at the start of HAART, whereas bars below the zero line indicate worsening QoL.*

Less than half (43%) of the 285 patients already receiving HAART at inclusion were asymptomatic. These patients had been on HAART for a median (inter-quartile range) of 663 (496-795) days. The majority had initiated HAART in 1996 and 1997. Patients were predominantly male and on average 42 (9) years old. No significant difference in QoL between asymptomatic and symptomatic patients, a different pattern of change over time, or a significant change over time was found. Compared to Dutch age and gender matched population norms, both asymptomatic and symptomatic patients showed poorer QoL regarding social function, vitality and mental health with effect sizes ranging from moderate to large[54]. Asymptomatic patients were comparable to population norms regarding pain, whereas symptomatic patients showed higher levels of pain (Figure 5.6.1.2.).

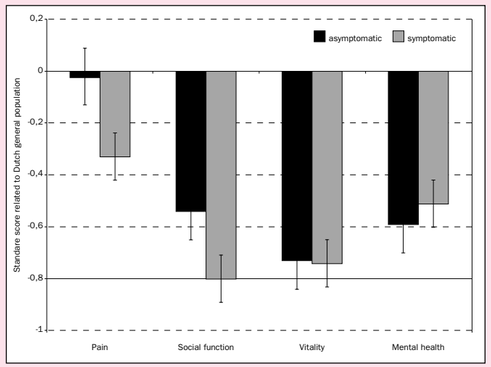

Figure 5.6.1.2: *QoL in pre-treated asymptomatic (black bars) and symptomatic (gray barts) patients on HAART in the focus group compared to Dutch general population norms. Values are means (standard errors). Bars above the zero line indicate better QoL compared to general population, whereas bars below the zero line indicate poorer QoL.*

In conclusion, QoL improved in symptomatic patients following initiation of HAART but not in asymptomatic patients. Although the QoL remained stable during prolonged HAART, it was reduced compared to that of the general Dutch population. This implies that QoL should remain a concern in the management of HIV-1 infection, especially in light of increasing emergence of long-term toxicities, rapidly evolving treatment regimens, and indeterminate longevity of the therapeutic effectiveness of currently available regimens.

5.6.2. Adherence

From the advent of antiretroviral combination therapy, the patients' ability to adhere to their prescribed regimen has been considered the "Achilles heel" in the treatment of HIV-1 infection. Sub-optimal patient adherence has shown to be related to inadequate viral suppression[55-57], reduced exposure to antiretroviral drugs[58,59], the emergence of viral resistance[60], and HIV-1 disease progression and mortality[60]. The rates of virologic failure sharply increase when less than 95% of a prescribed dose of protease inhibitors is actually taken[61]. In addition to taking adequate prescribed medication, antiretroviral drugs need to be taken according to the correct time-schedule, and for several drugs, dietary prescriptions. These issues prompted the question 'to what extent do patients report adherence to their prescribed antiretroviral therapy regimen for HIV-1 infection?'

Patients enrolled in the focus group completed a self-report questionnaire on adherence each time when plasma concentrations of protease inhibitors or nevirapine were measured (see also paragraph 5.8). Patients were informed that their responses would remain confidential and would have no consequences in terms of their treatment. They were asked how many days in the past week they had taken all medication in accordance with time and dietary prescriptions.

Data from patients who completed a questionnaire at the first pharmacokinetic measurement between May 1998 and June 1999 and who were prescribed indinavir, nelfinavir, saquinavir, ritonavir, nevirapine, or ritonavir/saquinavir as part of their antiretroviral regimen, were analysed first. Eighty-six percent of those patients completed a questionnaire on adherence[5] and about half of those patients reported to have taken all antiretroviral medication according to time schedule and dietary instructions, if applicable, in the past week. Patients reporting deviation form their prescribed regimen showed significantly lower drug exposure compared to fully adherent patients and had a decreased likelihood of having suppressed plasma HIV-1 RNA.

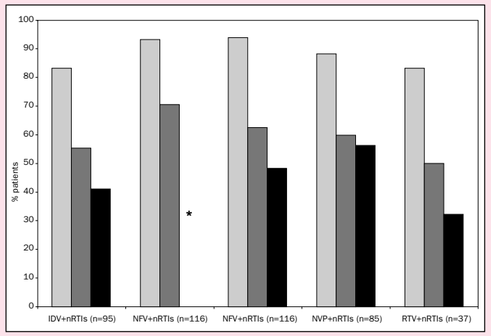

Figure 5.6.2.1: *Patient reported adherence in the five largest treatment groups of the focus group. First bars represent patient taking all medication, second bars patients taking all medication on time and third bars patients taking all medication on time and according to dietary requirements*
**= not assessed. Note: refers to adherence to entire regimen, including nRTIs.*

By November 2000, 91% of the patients in the focus group completed at least one adherence questionnaire. Patients completed a median of 6 (range 4-8) questionnaires during follow-up in the focus group. Figure 5.6.2.1 shows the updated percentages of reported adherence in the five largest treatment groups on the first completed questionnaire.

The percentages of patients who were considered fully adherent ranged from 32% for those prescribed a regimen containing ritonavir as a single protease inhibitor, to 56% for those prescribed a regimen containing nevirapine. Figure 5.6.2.2 shows the extent to which adherence was reported among patients who completed a questionnaire at 16, 48, 96, 144 and 192 weeks following initiation of new therapy. The percentage of fully adherent patients was highest at 16 weeks, 67%, compared to at 48 weeks (55%), 96 weeks (45%), 144 weeks (39%), and 192 weeks (42%) ($p<0.01$). When, age, gender, HIV-1 disease stage, and the PI(s) or NNRTI(s) used as part of the regimen were taken into account this effect remained statistically significant.

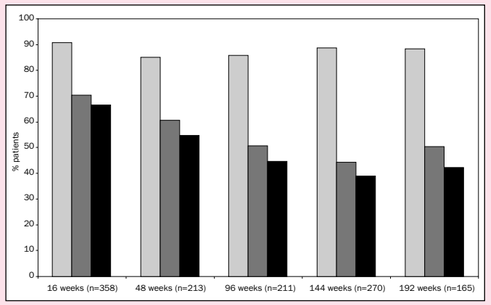

Figure 5.6.2.2: *Reported adherence in the focus group at specified time intervals following HAART initiation.*
First bars represent patient taking all medication, second bars patients taking all medication on time and third bars patients taking all medication on time and according to dietary requirements.

The median percentage of completed questionnaires on which patients reported deviation from their prescribed regimen was 50%. Table 5.6.2.1 shows the results from a multiple logistic regression analysis. Being asymptomatic at initiation, and having received HAART for one year or more was associated with reporting deviation of the prescribed regimen on more than 50% of completed questionnaires.

Taken together, we conclude that only about half of all patients took all antiretroviral medication in accordance with time and dietary prescriptions in the past week. It is of importance to note that deviation from the prescribed regimen was associated with lower drug exposure and a decreased likelihood of having suppressed plasma HIV-1 RNA, in other words: a lesser therapy effect. In that respect it is of major concern that patients who were asymptomatic at the start, or had received HAART for one year or more, were more likely to deviate from their prescribed regimen. It implies that the patients' ability to adhere to HAART requires continuous attention in the treatment of HIV-1 infection. We feel that monitoring the effect of HAART on QoL and monitoring adherence to HAART is most needed. For QoL this might be performed more appropiatly in a research setting. In line with the National Health Council (Gezondheidsraad) we recommend the inclusion of the monitoring of adherence to HAART into the patient care.

Variables	Multivariate OR (95% CI)	p-value
Asymptomatic (versus symptomatic)	1.8 (1.2 – 2.6)	<0.01
Duration of HAART		<0.01
< 1 year	Reference	
1 year – 2 years	2.1 (1.2 – 3.4)	
> 2 years	2.4 (1.5 – 3.7)	
Age		
< 35 years	Reference	0.70
35 – 40 years	0.7 (0.4 – 1.2)	
40 – 45 years	0.9 (0.5 – 1.6)	
> 45 years	0.9 (0.6 – 1.5)	
Male (versus female)	1.1 (0.6 – 2.0)	0.72

Table 5.6.2.1: *Predictors of lower levels of reported adherence in the focus group.*
OR= odds ratio. CI= confidence interval. HAART= highly active antiretroviral therapy.

5.7. Resistance to antiretroviral drugs

Although complete and prolonged suppression of HIV-1 replication is the primary object of antiretroviral therapy, this level of suppression is not achieved with the currently available combination therapies. Limited adherence (see paragraph 5.6.2), and differential efficacy of drugs[62], resulting in less than 100% suppression[47,63], allow ongoing low-level HIV-1 replication[64-66]. This ongoing replication under antiretroviral therapy will finally result in the selection of HIV-1 variants that can escape suppression of antiviral drugs, in other words that are resistant to the drugs. At the time that HAART was introduced in 1996, resistance of HIV-1 to nRTI's in particular was a relatively well-known feature and concern. Early reports of PI resistance showed multiple protease resistance mutations in viruses isolated from patients having a PI added to their regimen[67]. Taken together, resistance was clearly an issue to be studied from the moment large numbers of patients were having access to HAART. Another, more public health concern that arose from this was that prolonged treatment with these drugs, and consequently the selection of resistant HIV-1, could result in the transmission of these viruses to uninfected persons.

In the ATHENA study both questions were addressed by determining resistance of HIV-1 to antiretroviral drugs in the focus group. Resistance measurements were based on the isolation of HIV-1 RNA from the plasma of patients and amplification of the protease and (part of) the reverse transcriptase gene of the virus. Products were used in two ways. HIV-1 RT and protease were genotyped by using amplified genes in a sequence procedure. Subsequently, results obtained were compared to wild-type sequences of RT and protease and scanned for so called mutations associated with resistance. Mutations directly associated with resistance, and mutations associated with resistance mainly in combination with other mutations, were used to give a resistance score: the assumed level of loss of sensitivity to antiretroviral drugs (a 'virtual phenotype'), based on the available literature and results of large scale phenotyping. Genotyping was performed in the virological departments of the UMCU in Utrecht, the LUMC in Leiden and the AZR-Dijkzigt in Rotterdam and the department of Human Retrovirology at the AMC-UvA in Amsterdam by using the same RNA isolation, amplification and sequencing protocol. Results were authorized by the AMC-UvA before being added to the ATHENA sequence database. Authorization was based on alignment and comparison of sequences generated with subtype B consensus sequences. HIV-1 RT and protease were also used for phenotyping these genes by introducing them each separately in a standardized background and subsequently growing the resulting viruses in the absence and presence of different concentrations of antiviral drug. Phenotyping was done in only a limited number of patients to confirm the genotypic results and was performed in the department of virology of the UMCU in Utrecht and the AMC-UvA in Amsterdam.

5.7.1. Prevalence of strains of HIV-1 resistant to antiretroviral drugs

In approximately 9% of the participants in the Amsterdam cohort studies, resistance to zidovudine was found amongst homosexual men and drug users[68] who seroconverted as early as 1995. Similar percentages were found in a group of 82 individuals with documented primary HIV infection[69]: primary resistance associated mutations in protease were found in 4%. Recent studies among newly infected individuals in the USA and Canada report resistance of between 16 and 24 % to both RT and protease inhibitors[70-72]. An indication of the overall situation amongst the HIV-1 infected population in the Netherlands could be deduced from samples obtained at baseline from the naïve patients in the focus group, although the (approximate) date of seroconversion is unknown. From 186 patients the protease was genotyped and in one (0.5%) a primary resistance associated mutation was found. Three (1.7%) of 173 patients had a resistance-associated mutation in RT. These percentages are lower compared to those reported in the studies from the USA and Canada. One explanation may be that wide spread use of antiretroviral drugs started earlier in the USA and Canada than in Europe. Moreover, there may be differences in adherence to drugs between patients in Europe and the USA, related to the differences in accessibility to health care and antiretroviral drugs. More important perhaps is the possibility of selection of a predominantly wild-type virus population, which may occur after a certain period of time after transmission of a predominantly resistant virus population in an untreated individual. Finally, we have to take into account that in ATHENA, the number of patients from whom baseline plasma samples were available appeared to be limited which, together with the unknown time between transmission and sampling at the start of the new therapy, may underestimate the degree to which resistant viruses are transmitted.

