REPORT 2004

MONITORING OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN THE NETHERLANDS

STICHTING HIV MONITORING

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on behalf of
the Netherlands
collaborative
HIV treatment
centres

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Participating hospitals

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Ziekenhuis Rijnstate Arnhem

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Introduction

Frank de Wolf

The HIV Monitoring Foundation was appointed in 2001 by the Dutch Minister of Health. As the executive organisation for the registration and monitoring of HIV infected patients in follow-up in the Dutch Treatment Centres, its mission is to study the natural history and the effects of treatment of HIV and to further the knowledge and understanding of the epidemiology as well as the course of the treated and untreated HIV infection.

In this report, data will be presented on the changes in the HIV infected population in the Netherlands after the introduction of HAART approximately 