5.7.2. Development of resistance during treatment with HAART

HIV-1 RT and protease genes obtained at the time of virological failures from patients in the focus group were used for genotyping, irrespective of the antiretroviral drug regimen used at the time of failure. Failure was defined as HIV-1 RNA levels of >1000 copies/ml 24 weeks after the start of HAART (the first failure) and subsequently at 24 weeks after the start of any new HAART regimen (and at the start of the second, third and so on). Sequences obtained at failure were compared to sequences obtained at baseline, i.e. at the start of HAART. In total 462 patients in the focus group of 554 had a HAART start date properly recorded after correcting for the difference between the intake into ATHENA and their actual date of starting HAART. In 227 of the 462 patients, baseline samples were no longer available, leaving samples of 235 patients available for sequencing HIV-1 RT and protease. In 4 samples no results could be obtained. In 219, both RT and protease could be sequenced and in 12, only

protease but not RT could be sequenced. Thus, the efficiency of the sequencing procedure at baseline reached levels of between 93.2 and 98.3%. Primary resistance associated mutations[73] at baseline were found in RT in 34 patients, 3 of them being naïve, and mutations were found in protease in 4 patients, one being naïve. Multiple (2 or more) resistance-associated mutations were found only in the pre-treated patients, 17 patients with multiple primary resistance associated mutations in RT and one patient with multiple primary resistance-associated mutations in protease. In other words, primary resistance-associated mutations were found at baseline mainly in pre-treated patients and mutations in protease at baseline were relatively limited, indicating the limited use of protease inhibitors and the more extensive use of RT inhibitors prior to the official introduction since 1996 of protease inhibitors.

Of the 462 patients, 111 (24%) showed virological failure after

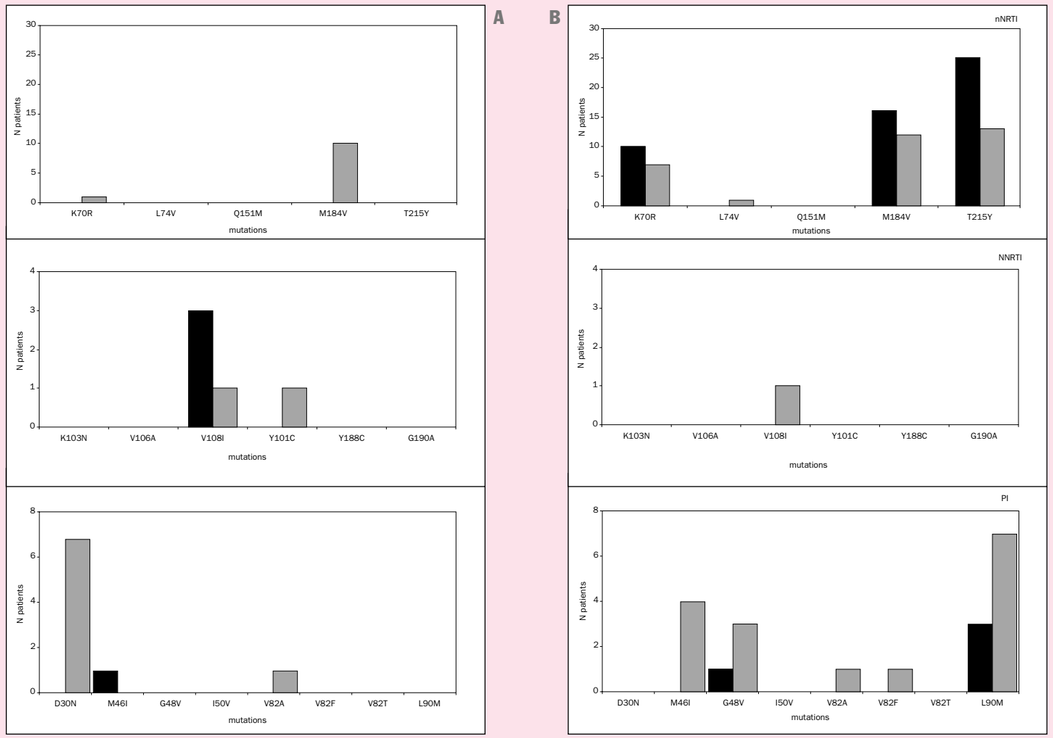

Figure 5.7.2.1: *Resistance-associated mutations in naïve (A) and pre-treated (B) individuals at baseline (black bars) and at the first failure (gray) 24 weeks after start of HAART*

24 weeks on HAART, i.e. had HIV-1 RNA concentrations of >1000 copies/ml in plasma. A sequencing procedure could be performed on a total of 62 of the 111 (55.8%), 31 naïve and 31 pre-treated, patients. From the remaining 49 patients no plasma samples at first therapy failure were available. In 49 of the 62 patients both RT and protease could be obtained, 26 naïve and 23 pre-treated patients. In 4 patients only protease was obtained. No results were obtained in samples from the remaining 9 patients. Thus, also at therapy failure, the efficiency of sequencing was high, ranging from 79 to 85.5%.

In 33 patients, 14 naïve and 19 pretreated, primary resistance associated mutations were found. All naïve and 17 of the 19 pre-treated patients were on therapy and two were not. Of the 20 patients without primary resistance-associated mutations 17 (13 naïve and 4 pretreated) were not on therapy at the moment of failure and 3 were. These three apparently failed therapy for reasons other than the major ones, namely therapy interruption and resistance. It appeared that the latter two could be distinguished based on viral load. When off therapy, the median HIV-1 RNA level in the naïve patients was 4.3 log copies/ml (IQR 4.0-5.5) and in the pre-treated patients it was 5.0 log (4.9-5.3), whereas when on therapy, these figures were 3.5 log (3.2-4.1) and 3.5 log (3.3-4.2), respectively. This may also indicate a partial effect of therapy despite resistance and the relative loss of replication capacity (fitness) of resistant compared to wild type viruses.

Another indication of resistance as the cause of viral rebound might be the time on therapy. Naïve patients failing on therapy without having primary resistance-associated mutations in RT or protease are on that therapy for a median of 56 days (IQR 42-96). When primary resistance-associated mutations are found, the median number of days on therapy is significantly higher: 227 (range 190-351) days. The same difference is found for pre-treated patients. These findings indicate that therapy interruption takes place soon after starting the first HAART regimen and is probably related to toxicity and side effects (see paragraph 5.5.5). In practice, these findings are of importance in that therapy failure characterized by relatively low HIV-1 RNA levels after a long period of HAART may indicate resistance as the cause in contrast to failure characterized by relatively high HIV-1 RNA concentrations after a short period of HAART.

In Figure 5.7.2.1 the mutations found in the naïve and pre-treated patients at baseline and first failure are summarized.

At baseline, in 3 naïve patients, the 108I mutation in RT was found and in one the 46I mutation in protease was detected. Among the pretreated patients at baseline, mutations 70R, 184V, 215Y were found in RT and 48V and 90M in protease, indicating pre-HAART usage of nRTI's like zidovudine and lamivudine and usage of PI's. First failure mutations in the naïve patients were in RT 70R, 184V, 108I and 181C, and in the pre-treated patients they were 70R, 74V, 184V, 215Y, and 108I. The protease mutations found in the naïve patients were 30N and 82A. In the pre-treated patients mutations in protease were 46I, 48V, 82A, 82T, and 90M. Thus, a broadening of resistance-associated mutations was already observed at the time of the first failure 24 weeks after the start of HAART. Multiple resistance-associated mutations were found predominantly in the pre-treated patients, indicating an accumulation of mutations following the addition of new antiretroviral drugs on top of the pre-HAART combination.

5.7.3. Confirmation of genotypic outcomes by determining the virus phenotype for RT and protease

Part of the resistance protocol of the ATHENA project was the phenotypic confirmation of the results of HIV-1 RT and protease genotyping. RT and protease genes of HIV-1 isolated and amplified from plasma were incorporated into a standard HIV-1 background and subsequently cultured with or without given concentrations of the various RTI's and PI's. This phenotyping procedure was successfully completed in 42% of the total number requested and so, in total, the result of genotyping 38 RT and 125 protease

genes could be compared with those of phenotyping. Ninety percent of the wild-type protease sequences were confirmed phenotypically. The remaining 10% were discordant because in spite of a wild-type genotype, sensitivity to PI's was diminished. Of the protease sequences with resistance-associated mutations, 70% were also confirmed by phenotyping to be resistant virus. Discordant results were found in 30%, where resistant genotypes were phenotyped as wild type.

		Phenotype: Wild type		Phenotype: Resistant	
Protease	**N**	**N**	**(%)**	**N**	**(%)**
Genotype:					
- Wild type	82	74	(90)	8	(10)
- Resistant	43	13	(30)	30	(70)
Total	125	87	(70)	38	(30)
RT	**N**	**N**	**(%)**	**N**	**(%)**
Genotype:					
- Wild type	15	14	(93)	1	(7)
- Resistant	23	0	(0)	23	(100)
Total	38	12	(32)	24	(63)

Table 5.7.3.1: *Comparison of the results of genotyping and phenotyping of HIV-1 RT and protease*

The results for RT were to a certain extent the same, 93% of the wild-type sequences were confirmed by phenotyping and 100% of the resistant sequences were; 7% of the wild type sequences appeared as resistant when phenotyped. When analysed in more detail, the results between resistant genotypes and phenotypes were less concordant, especially when combinations of resistance-associated mutations relating to specific antiretroviral drugs were compared to the phenotypic results for RT relative to those same drugs.

Our findings, although limited in number, show that there is a discrepancy between the results of resistance determination by way of sequencing HIV-1 RT and protease versus culturing RT and protease in a standard HIV-1 background in the presence of the various antiretroviral drugs. The disadvantage of phenotyping is the intrinsic selection of the fittest virus in culture. If heterogeneity exists in vivo as a result of virus growing under therapy-induced selective pressure, this can frequently be shown from sequencing. In culture, however, the most fit, often the wild type virus, will overgrow the less fit, often the drug resistant strains. On the other hand, 7 and 10% of cultures indicated a decreased sensitivity to RT and protease inhibitors respectively, whereas genotyping did not reveal any resistance-associated mutations.

5.7.4. Conclusions and recommendations

Determination of resistance was a 'high profile' issue in ATHENA. It was important that between the four virology laboratories an identical protocol was achieved that gave comparable results of sequencing of HIV-1 RT and protease genes. Moreover, a table of resistance-associated mutations was produced between these four laboratories, guiding the interpretation of sequencing results in terms of levels of resistance to the various antiretroviral drugs. In addition, a quality control system was set-up and used to evaluate the ability of laboratories to achieve sufficient sensitivity and specificity. It is recommended to add this system to other quality control systems used in the virological patient care. With the ATHENA experience and the QC system in place, the four laboratories involved are very well able to perform the necessary genotypic resistance measurements for the HIV/AIDS hospitals in The Netherlands. Genotypic determination of resistance appears to be feasible and is, based on the ATHENA results, recommended from the start of HAART, especially when patients are sub-optimally treated before, but also in those that are therapy naive. Although low, the prevalence of resistant strains in untreated patients may be underestimated and it may be expected that the transmission of resistant strains will increase with the rise in the number of people on treatment, as has been shown by a number of studies from the USA, Canada and Switzerland. Other studies have shown the positive effects of knowing the genotypic resistance patterns in terms of the choice of antiretroviral drug regimens and on the effect of antiretroviral therapy on virus levels. Until now, we have not been able to confirm the results of those studies. The number of patients failing therapy, for which genotypic resistance data are available, is too limited. However, based on studies by others, we recommend the determination of genotypic resistance at virological failure, especially when failure happens after a relatively prolonged period of time on therapy. In addition, it is recommended to add to the genotypic results a phenotypic 'interpretation': a virtual phenotype based on the known and published results of the phenotypically determined degree of loss of sensitivity to antiretroviral drugs. The aim is to give the patient and the treating physician a realistic choice for alternative antiretroviral drug combinations. Despite the relatively high sensitivity and specificity of genotyping, discrepancies are found between genotypic and phenotypic results. Although the sensitivity of the phenotypic assay is low, it may be of importance to keep options for phenotypic determination of resistance open, especially for these specific cases.

5.8. Antiretroviral drug levels

There is increasing evidence of the existence of relationships between plasma concentrations of antiretroviral drugs and their pharmacological effect[17,74-84]. This is especially true for representatives of the classes of HIV-1 protease inhibitors and the non-nucleoside reverse transcriptase inhibitors. However, to date there is no evidence indicating that the routine determination of plasma concentrations, or Therapeutic Drug Monitoring (TDM), of antiretroviral drugs results in reduced HIV-1 related complications and death. Therefore we investigated whether the "determination of concentrations of antiretroviral drugs in plasma contributes to an improved HIV-1 related morbidity and mortality".

To be able to address this issue, a randomised, controlled study has been conducted. In the focus group patients were randomised to two study arms: a group of patients for whom the plasma drug concentration was reported to their physician, together with advice (intervention arm or TDM report group), and a group of patients for whom plasma drug concentrations were determined without reporting the result or giving advice to the physician (control arm). Owing to the randomisation, the two study arms had to be equal, except in terms of reporting the drug concentrations together with advice from a pharmacologist. Blood samples were collected from these patients at regular time intervals (preferably, together with each viral load measurement) for measurement of plasma concentrations of the protease inhibitors indinavir, nelfinavir, ritonavir, saquinavir, amprenavir and lopinavir, and of the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz. For the interpretation of results, concentration ratios were used: the measured concentrations of a drug as compared to the time-adjusted average concentration of the same drug as measured in a reference population of HIV-1-infected individuals. A concentration ratio of 1 indicates that the measured concentration in an individual is equal to the average concentration in a reference population.

In this report, data will be presented for the treatment-naive patients who started to use indinavir, nelfinavir, ritonavir, saquinavir, or nevirapine. Viral load response was used as an indicator of treatment outcome. Patients in the TDM report group received advice from the pharmacologist according to the rules as summarised in table 5.8.1.

CR	Advice
Nelfinavir 1250 mg bid	
< 0.75, 1st time	Discuss intake with food
< 0.75, 2nd time	Increase dose to 1500 mg bid with food
> 2.0	Decrease dose in the event of toxicity
Nelfinavir 1500 mg bid	
< 0.75	Increase dose to 1750 mg bid with food; add ritonavir 100 mg bid, or change regimen
> 2.0	Decrease dose in the event of toxicity
Indinavir 800 mg tid	
< 0.75	Increase dose to 1000 mg tid or give Indinavir/RTV combination
> 2.0	Decrease dose in the event of toxicity
Indinavir 400 mg + ritonavir 400 mg bid	
< 0.50	Increase indinavir dose to 600 mg bid
> 2.0	Decrease dose in the event of toxicity
Indinavir 800 mg + ritonavir 100 mg bid	
< 0.25	Increase ritonavir dose to 200 mg bid
> 2.0	Decrease dose in the event of toxicity
Saquinavir 1200 mg tid or saquinavir 400 mg bid (+ ritonavir 400 mg bid)	
< 0.75	Check compliance, increase dosage if necessary
≥ 5	Decrease dose in the event of toxicity
Saquinavir 1200 mg bid	
< 0.75	Check compliance, increase dosage if necessary
≥ 2	Decrease dose in the event of toxicity
Ritonavir 600 mg bid or ritonavir 400 mg bid (+ saquinavir 400 mg bid)	
< 0.75	Check compliance, increase dosage if necessary
≥ 2	Decrease dose in the event of toxicity
Nevirapine 200 mg bid	
< 0.9	Check compliance; increase dosage if necessary. Cave! This is not true if use of nevirapine is <2 weeks
≥ 2	Decrease dose in the event of toxicity
Efavirenz 600 mg qd	
< 0.5	Check compliance, increase dosage if necessary
≥ 2	Decrease dose in the event of toxicity

Table 5.8.1: *The pharmacologist's advice; CR = concentration ratio*

5.8.1. Nelfinavir

Ninety-two patients were randomised: 41 in the TDM report group and 51 in the control group. The randomisation procedure did not result in two group of similar size.

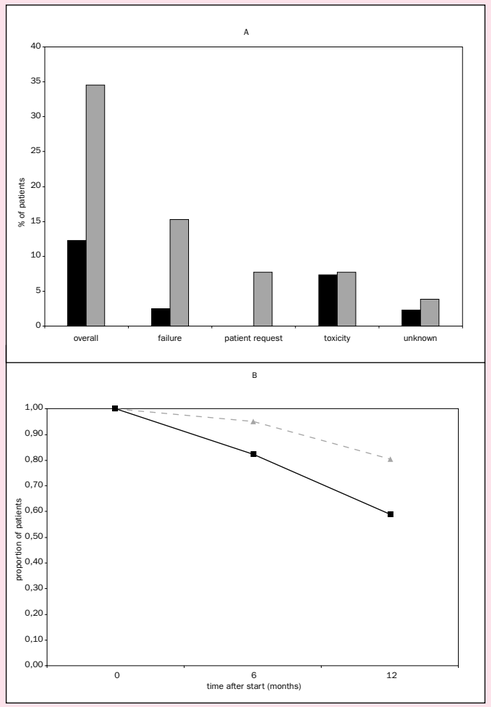

Figure 5.8.1.1: *A) Percentage of naïve patients discontinuing nelfinavir 1250 mg BID during one year of follow-up on patient's request, for reasons of toxicity or failure and B) proportion of patients with a successful response (HIV-RNA levels <500 copies/ml) to nelfinavir 1250 BID (NC = F analysis). Black represents patients randomised to therapeutic drug monitoring; gray the control patients.*

The reason for this was a randomisation procedure that also used factors other than treatment experience to stratify patients (e.g. study site, concomitant use of other PIs). However, no significant differences in baseline characteristics were found between the TDM report and the control group. After one year of follow up, significantly fewer patients in the TDM report group had discontinued nelfinavir than in the control group: 12.2% vs. 35.3% (p=0.01; figure 5.8.1.1). This was mainly driven by a lower rate of discontinuation owing to virological failure: 2.4% in the TDM report group vs. 17.6% in the control group (p=0.02). The TDM report group showed a higher proportion of patients with a viral load below 500 copies after 6 (95.1% vs. 82.4%; p=0.06) and 12 (80.5% vs. 58.8%; p=0.03) months of treatment (figure 5.8.1). In seven patients with virological failure, HIV-1 RT and protease was isolated and genotyped. In five patients, mutations in protease and RT were shown, in one patient only mutations in protease were observed, and in another patient there were just RT mutations. Fewer patients in the TDM report group developed virological failure than in the control group, which stresses the importance of TDM in the prevention of resistance.

5.8.2 Indinavir

Fifty-five patients were randomised: 28 in the TDM report group and 27 in the control group. There were no significant differences between the TDM report group and the control group in baseline characteristics with the exception of a signifi-

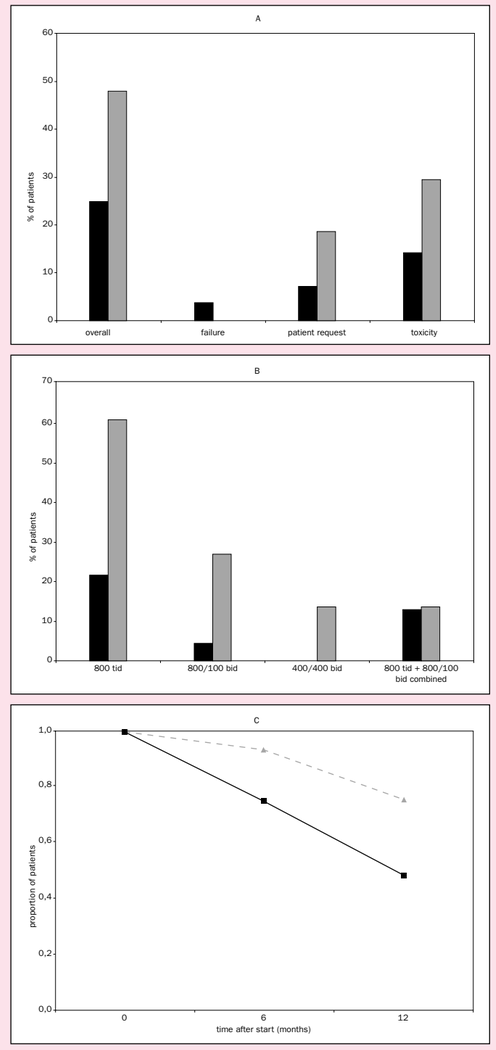

Figure 5.8.2.1: *A) Percentage of naïve patients discontinuing indinavir during one year of follow-up on patient's request, for reasons of toxicity or failure and B) percentage of patients discontinuing indinavir 800 TID, 800/100 BID, 400/400 BID or 800 TID combined with 800/100 BID because of toxicity. The proportion of patients with a successful response (HIV-RNA levels <500 copies/ml) on indinavir (NC = F analysis) is depicted in C. Black represents patients randomised to therapeutic drug monitoring; gray the control patients.*

cantly lower baseline CD4 cell count in the TDM report group (p=0.03, Mann-Whitney U test). After one year of follow up a non-significant trend of fewer discontinuations of indinavir in the TDM report group vs. the control group was observed: 25.0 vs. 48.1% (p=0.07; figure 5.8.2.1). This was mainly driven by a significantly lower rate of discontinuation because of toxicity in patients using indinavir 800 mg TID or indinavir 800 mg + 100 mg ritonavir BID: 9.5% in the TDM report group vs. 40.0% in the control group (p=0.03; figure 5.8.2.1). The TDM report group showed a higher proportion of patients with a viral load below 500 copies after 6 (92.9 vs 74.1%; p=0.06) and 12 (75.0 vs 48.1%; p=0.04) months of treatment (figure 5.8.2.1).

5.8.3. Saquinavir

Four patients using saquinavir 1200 mg BID in combination with nelfinavir 1250 mg BID were randomised: 2 in the TDM report group and 2 in the control group. All patients besides one continued to use this combination. No virological failure was observed. No further analysis was executed due to the small number of patients.

5.8.4. Ritonavir

Twenty patients using ritonavir (600 mg BID or in combination with indinavir 400 mg BID) were randomised: 10 in the TDM report group and 10 in the control group. There were no significant differences in baseline characteristics between the TDM report group and the control group. After one year of follow up, no difference in the overall discontinuation of ritonavir could be observed between the TDM report group and the control group. An occurrence of note was that 50% of the patients in the TDM report as well as in the control group switched from a regimen containing indinavir and ritonavir 400 mg BID to nevirapine or indinavir/ritonavir 800/100 mg BID. In the control group this switch took place on patient request, in the TDM report group it was mainly a result of toxicity (figure 5.8.4.1). No differences could be seen in the proportion of patients with a viral load below 500 copies after 6 and 12 months (figure 5.8.4.2). The small proportion of patients with a successful response is mainly owing to the discontinuation of treatment and not to virological failure.

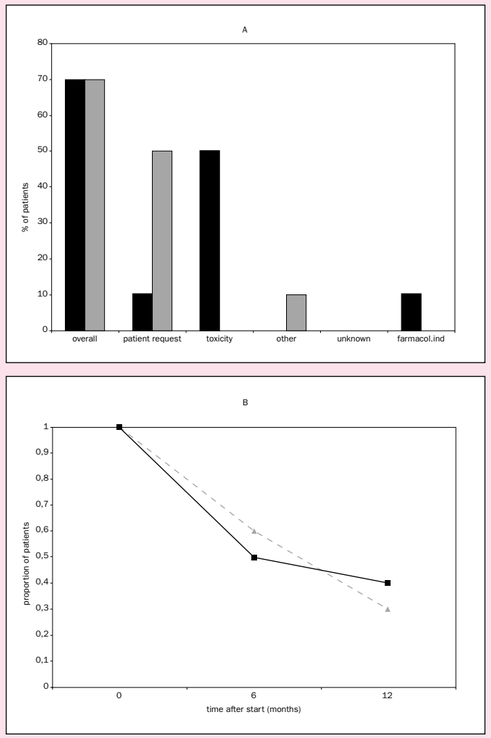

Figure 5.8.4.1: *A) Percentage of naïve patients discontinuing ritonavir during one year of follow-up on patient's request, for reasons of toxicity or on pharmacological advice and B) proportion of patients with a successful response (HIV-RNA levels <500 copies/ml) on ritonavir (NC = F analysis). Black represents patients randomised to therapeutic drug monitoring; gray the control patients.*

5.8.5. Ritonavir + saquinavir 400 mg bid

Thirteen patients were randomised: 6 in the TDM report group and 7 in the control group. There were no significant differences in baseline characteristics between the TDM report group and the control group. After one year of follow up no difference in the overall discontinuation of ritonavir plus saquinavir 400 mg BID could be observed between the TDM report group and the control group. No differences could be seen in the proportion of patients with a viral load below 500 copies after 6 and 12 months.

5.8.6. Nevirapine

Forty-seven patients were randomised: 24 in the TDM report group and 23 in the control group. Eighteen patients could not be included in the analysis because of follow up of less than one year. Twenty-nine patients were eligible for analysis: 16 in the TDM report group and 13 in the control group. There were no significant differences in baseline characteristics. After one year of follow up no difference in the overall discontinuation of nevirapine could be observed between the TDM report group and the control group. Few patients discontinued the nevirapine-containing regimen. In all cases the reason was toxicity: 12.5% in the TDM report group vs. 7.7% in the control group. The major side effect of nevirapine (rash) seems not to be related to plasma levels. Therefore, non-completers were excluded from the analysis of the viral load data. After 6 months and 1 year of follow up over 90% of the patients in the TDM report group, as well as the control group had a viral load below 500 copies/mL.

5.8.7. Efavirenz

Two treatment-naïve patients have been randomised in the control group. Both patients had less than 1 year of follow up and no further analysis was conducted.

5.8.8. Conclusions and recommendations

We conclude that Therapeutic Drug Monitoring of indinavir and nelfinavir in treatment-naïve patients results in an improved outcome of therapy. In this respect, the ATHENA study is the first randomised clinical trial worldwide to show this benefit. However, for ritonavir, saquinavir and nevirapine no benefit of TDM on the outcome of therapy could be demonstrated in this analysis. This may be a result of involving only a small group of patients. This is especially true for nevirapine; with a large number of patients with a short follow up and a low level of events, analysis should be repeated at a later stage. Further analysis of other drugs and treatment-experienced patients in ATHENA will be conducted in the near future. Together with the Dutch Association of AIDS Physicians (NVAB) we recommend Therapeutic Drug Monitoring as routine care for treatment-naive patients.

5.9. Costs and benefits

5.9.1. Introduction

The introduction of HAART in 1996 was accompanied by increased concern about the costs of care for patients with HIV-1 infection. Short term studies indicated a reduction in overall health care costs[85,86], however, long-term implications remained unclear and the costs of HAART became one of the central issues in the ATHENA project. Data from the ATHENA cohort were used to describe the effects of the introduction of HAART on costs for the Dutch health care system during the years 1996-2000. The cost consequences were studied from a societal perspective, addressing direct and indirect, medical and non-medical cost components. An emphasis was put on the direct medical costs and in particular the costs of in- and out-patient HAART medication and hospital care.

5.9.2. Costs of HAART and costs of hospital care

By linking the degree of care and other uses of resources with unit costs, the expense of care could be analysed. Case report forms were used to collect data on patients' a) use of HAART and b) visits to the outpatient hospital clinic. These forms were completed for all ATHENA participants. The hospital information system was used to collect data on all in-hospital resource use in a subset of 485 patients, both retrospectively from the start of HAART onwards and prospectively until the end of observation. Questionnaires were used to collect data on patients' work status at inclusion in ATHENA and during follow-up. Unit costs of in-patient hospital days and outpatient hospital visits were based on Dutch health costing guidelines[87], weighted for the distribution of patients over academic and non-academic hospitals. Unit costs of in-hospital day-care treatment and unit costs of most diagnostic and therapeutic procedures were based on COTG-tariffs. As the analysis presented here takes an economic rather than financial perspective, the 5% trimmed mean of available tariffs (73%) was taken as a proxy for the unit costs of diagnostic and therapeutic procedures for which no tariffs were available (27%). The daily costs of different types of medication were derived from the Dutch Farmacotherapeutisch Kompas[88]. Unit costs of HIV-1 RNA load and genotypic resistance measurements were derived from real cost data available in the Academic Medical Center (AMC) hospital ledger and the buying-department, including the costs of personnel, materials, and overheads. Overhead costs were calculated from pro rata cost allocation after distinguishing production from non-production centres. The costs of non-production centres were lowered, as a result of revenues generated by their external activities, before the 'back-office' costs were allocated to the production centres such as the department of Human Virology. The resulting costs were allocated pro rata to the production centres based on the total costs of these centres without correction for revenues from external production. Within the production centre no further 'back-office' costs were identified in this study. The ratio of the allocated 'back-office' costs to the total costs of the production centre was used to raise the costs of personnel and materials for viral load and genotypic resistance measurements. The cost data were based on 1999-2000 unit prices and no price indexing was done on historical data.

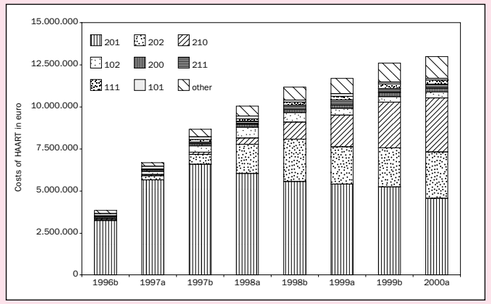

Figure 5.9.2.1: *Costs of HAART use per half year by type of combination regimen. Total number of patients: 3305. Costs are in euros. First and second half of each year is indicated by a and b, respectively. Regimens are: 201: 2nRTI's+1PI - 202: 2nRTI's+2PI's - 210: 2nRTI's+1NNRTI - 102: 1nRTI+2PI's - 200: 2nRTI's - 211: 2nRTI's+1NNRTI+1PI - 111: 1nRTI+1NNRTI+1PI - 101: 1nRTI+1PI*

Data were available for 3,305 ATHENA patients on their use of HAART between July 1st, 1996 and June 30th, 2000. Total costs of HAART use for these patients amounted to 77.8 million euros. Regimes consisting of 2 nRTI's plus 1 PI, 2 nRTI's plus 2 PI's, 2 nRTI's plus 1 NNRTI, and 1 nRTI plus 2 PI's accounted for 55, 16, 12 and 3.8 % of these costs, respectively, or in total, 86%. Of the 2 nRTI's plus 1 PI regimens, the combinations stavudine plus lamivudine plus indinavir and zidovudine plus lamivudine with indinavir, saquinavir, nelfinavir or ritonavir were most frequently prescribed.

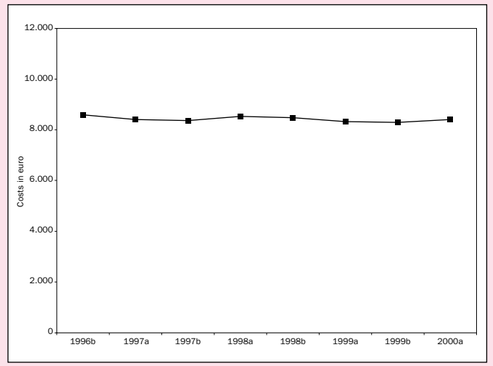

Figure 5.9.2.2: *Costs of HAART per person year in each half year since its introduction in 1996. Number of patients: 3305; person years: 9270. a indicates the first and b the second half of each year. Costs are in euros.*

The costs of HAART use per half-year interval more than tripled in the first years after introduction, with a steep increase during the first 18 months followed by a gradual increase to 13.02 million euros in the first half of 2000 (figure 5.9.2.1).

The relative contribution of the 2 nRTI's plus 1 PI regimens decreased, whereas the relative contribution of 2 nRTI's plus 1 NNRTI regimens increased. The increase in total costs could be fully accounted for by rising numbers of patients on HAART, for the mean costs per person-year hardly changed over the years

Whereas the costs of HAART use per person-year remained stable over time, the costs of in-hospital admissions decreased from 2,408 euros per person-year in the second half of 1996 to 444 euros per person-year in the first half of 2000 (figure 5.9.2.3). By that time the number of in-patient days per person-year had dropped to 1.17. For combination therapies with the highest numbers of person-years, in-patient days per person-year were 2.63 (2 nRTI's plus 1 PI), 1.08 (2 nRTI's plus 2 PI's), 1.47 (2 nRTI's plus 1 NNRTI) and 2.04 (1 nRTI + 2PI's) respectively. Non-HAART periods in-between or following HAART accounted for 8.42 in-patient days per person-year.

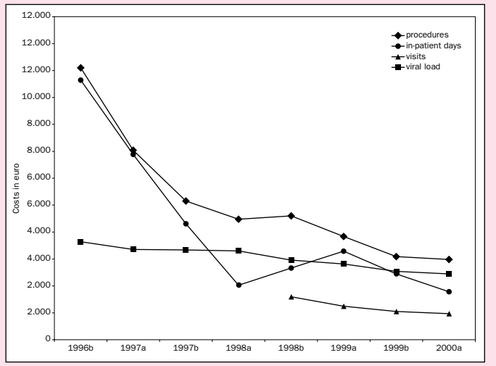

Figure 5.9.2.3: *Cost per person year, in each half year since the introduction of HAART, for major resources in HIV care. First and second half of each year is indicated by a or b, respectively. Numbers of patients and person years for procedures, in-patient days, visits and viral load, were 485 and 1.454, 485 and 1.454, 3186 and 4.207, and 3198 and 9.230, respectively. Costs are in euros.*

Only prospective data were available for the costs of consultations by the AIDS treating specialist. The costs per person-year of consultations gradually declined from 392 euros in the second half of 1998 to 238 euros in the first half of 2000. For the above-mentioned regimens and the 2 nRTI's combinations, these costs ranged from 260 to 295 euros, slightly below the 304 euros per person-year for non-HAART periods. On average, patients visit the AIDS treating specialist nearly 5 times per person-year. The numbers of day-care treatments per person-year were low for the 1996-2000 period, ranging from 0.13 to 0.05. The costs per person-year turned out to be negligible.

The unit costs of viral load and genotypic resistance measurements were 172 and 179 euros respectively. The number of viral load assessments per person-year decreased between 1996 and 2000 from 5.28 to 3.56. The costs per person-year decreased from 910 euros to 613 euros. Data on genotypic resistance were available for the 1999-2000 period. Genotypic resistance was determined 0.72 times per person-year, costing approximately 125 euros per gene per person-year.

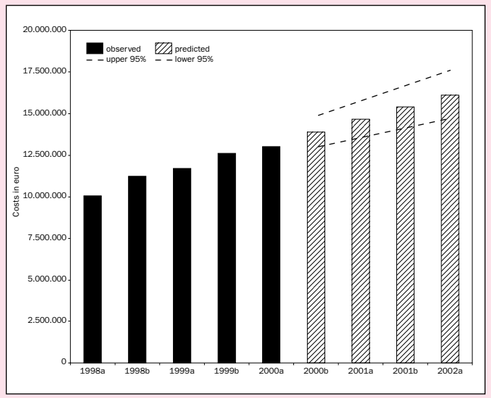

Figure 5.9.2.4: *Predicted total costs of HAART use per half year based on linear extrapolation of recent developments. Predictions are made for the last half year of 2000, 2001 and the first half year of 2002. Half years are indicated by a (first) and b (second), respectively. Costs are in euros.*

The declining costs per person-year of major hospital care components with stable costs of HAART per person-year resulted in an increase in the relative contribution of HAART to the total costs of anti-HIV-1 treatment.

The costs of anti-HIV-1 medication and HIV-1 care were forecasted by extrapolation over the two years immediately following the end of the observation period. The extrapolation was based on linear regression modelling of distinct subgroup developments, using data from 1998 to June 2000. To forecast the total costs of HAART use for the period July 2000 - June 2002, for example, we first predicted the costs for each of the major HAART regimens separately, and then estimated total costs by summing the regimens. Given the short prediction period of two years, no discount rate was applied. The total costs were predicted to increase further from 13.02 million euros per half-year in the first half of 2000 up to 16.11 (95% CI: 14.66 -17.57) million per half-year in the first half of 2002 (Figure 5.9.2.4). This growth reflects an expected continuing increase in the number of patients simultaneously on HAART, for the mean costs of HAART per person-year are likely to decrease slightly, by 100 euros during these years.

5.9.3. Changes in work status under HAART

Work status data from questionnaires (N=2,276) at inclusion - on average 1.54 years after start of HAART - and at the latest visit to the out-patient hospital clinic - 2.93 years after start of HAART - showed no marked change in the percentage of patients with a paying job, 55.7 versus 56.2 respectively. The average number of hours worked each week was 34.95 at inclusion (N=1,204) and 33.54 at the latest hospital visit (N=1,027). Less than 9 per cent of patients reduced their number of working hours by half because of HIV/AIDS, 6.6 per cent by two-thirds because of other reasons, whereas 6.3 percent increased their number of working hours by 45 per cent. HAART patients at work reported to have worked almost as efficiently (scoring 9 on a scale of 1 to 10) as they would normally have done.

5.9.4. Conclusions and recommendations

With most in-patient hospital days generated at disease onset and at the end of life[89], the decreased morbidity (CDC-B and -C events) and mortality rates after the introduction of HAART (see paragraph 5.4) resulted in the substantially lower number of 1.5 in-patient days per person-year in 1999/2000. Based on 1995 projections of patient care without the option of HAART, the number of in-patient days per person-year might well have been around 30 in 1999[90]. This difference alone comes to 8,000 euros saved per person-year in the Netherlands, which is just a little below the costs of HAART itself per person-year. Moreover, the cost savings resulting from deferred in-patient diagnostic and therapeutic procedures that would have accompanied these foregone in-patient days most likely offsets the extra costs of the assessment of HIV-1 RNA load and genotypic resistance. In addition, most patients kept working with a small loss of efficiency - even after 3 years following the start of HAART - thereby restricting the societal costs of lost production.

These observations coincide with those of other studies showing a positive effect of the introduction of HAART on non-drug health care costs, especially in terms of medical centre expenditures[85,86,91-94]. In the short term HAART may be considered a minor health economic issue despite its rising costs. With many HAART patients apparently working more owing to a prolonged survival period, overall cost savings at the societal level will probably occur[95]. With the proposed infrastructure in place for ATHENA in the years to come and the recently developed and implemented direct data retrieval procedures from hospital information systems, we recommend that data be collected discontinuously, e.g. for a half-year period every two years. This pace will probably suffice to keep track of the potential antecedents of changes with regard to the economic impact of HAART: sub-optimal therapy adherence, rising incidence of toxicity-related morbidity and mortality, etc.

Guidelines

6. Guidelines for the treatment of HIV-1 infection

In 1996/1997 guidelines for the treatment of HIV-1 infection were produced40,42 based on experiences and published results of phase III trials with combinations of new antiretroviral drugs. Therapy should be started based on one or a combination of criteria as summarised in Table 6.1 and 95% of the 2323 patients in ATHENA at that time were started on new therapy accordingly.

Guidelines 1997	Naïve patients %	Pre-treated patients %
HIV-1 RNA >104 c/ml	75	40
CD4+ T cells <500/mm3	79	78
CDC class B	19	29
CDC class C	26	43
At least one of these	95	95

Table 6.1: *percentage of patients that started HAART according to the 1996/1997 guidelines for the treatment of HIV-infection*

Triple combination therapy of two nRTI's and one PI was the most frequent starting combination. In December 2000, the new Guidelines for antiretroviral therapy in The Netherlands[44] were published. These guidelines, produced by the Dutch Association of AIDS Physicians (NVAB) were an updated version of the 1996/1997 guidelines following the introduction and registration of new antiretroviral drugs and new insights with respect to effective dosages, schedules and dietary instructions. Essentially, the criteria for the start of antiretroviral combination therapy did not change, except for the judgement of the number of $CD4^+$ T cells and the precise concentration of HIV-1 RNA in plasma. According to the new guidelines, it is now advised to start treatment with new antiretroviral drug combinations if $CD4^+$ T cell counts in asymptomatic HIV-1 infected patients are below 350 cells/mm^3, irrespective of the HIV-1 RNA concentration[7]. If $CD4^+$ T cell numbers are above 500 per mm^3, treatment is advised when HIV-1 RNA levels are >30000 copies per ml and should be considered when levels are between 5000 and 30000 copies per ml. When $CD4^+$ T cell numbers are between 350 and 500, again it is advised to start antiretroviral combination therapy depending on the concentration of HIV-1 RNA: when less than 5000 copies per ml one could consider therapy, when above 5000 copies one is advised to start therapy. In table 6.2 these new start criteria are applied to the entire ATHENA population of 3348 patients as of 1 November 2000. When applied, the new criteria would not have greatly influenced the decision to start HAARTin the ATHENA cohort. In other words, the criteria outlined in the Guidelines of December 2000 would also have meant that most of the patients participating in the ATHENA cohort started HAART accordingly. In only 1% of the cases therapy was started in conflict with the advice in the guidelines.

In a further analysis the effect of new therapy on clinical outcome of infection, the effect on HIV-1 RNA levels and the effect on $CD4^+$ T cells will be investigated. At present however, the follow-up period of the various patient groups is too short.

	Total N (%)	Naïve N (%)	Pre-treated N (%)
CDC-B	1282 (38)	438 (23)	844 (58)
CDC-C	898 (27)	286 (15)	612 (42)
CDC-A + CD4<350	1322 (40)	895 (47)	427 (30)
CDC-A + CD4 350-500 + RNA<5000	44 (1)	18 (10)	26 (2)
CDC-A + CD4 350-500 + RNA >5000	224 (7)	187 (10)	37 (3)
CDC-A + CD4 >500 + RNA <5000	34 (1)	6 (0.3)	28 (2)
CDC-A + CD4>500 + RNA 5000-30000	47 (1)	41 (2)	6 (0.4)
CDC-A + CD4>500 + RNA >30000	92 (3)	83 (4)	9 (1)

Table 6.2: *Numbers and percentages of patients at start of HAART according to the December 2000 Guidelines for antiretroviral therapy in The Netherlands.*

Conclusions, Discussion & Recommendations

7. General conclusions, discussion and recommendations

7.1. Conclusions

The ATHENA project has reached its primary goal. Collection of relevant data for the monitoring of the effect of new (i.e. since July 1996) antiretroviral treatment of large groups of HIV-1 infected patients in the Netherlands is in place. Twenty-two hospitals participate, including all Centres for HIV and AIDS appointed by the Minister of Health in 1990, except the Andreas Ziekenhuis in Amsterdam, three sub-centres and six affiliated centres. A project bureau for ATHENA is organised as part of the National AIDS Therapy Evaluation Centre (NATEC) in the Academic Medical Center of the University of Amsterdam, the reference hospital for HIV and AIDS in the Netherlands. The infrastructure built with the financial support of the Ministry of Health and the National Health Insurance Council is able to collect data at each of the sites directly, i.e. decentralised data-entry facilities are operational. As well as the hospitals, 12 medical microbiological laboratories are involved in the detection and quantification of HIV-1 RNA in peripheral blood. Four of them are acknowledged as reference laboratories and perform genotypic resistance measurements. Two of these are also able to perform phenotypic resistance measurements, although the capacity in terms of numbers is limited.

With the data collected, the ATHENA project was able to produce the following answers to the research questions defined in the grant proposal of August 1997.

What are the changes following introduction of new anti-HIV-1 treatment on the HIV-1 related morbidity and mortality?

- After the introduction of combination regimens including at least one antiretroviral drug registered since 1996, HIV-1 related morbidity and mortality declined dramatically in the patients included in the ATHENA cohort. The relative proportion of non-HIV-1 related morbidity increased and first results indicate that this changing pattern is due to the toxicity of the antiretroviral drugs used.
- No differences were observed between the various HIV-1 transmission-risk groups. This indicates that, on therapy, male homosexuals, drug users and the heterosexual population benefit equally from new antiretroviral therapy.

What are the determinants of long-lasting therapy failure?

- Therapy failure, defined as HIV-1 RNA plasma concentration above 500 copies/ml after 24 weeks of HAART, is seen more frequently in patients treated with less efficacious antiretroviral drug combinations in the period before the introduction of HAART.
- Therapy naïve patients with relatively high $CD4^+$ T cell numbers at baseline did respond better to new antiretroviral therapy in terms of HIV-1 RNA decline to below 500 copies per ml. The concentration of HIV-1 RNA in plasma at baseline was of less importance for therapy success or failure at 24 weeks.
- Other factors determining therapy outcome are antiretroviral drug concentrations reached in plasma and the (pre-) existence of resistance to antiretroviral drugs.
- HAART regimens were changed very often. In 10% of the whole treated population clinical signs and symptoms related to toxicity are seen and this percentage has so far remained constant over time, although the pattern of signs and symptoms recorded changes over time.
- The most important factors related to therapy change were therapy failure and toxicity of the regimen used. Toxicity appeared to be an increasing problem: from 21% of the patients changing regimen in 1996 to 43% by the end of 1999.

What are the changes in the quality of life and the functionality of patients treated with the new anti-HIV-1 combination therapy (discerning patients with and without symptoms of HIV-1 disease) and to what extent do patients adhere to the therapy prescribed and the medical instructions?

- Quality of life improved after initiation of new antiretroviral therapy, especially in the group of symptomatic HIV-1 infected patients. Quality of life remained stable during prolonged new combination therapy, but remained reduced compared to that of the general Dutch population.
- Only about half of all patients took all antiretroviral medication in accordance with time and dietary prescriptions. Deviations from the prescribed regimen were associated with lower drug exposure and a decreased likelihood of having suppressed plasma HIV-1 RNA. Patients who were asymptomatic at the start of antiretroviral therapy were more likely to deviate from their prescribed regimen.

What are the changes, following introduction of new anti-HIV-1 treatment, to the incidence of resistant virus strains?

- The prevalence of HIV-1 strains resistant to antiretroviral drugs in untreated patients was low (0.5% PI's and 1.7% for RTI's). This may be an underestimation for two reasons. One is the composition of the focus group that is not representative of the whole HIV-1 infected population; the other is the unknown length of time between infection and start of therapy in these naïve patients. Other studies have shown the positive influence of knowledge of genotypic resistance patterns on the choice of antiretroviral drug regimens and on the effect of antiretroviral therapy on virus levels.

Does the measurement of HIV-1 resistance to antiretroviral drugs, as well as the determination of the concentration of different drugs in the blood, contribute to the improvement of HIV-1 related morbidity and mortality?

- At baseline, 70.5% of the pre-treated patients, as measured in the focus group, showed primary resistance-associated mutations in RT and 6.8% in protease; 38.6% had multiple mutations. This has implications for the choice of the HAART regimen in this particular group.
- When therapy failure occurs after a relatively long period of antiretroviral treatment, resistance is frequently found. In 93.9% of the patients failing within the first 24 weeks of their HAART regimen resistance-associated mutations were detected. Resistance measurement at therapy failure will contribute to the choices of therapy regimens following virologic failure on the previous regimen and will help in keeping the concentration of HIV-1 as low as possible.
- The ATHENA study includes the first randomised clinical trial worldwide showing the benefit of Therapeutic Drug Monitoring (TDM) of indinavir and nelfinavir in that it improved therapy outcome in treatment-naive patients.

What are the long-term implications of introducing new anti-HIV-1 drugs to the Dutch healthcare system?

- The decreased HIV-1 related morbidity and mortality rates after the introduction of HAART resulted in 1.5 in-patient days per person-year in 1999/2000. The number of in-patient days per person-year would have been around 30 in 1999 without the use of HAART. This difference between in-patient days with and without HAART saves 8,000 euros per person-year and is just below the cost of HAART per person-year itself.
- The cost savings resulting from deferred in-patient diagnostic and therapeutic procedures that would have accompanied these foregone in-patient days most likely offsets the extra costs of the assessment of HIV-1 RNA load and genotypic resistance.

- In addition, most patients kept working with a small loss of efficiency - even after 3 years following the start of HAART - thereby restricting the societal costs of lost production.

Is structural registration of the clinical course of the treated HIV-1 infection effective in order to optimise anti-HIV-1 treatment? If so, what is an appropriate organisation for this registration?

- The information collected covers most aspects of the treatment of HIV-1 infection with new, as well as old combinations of antiretroviral drugs. It encompasses the virologic effect in terms of changes in the amount of virus in individual patients as well as in the infected population and the evolving genotype and phenotype of the virus under antiretroviral therapy both in individual patients and in the population. Immunological data are also available on an individual and population level. With the clinical data on signs and symptoms of the infection, the information collected in the ATHENA project allows us to track changes in the course of infection as a result of the treatment of patients with new antiretroviral therapy.
- Reports were produced on a yearly basis, at least one separate ATHENA meeting was organised in 1998, contributions were made to informative meetings organised by the Dutch Association of AIDS physicians (NVAB) and contributions were made to several advisory and consensus meetings, organised by the NVAB as well as the Health Council. An ATHENA website is under construction.

7.2. Discussion

A number of cautionary statements have been drawn up for a proper evaluation of the current and future validity of the answers to research questions. Some of them have to do with the design of the ATHENA study, others with trends in the HIV-1 epidemic and the available treatment options. The patients followed within the framework of the ATHENA project form an observational cohort. Serious biases can be present when comparing the outcomes from the use of antiretroviral therapy regimens in such a cohort. Patients included in the cohort may differ in terms of prognosis at the time they started new antiretroviral therapy. Therefore, conclusions comparing regimens that are based on results obtained in the ATHENA cohort, although informative, should be carefully drawn.

The ATHENA cohort has proven to be of value in observing and reporting the changes in the course of HIV-1 infection and AIDS in a treated population. In the present cohort patients that are not on antiretroviral therapy are excluded. Using historical data, as from the Amsterdam cohort studies, can only make comparisons between a treated and an untreated infection. Moreover, patients who were considered not to be eligible for participation in the study most probably are a distinct group, again biasing interpretation of the results with regard to the natural history of the treated HIV-1 infection. One of the important patient groups that is at present largely excluded is the group of foreigners unable to read and understand one of the modern languages and the group of asylum seekers not willing to sign papers for obvious reasons. Other issues that complicate interpretation are the differences in follow-up frequencies of patients and, more importantly, differences in the collection and especially storage of patient materials.

For efficiency reasons, more elaborate and costly data collection in the ATHENA project was performed in a subgroup, referred to as the 'focus group'. When projecting the results obtained from this group on the whole study population, one should take into account that due to the delayed start of the project, the focus group is not a completely representative selection.
We observed a major difference between patients who were sub-optimally treated with antiretroviral drugs before the start of new treatment and patients who were naïve with respect to antiretroviral treatment. Although this difference has been reported frequently, also in controlled randomised studies, results from the ATHENA cohort should be taken cautiously. The pre-treated group of patients had lower $CD4^+$ T cell counts at the start of new therapy, indicating that they were in a more advanced stage of HIV-1 infection than the treatment naive group. This may influence the effect of new antiretroviral treatment with respect to a decline in viral load and an increase in $CD4^+$ T cells. Nevertheless, the impact of new antiretroviral therapy on virus production and immunological status is substantial in both the naive and pre-treated group. An almost constant proportion of 80% in the naive and 50% in the pre-treated population has HIV-1 RNA levels below the quantification limit of 500 copies per ml, as measured over a period of 144 weeks. Based on $CD4^+$ T cell counts, the immune status of patients in all groups improved. In the naive population almost 90% and in the pre-treated population around 85% have $CD4^+$ T cell counts >200 cells/mm^3. The decreased amount of HIV-1 in the infected population after the introduction of HAART might result in a further reduction of HIV-1 transmission, although the clinical improvement under treatment could counteract this as it may result in higher sexual activities. Moreover, the lack of information about certain (untreated) groups within the HIV-1 infected population, referred to earlier, may have a negative impact as well. Implementing a registration of new HIV-1 infections as part of a future system may give insight into the changes in the incidence of infection.

The price for a relatively successful treatment of HIV-1 infection was and is, unfortunately, the toxicity of the drugs used. Neuropathy, loss of libido, lipodystrophy, pancreatitis, diabetes and nephrolithiasis as the most frequently recorded signs and symptoms, and although some of these are reversible, given the longevity of antiretroviral therapy it is of high importance to continue the registration of toxicity over a prolonged period of time. In addition, certain drug toxicities may result in morbidity or even mortality changes. Moreover, the diminished tolerance for antiretroviral drugs will in the end lead to a lesser degree of adherence to the drug regimen and subsequently to limited suppression of virus replication. In turn, this may change the course of the infection again, including the selection and subsequently the transmission of resistant virus strains.

Irrespective of toxicity, we have found that only about half of the patients in the focus group took all antiretroviral medication in accordance with time and dietary prescriptions. Indeed, deviation from the prescribed regimen appeared to be associated with lower drug exposure and lesser therapy effect. Adherence to time and prescriptions of antiretroviral drug regimens in relation to toxicity has still to be studied. However, it is to be expected that a substantial proportion of patients treated with antiretroviral drug combinations do not reach drug levels sufficient to block virus replication. In the focus group of the ATHENA cohort we found that therapy outcome could be improved in this respect by therapeutic drug monitoring, i.e. the regular measurement of drug concentrations in blood. This, together with monitoring the intake of drugs and the monitoring of adverse events and toxicity, may be of high importance in the containment of the development and spread of resistance.

At present, resistance of HIV-1 to antiretroviral drugs at the start of new therapy is mainly a problem in the patients who were sub-optimally treated before they started with HAART. Less resistance-associated mutations were found at baseline in the naïve group. This may indicate a limited spread of resistant HIV-1 in the recent history. However, as the exact stage of infection in the naïve ATHENA population is largely unknown, it is uncertain if this is really the case. After transmission, the predominantly resistant population may revert to a so-called wild type population in a patient not treated with antiviral drugs. So, the question about transmission of resistance strains, although possible,

remains unanswered and only registration of relatively recent infections will give us a clue. Nevertheless, an indication of the size of the problem can be derived from the difference between naïve and pre-treated patients with respect to genotypic resistance at the moment of failure. In the focus group, naive patients show very limited genotypic resistance to antiretroviral drugs when the therapy used fails, whereas pre-treated patients show a high prevalence of resistance. This may indicate that the transmission of resistant HIV-1 and therefore pre-existing resistance to drugs is still a limited problem.

As a spin-off from the genotypic determination of resistance-associated mutations in RT and protease, we were able to determine the HIV-1 subtype of a subgroup of patients in the focus group. As expected from the composition of the focus group, most of the patients are infected with a B subtype of HIV-1. However, almost 10% of the focus group population sequenced appears to be infected with a non-B subtype. C and E are the most prevalent non-B subtypes found. Re-analysing RT and protease sequences produced in relation to the determination of resistance, together with sub-typing of new HIV-1 cases, will give the opportunity to achieve more insight into the changes in the epidemiology of the infection.

Although the situation of the individual patient has improved with the introduction of HAART, HIV-1 infection and the treatment of it is far from stable. The effect of the current treatment is less than 100%. In other words there is no eradication of HIV-1. Adherence to the antiretroviral drugs is difficult and consequently, drug levels may be too low. Ongoing replication under antiretroviral therapy will inevitably lead to resistance. The long-term effect on the course of the infection of ongoing low-level replication of (resistant) HIV-1 is still unknown.
In addition to those already available, new drugs will be introduced and will add to the possibilities of containment of HIV-1 replication, but most probably also to the already extensive drug toxicity problems. Toxicity caused by antiretroviral chemotherapy will change the course of infection and will have an impact on morbidity and mortality in the treated groups.
The less than 100% effectiveness of the drugs used will also result in ongoing transmission of HIV-1, although for at least some time at a lower level. Together with the HIV-1 infected individuals entering from endemic areas, this may add to the number of infected patients in the Netherlands.

7.3. Recommendations for permanent registration of the clinical course and of the therapy of the infection with HIV-1

Medical, social and personal perspectives of HIV-1 infected patients in The Netherlands have been substantially improved following the introduction of HAART in mid 1996. Nevertheless, HIV/AIDS remains a significant issue with respect to individual health, health care and public health. The HIV/AIDS situation has not stabilised. It is clear that in spite of HAART, replication of HIV-1 continues. This ongoing replication, together with limited adherence to the drug regimens increases the risk of resistance. Toxicity of the chemotherapy used is an increasing problem that will have an impact on individual health and health care. The ATHENA data confirm the shift of the infection towards other risk groups besides that of men having sex with men, and show the introduction of non-B HIV-1 variants.
The 'natural history' and the course of the HIV-1 infection and HIV-1 related disease will change. The initial changes have been recorded through the ATHENA project. Both patients and treating physicians have benefited from ATHENA, in that it has improved knowledge of the effect of treatment and the determinants of success and failure. This has traded off against the effort of data collection. Further development of ATHENA towards an open system that provides information about the epidemiology of HIV, the antiretroviral treatment of HIV and the effect of treatment on the course of HIV infection is highly recommended.

Independent post-marketing surveillance will then be feasible, which is of importance especially when drugs are introduced into the market after a relative short period of clinical trial evaluation, as is the case with antiretroviral drugs.

With this general recommendation in mind, a number of issues discussed in chapters 4 and 5 could be solved, without changing the observational nature of the cohort structure.
Firstly, it is highly recommended that all HIV-1 and HIV-2 infected individuals be included. By also considering non-treatment as a clinical decision, this group of patients can be followed in the same way as the treated population. Subsequently, every patient should be registered, without judging the ability of a patient to participate in sub-studies. If, after transforming the ATHENA project into a registration project for HIV and the treatment of HIV, an informed consent is still necessary, then every effort has to be made to produce informed consent forms in a range of languages. Finally, new HIV-1 (and HIV-2) infections should be registered. Nowadays, the majority of new HIV-1 infections will be diagnosed or confirmed in the outpatient clinic of one of the 22 HIV/AIDS hospitals. Knowledge of the prevalence and incidence of new infections is of importance for the epidemiology of HIV and a collaborative proposal with the RIVM and the GG&GD-Amsterdam for registration is in progress.

Another recommendation is to protocolise the follow-up scheme of patients, as well as the collection of patient materials. From the cost effectiveness study in ATHENA it appeared that the average follow-up frequency is 4,9 per year. Registration at a regular interval of once per three months of a set of key data, as well as collection and storage of patient materials, should therefore be feasible without too big a burden on the budget for HIV/AIDS care. However, it should be recognised that the storage of patient materials needs special financial attention.

It is recommended to include the genotypic determination of resistance of HIV to antiretroviral drugs and the therapeutic monitoring of antiretroviral drugs (TDM) in the care of HIV-infected patients. Genotypic resistance measurement at the start of (new) antiretroviral therapy is recommended for two reasons. It would improve the effectiveness of the (new) regimen and it would provide information on the prevalence of drug resistant HIV strains, which is of public health importance. Genotypically determined results on HIV resistance should be accompanied by a phenotypic interpretation. This will be feasible when easier and quicker methods for the determination of the sensitivity of HIV from a patient for antiretroviral drugs become available. Results of TDM and of resistance measurements should be part of the monitoring of HIV.

In summary, we recommend the ATHENA project to be reorganised. This should result in a registration of HIV and AIDS, together with an HIV/AIDS treatment registration, as part of the HIV/AIDS care. It should provide physicians, hospitals and health care institutes, as well as health insurance institutes and the government with information on the usage and effect of antiretroviral therapy (including toxicity), the introduction of new drugs and drug regimens, and the (long-term) development of HIV-1 and AIDS in a treated population. It should also provide essential information on the prevalence and incidence of new infections and the course of infection in untreated groups, as well as the introduction and spread of various sub-types of HIV-1 in the country and the development and spread of resistant HIV-1 strains.

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Stichting HIV Monitoring

Addendum
Stichting HIV Monitoring

(december 2000)

Frank de Wolf, Joep Lange & Paul Drosten

Inleiding

AIDS en HIV zijn 15 jaar na de eerste diagnose en de ontdekking van het virus inmiddels vaste elementen geworden in de zorg. De HIV en AIDS epidemie is een enorm probleem in met name Afrikaanse landen ten zuiden van de Sahara en in Zuidoost Azië. In West-Europa lijkt de epidemie zich enigszins te stabiliseren. Tot en met 1999 zijn naar schatting tussen de 410.000 en 620.000 personen met HIV geïnfecteerd. In 1999 overleden er tussen de 5300 en 7900 mensen (Bron: UNAIDS, juni 2000). Cumulatief zijn in Nederland tot eind 1999 naar schatting 13.000 volwassenen en kinderen geïnfecteerd met HIV. De schatting van het aantal AIDS diagnoses tot en met 1999 is 6100 en het aantal sterfgevallen 3900, waarvan 200 in 1999 (Bron: RIVM). Het aantal HIV-geïnfecteerden op dit moment ligt vermoedelijk tussen de 5000 en 7000. HIV geïnfecteerden worden in Nederland sinds 1987 behandeld met antiretrovirale middelen. Eerst vooral in trial-verband, later ook als onderdeel van de reguliere zorg. Sinds medio 1996 geldt dat HIV-geïnfecteerden standaard kunnen worden behandeld met een combinatie van antiretrovirale middelen met een verschillend werkingsspectrum. Meestal bestaat het behandelregiem uit een combinatie van twee HIV-RT remmers en één of twee HIV-protease remmer(s).

Met de huidige antiretrovirale middelen kan de HIV-infectie niet tot stilstand worden gebracht (1-14). Er blijft ook bij zeer krachtige anti-HIV therapie sprake van voortgaande vermenigvuldiging van HIV, zij het op een laag tot zeer laag niveau. Die replicatie kan ook weer worden 'aangezet', indien er voldoende prikkeling is van met HIV geïnfecteerde cellen in het lichaam en/of de behandeling met anti-HIV middelen wordt gestopt of minder effectief wordt. Dat laatste kan gebeuren, omdat voortgaande vermenigvuldiging ondanks behandeling met anti-HIV middelen kan leiden tot het resistent worden van HIV tegen die middelen. Bovendien ontstaat zo ook kruis-resistentie tegen anti-HIV middelen uit dezelfde klasse. De huidige antiretrovirale therapie leidt dus in het beste geval tot het in meer of minder sterke mate vertragen van de infectie met HIV.

De HIV gerelateerde morbiditeit is gedaald als gevolg van de behandeling met een combinatie van anti-HIV middelen met een verschillend werkingsspectrum. Cijfers afkomstig uit de monitoring van de behandeling van HIV (het ATHENA project) laten zien dat de incidentie van CDC-B events daalt van 0.25 per persoonsjaar follow-up in het laatste half jaar van 1996 tot 0.04 in 1999. Voor CDC-C events zijn deze cijfers 0.27 in 1996 en 0.04 in 1999. De HIV-gerelateerde mortaliteit daalde van 0.07 in 1996 tot 0.03 in 1999 (Third Interim Report ATHENA Project, June 2000). Echter, het is nog niet duidelijk wat op langere termijn het effect zal zijn en hoe de vertraagde, maar wel voortgaande vermenigvuldiging van HIV de morbiditeit en mortaliteit zullen beïnvloeden. Uitkomsten van mathematische modellering laten zien dat, afhankelijk van de mate van het gebruik van antivirale middelen in de geïnfecteerde populatie, de mortaliteit over een periode van 10 jaar zal dalen(15). Effectiviteit van de gebruikte antiretrovirale therapie en veranderingen in risicogedrag kunnen echter het effect op de HIV-gerelateerde mortaliteit sterk beïnvloeden. De samenstelling van de antiretrovirale combinatie is, door toegenomen ervaring, nieuwe inzichten en ontwikkelingen veranderd. In de periode medio 1996 – eind 1999 bestond de initiële behandeling van 67-68% van de HIV-geïnfecteerden uit een combinatie van 2 nucleoside RT-remmers en 1 protease remmer. Wanneer in dezelfde groep wordt gekeken naar de laatste behandeling, dan blijkt dat tussen de 40 en 50% bestaat uit 2 nucleoside RT-remmers en 1 protease remmer. In de rest van de populatie blijkt behandeling dan te bestaan uit 2 nucleoside RT-remmers plus 2 protease remmers of 2 nucleoside RT remmers plus 1 protease remmer en 1 non-nucleoside RT remmer (Third Interim Report ATHENA project, June 2000).

Belangrijk probleem bij de behandeling met antiretrovirale middelen is het optreden van bijwerkingen. Eén van de bevindingen uit de monitoring van de behandeling van HIV is dat de initiële anti-HIV behandeling van 32 tot 40% van de patiënten wordt gewijzigd om redenen van bijwerkingen (Third Interim Report ATHENA project, June 2000). Ook na de eerste verandering zijn daarop volgende therapiewijzigingen vaak nodig door bijwerkingen, naast het virologisch falen van de behandeling. Complicaties die zich voordoen en die leiden tot wijziging van de behandeling zijn vrij ernstig: veranderende leverfunctie (lever enzym stijging), gastro-intestinale, hematologische en neurologische aandoeningen komen veel voor.

Frequente therapiewijziging door toxiciteit, samen met het punt dat de kans op virologisch succes afneemt naar de mate waarin behandeling vaker wordt gewijzigd (de eerste klap is een daalder waard) en dat slechts de helft van de patiënten alle relevante instructies volgt bij het slikken van de anti-HIV middelen, is aanleiding voor zorg over het ontstaan van een aanmerkelijk resistentieprobleem. Resistentie in Nederland wordt op dit moment vooral gevonden in de groep geïnfecteerden die (ineffectief) werden behandeld in de periode vòòr medio 1996. Virologisch falen wordt het meest gezien in deze groep en resistentie tegen RT remmers komt voor bij 67,5% en tegen protease remmers bij 22,5% op het moment dat deze groep start met een combinatie therapie van 2 RT remmers en een protease remmer (Third Interim Report ATHENA project, June 2000).

Conclusie is, dat de anti-retrovirale combinatie behandeling van HIV-geïnfecteerden gecompliceerd is en bovendien onderhevig is aan snelle veranderingen als gevolg van nieuwe ontwikkelingen en inzichten. De in 1998 door de Gezondheidsraad geadviseerde concentratie van gespecialiseerde zorg vanuit daartoe aangewezen behandelcentra blijft dan ook nodig. Bovendien is het uiterst wenselijk om de effecten van behandeling in de populatie van HIV-geïnfecteerde personen en personen at risk voor de infectie met HIV te blijven monitoren en de gegevens die daaruit voortkomen in te zetten voor verbetering van richtlijnen, tijdige signalering van (nieuwe) complicaties van behandeling, snelle ontwikkeling en introductie van nieuwe behandelstrategieën en advisering aan behandelaars. Daartoe zou de in het ATHENA project opgebouwde infrastructuur, aangevuld met de advies en expertfunctie en samen met de in NATEC gerealiseerde infrastructuur integraal, maar herkenbaar onderdeel moeten zijn in de bekostiging van de centrumziekenhuizen voor HIV en AIDS. Hiervoor zijn inmiddels namens NATEC en door het AMC samen met de twee andere grote Amsterdamse HIV/AIDS centra, het OLVG Amsterdam en het Slotervaart Ziekenhuis Amsterdam, en met ZAO-zorgverzekeringen en ZN/KPZ -regio Amsterdam voorstellen gedaan aan de Minister van Volksgezondheid, Welzijn en Sport. Als vervolg daarop volgt hieronder een globale beschrijving van een door het AMC op te richten Stichting HIV Monitoring, waarbinnen organisatorisch vorm wordt gegeven aan de bestaande samenwerking tussen de HIV/AIDS centra en subcentra op het gebied van de nationale trials (NATEC) en de nationale monitoring van (de behandeling van) HIV (ATHENA).

Waarom een stichting?

De keuze voor een stichting als organisatievorm is gebaseerd op een aantal overwegingen. Allereerst is er de duidelijke wens vanuit de deelnemende behandelaars om het nationale en multi-center karakter van NATEC en daarmee de 'toegang' tot nieuwe antiretrovirale middelen, alsmede van ATHENA voor de monitoring van HIV steviger in de HIV/AIDS zorg te verankeren. De inmiddels sinds jaren opgebouwde - goed functionerende - samenwerking met behandelaars en laboratorium specialisten uit de verschillende HIV/AIDS centra wordt zo verder verstevigd. Een aantal functies die in NATEC voor de uitvoering van trials en voor de monitoring van HIV zijn ontwikkeld kunnen dan zo worden ondergebracht dat:

- gegevens kunnen worden gebruikt in een niet gebonden, open expert system, nodig voor professionele consen-

susvorming over diagnostiek en behandeling van HIV.
- gegevens beschikbaar zijn voor advisering van en aan overheid, instellingen en patiënten en voor wetenschappelijk onderzoek.
- er garanties zijn voor de privacy van gegevens.

Een tweede overweging is dat de huidige gegevensverzameling en de huidige infrastructuur van zowel NATEC als ATHENA betaald is door de overheid. Tenslotte geeft de recente ontwikkeling van het onderbrengen van de HIV/AIDS zorg onder de Wet Bijzondere Medische Verrichtingen (WBMV) aanleiding om voor nationale deelname aan trials, monitoring van behandeling en kwaliteitsborging van de zorg te kiezen voor de stichting als organisatievorm, vergelijkbaar met de integrale kanker centra.

Doel van de Stichting HIV Monitoring

Doel van de stichting is bij te dragen aan de ontwikkeling van kennis over de diagnostiek en de behandeling van HIV.
De stichting doet dat door een landelijk netwerk te coördineren waarin
- Geanonimiseerde gegevens van HIV-geïnfecteerde patiënten en hun antiretrovirale behandeling worden verzameld en beheerd
- Gegevens worden bewerkt ten behoeve van onderzoek en advisering aan overheid en andere instanties
- Gegevens via een expert system beschikbaar worden gesteld aan behandelaars van HIV-geïnfecteerden
- Gegevens beschikbaar worden gesteld voor wetenschappelijk onderzoek en consensus vorming.

Deze kernactiviteiten van de stichting sluiten aan bij die van NATEC en die van het ATHENA project zijnde het verzamelen, bewerken en beschikbaar stellen van geanonimiseerde gegevens over HIV-geïnfecteerde personen en hun behandeling, al dan niet in trialverband.

Organisatie van de Stichting HIV Monitoring

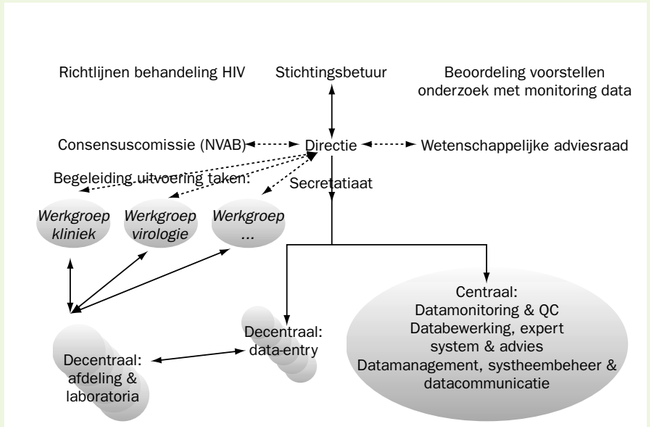
Functies
De activiteiten van de stichting worden ondersteund door decentrale en centrale functies.
Decentrale functies zijn: de daadwerkelijke verzameling van patiënt gegevens, de invoer van gegevens in databestanden, de opbouw en het onderhoud van een decentrale database plus uitvoering en onderhoud van de routines voor transport van gegevens naar de centrale monitoring database. Onderscheiden worden de verzameling en verwerking van gegevens in verband met trials (NATEC) en die in verband met monitoring van het klinisch cohort (ATHENA).

Er zijn globaal vier centrale functies. Allereerst is er de kwaliteitsbewaking en monitoring van data die in de centrale database worden ingevoerd. Dan is er het onderhoud en datamanagement van de centrale database en het data warehouse, plus de datacommunicatie en het beheer van het systeem. Vervolgens is er de (voor-) bewerking van gegevens bestanden voor het gebruik van gegevens en tenslotte is er de bewerking van gegevens in relatie tot de advies-, onderzoek-, consensus-, en expertfunctie. Ook voor de centrale functie geldt het onderscheid tussen trials (NATEC) en monitoring van het klinisch cohort (ATHENA).
Het onderscheiden van de functies in die voor trials en die voor het monitoren van het klinisch cohort heeft vooral te maken met de wijze waarop gegevens van patiënten worden verzameld. Deze is voor trials naar hun aard anders dan voor monitoring van een cohort. Het onderscheid zal er dan ook vooral zijn op enerzijds het niveau van decentrale verzameling, data entry en databasing en anderzijds op het niveau van centrale data-analyse voorbereiding en de analyse zelf. Met andere woorden bij de uitvoering van die functies die vooral worden gestuurd door de aard van de studie. Functies, die voor de uitvoering van trials en monitoring van het klinisch cohort overlappen zijn onder meer de centrale data kwaliteitsbewaking, het datamanagement, het systeembeheer en de datacommunicatie.

Bestuur, Directie, Wetenschappelijke Adviesraad en Consensuscommissie

Bestuur

Er wordt uitgegaan van een situatie, waarbij de monitoring van HIV integraal onderdeel is van de WBMV bekostigingssystematiek van de zorg. De activiteiten van de stichting HIV Monitoring zouden dan gefinancierd moeten worden via de centrumziekenhuizen voor HIV en AIDS. In die situatie dient het bestuur van de stichting in ieder geval te bestaan uit een vertegenwoordiging namens de directies van die centrumziekenhuizen. Afhankelijk van het antwoord op de vraag of de infrastructuur van de stichting mede wordt gebruikt in verband met de registratie van HIV en de HIV-gerelateerde morbiditeit en mortaliteit kan tevens een vertegenwoordiging namens de GGD'en of het RIVM in het bestuur worden opgenomen. Voorts wordt voorzien in een vertegenwoordiger namens de AIDS behandelaren, alsmede een vertegenwoordiger namens de patiënten. De vertegenwoordiger namens de AIDS behandelaren wordt voorgedragen door de Nederlandse Vereniging van AIDS Behandelaren (NVAB); de patiënt vertegenwoordiger door de Nederlandse HIV Vereniging. Het bestuur van de stichting benoemt de directie en stelt jaarlijks de begroting en de jaarrekening van de stichting vast.



Directie

De directie van de stichting is belast met de organisatie van en de dagelijkse leiding over de decentrale en centrale activiteiten, alsmede het secretariaat van de stichting. De directie legt verantwoording af aan het bestuur van de stichting.

De wetenschappelijke adviesraad

De wetenschappelijke adviesraad van de stichting is een inhoudsdeskundige commissie met als taak bestuur en directie van de stichting te adviseren over het gebruik van gegevens voor onderzoek op basis van onderzoeksaanvragen. De raad kan tevens adviseren omtrent de privacy bescherming van gegevens. De raad wordt samengesteld uit personen die zich gekwalificeerd hebben op het gebied van de behandeling van HIV en AIDS, het onderzoek naar HIV en AIDS, alsmede de beleidsvorming op het terrein van HIV en AIDS. In de raad heeft tevens een vertegenwoordiging namens de patiëntenvereniging zitting.

De consensuscommissie

Er is een consensuscommissie, samengesteld door de Nederlandse Vereniging van AIDS behandelaren. In de consensuscommissie is eveneens een vertegenwoordiging namens de patiëntenvereniging opgenomen. Deze commissie heeft als taak bestuur en directie van de stichting te adviseren over met name de expertfunctie.

Werkgroepen van de stichting

Analoog aan de huidige organisatie van ATHENA wordt de uitvoering van de inhoudelijke taken van de stichting begeleid vanuit werkgroepen. Vooralsnog wordt voor de Stichting HIV Monitoring voorzien in twee werkgroepen.

Werkgroep Kliniek

In het ATHENA project wordt de uitvoering en afstemming van monitoring van het beloop van de behandeling van HIV met behandelaren afgestemd in de ATHENA werkgroep kliniek. Met de Nederlandse Vereniging van AIDS Behandelaren (NVAB) zal worden overlegd hoe in de Stichting HIV Monitoring de taken op het gebied van coördinatie en afstemming zullen worden gecontinueerd. Daarbij zal tevens aan de orde komen of separaat, dan wel als onderdeel van de werkgroep kliniek, een structuur moet worden gerealiseerd voor de monitoring van met name de farmacologie van de behandeling van HIV en voor de monitoring van bijwerkingen bij de behandeling van HIV.

Werkgroep Virologie

Met name in verband met de uitvoering van taken op het gebied van het bepalen van resistentie tegen antiretrovirale middelen, maar eveneens voor taken die betrekking hebben op protocollaire laboratoriumdiagnostiek en laboratorium follow-up van behandeling, alsmede taken op het terrein van de kwaliteitsbewaking is het de bedoeling de huidige ATHENA werkgroep virologie om te vormen tot de werkgroep virologie van de Stichting HIV Monitoring. Over de precieze invulling daarvan zal advies worden gevraagd aan de werkgroep klinische virologie van de Nederlandse Vereniging voor Medische Microbiologie.

De organisatie van de stichting kan worden weergegeven in onderstaand schema.

De kosten van de Stichting HIV Monitoring

De kosten voor de hierboven aangegeven functies van de Stichting HIV Monitoring (NATEC en ATHENA samen) zijn voorlopig begroot op in totaal 3 mln gulden per jaar (prijspeil 2000). Een en ander is weergegeven in het overzicht kosten Stichting HIV Monitoring. Het gegevensnetwerk, inclusief de decentrale ondersteuning van data-entry, de medewerkers en hard en software om het systeem te laten functioneren en de kwaliteit en privacy van de data te bewaken is begroot op ca 1.7 mln per jaar. De advies- en onderzoekfunctie en het expert system is begroot op in totaal ca 0.5 mln en secretariaat, coördinatie en directie zijn begroot op in totaal ca 0.8 mln per jaar.

Personeel en financieel beheer van de Stichting HIV Monitoring

In de afgelopen 30 maanden is voor het ATHENA project een infrastructuur opgebouwd die in staat is een deel van de kernactiviteiten van de stichting te realiseren. Geheel conform de OG-subsidietoewijzing voor ATHENA is deze infrastructuur onderdeel van het Nationaal AIDS Therapie Evaluatie Centrum (NATEC). NATEC bestaat inmiddels al geruime tijd en draagt zorg voor een landelijke coördinatie en evaluatie van therapietrials met nieuwe combinaties van anti-retrovirale middelen. Voor die taken heeft NATEC een ondersteunende functie en logistiek die aansluit bij die voor de monitoring van HIV en de behandeling van HIV. NATEC wordt rechtstreeks gesubsidieerd door het ministerie van Volksgezondheid, Welzijn en Sport. Zowel de OG subsidie voor ATHENA als de VWS subsidie voor NATEC zijn toegewezen aan het AMC in Amsterdam en administratief ondergebracht bij de AMC BV 'International Antiviral Therapy Evaluation Center (IATEC)'. De financiële en personele administratie van de Stichting HIV Monitoring kan hierop aansluitend eveneens worden ondergebracht bij IATEC.

Implementatie stappen

Stap	Deadline
Juridische voorbereiding statuten van de Stichting HIV Monitoring	November 2000 - Februari 2001
Besluitvorming RvB AMC + uitnodigen personen bestuur stichting	Januari-Februari 2001
Oprichting Stichting	Maart 2001
Benoeming Stichtingsbestuur	Maart 2001
Benoeming directie (1e keer door RvB AMC)	Maart 2001
Implementatie administratie en beheer stichting	April-Mei 2001
Onderbrengen functies en start activiteiten	September 2001
Juridische voorbereiding statuten van de Stichting HIV Monitoring	November 2000 - Februari 2001
Besluitvorming RvB AMC + uitnodigen personen bestuur stichting	Januari-Februari 2001
Oprichting Stichting	Maart 2001
Benoeming Stichtingsbestuur	Maart 2001
Benoeming directie (1e keer door RvB AMC)	Maart 2001
Implementatie administratie en beheer stichting	April-Mei 2001
Onderbrengen functies en start activiteiten	September 2001

Voorlopige schatting kosten Stichting HIV Monitoring

ITEM	FTE/JAAR		PL FL/JAAR		OL ITEM/ JAAR(FL)	N ITEMS /JAAR (FL)	OL JAAR (FL)	TOTAAL OL+PL/JAAR (FL)		OPMERKINGEN
	VAST	VAR	VAST	VAR	VAST	VAST	VAST	VAST	VAR	
DATA NETWERK										
decentraal										
overige lasten										
hardware compu's					1000	12.50	12500			n data-entry medewerkers x 3.000, afschr. 3 jaar
Software					1000	12.50	12500			data entry en retrieval software
Onderhoud					1000	12.50	12500			onderhoudscontract software
Personeel										
data-entry en administratie	12.50	2.50	812500	162500						data-entry/administr;1 uur/ dossier; 5000 pats
centraal										
overige lasten										
Server					10000	1.00	10000			30.000, afschrijving in 3 jaar
Software					10000	1.00	10000			datacommunicatie software
Software					10000	1.00	10000			database/data warehouse software
Onderhoud					10000	1.00	10000			onderhoudscontract software
hardware compu's					1000	4.00	4000			computers dataman. Etc. x 3.000, afschr. 3 jaar
Software					1000	7.50	7500			
Onderhoud					1000	4.00	4000			
hardware compu's					2000	4.00	8000			copmu's dataman/systeembeh/programmeur
automated retrieval software					3000	2.00	6000			te ontwikkelen software voor vraag-beantwoording
Personeel										
data-entry en administratie	0.50		32500							
data manager	2.00		240000							
systeem beheer	1.00		120000							
data monitoring	3.00		225000							
programmeur	1.00		120000							programmeren en programma-ondersteuning
subtotaal data netwerk	**19.00**	**2.50**	**1430000**	**162500**			**107000**	**1537000**	**162500**	
EXPERT SYSTEM										
centraal										
overige lasten										
hardware compu's					2000	4.00	8000			computers 2xfl6,000.00; afschr. 3 jaar
analitical software					1000	4.00	4000			analystische software
statistical software					1000	4.00	4000			
statistische software										
Rapportage					10000	4.00	40000			tenminste 2 rapporten per jaar + publicaties
Personeel										
klinisch epidemioloog	1.00		120000							analyse en statistiek
Biostatistiek	1.00		120000							analyse en statistiek
scenario analyse en modellering	1.00		120000							analyse, modelleren en scenario's
sociaal economisch onderzoek	0.50		60000							analyse, kosten-effectiviteitsbewaking
subtotaal expert system	**3.50**		**420000**				**56000**	**476000**		
COORDINATIE & BUREAU										
centraal										
overige lasten										
hardware compu's					1000	6.00	6000			computers 4xfl 3,000.00, afschr. 3 jaar
Software					1000	6.00	6000			software tbv bureau
post, telefoon etc etc					30000		30000			
Secretariaatskosten commissies & advies					20000		20000			
Reiskosten					75000		75000			bijdrage in de reiskosten Nederland en buitenland
Personeel										
Secretariaat medewerker	2.00		140000							
Coordinerend onderzoeksverpleegkundige	1.00		70000							
Coordinatie data-verzameling en monitoring	0.50		35000							
Coordinatie verzameling patient materiaal	0.50		35000							
leiding & algemene coordinatie	2.00		400000							
subtotaal coordinatie en bureau	6.00		680000				137000	817000		
TOTAAL GENERAAL	**28.50**	**2.50**	**2530000**	**162500**			**300000**	**2830000**	**162500**	

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STICHTING HIV MONITORING

Colophon

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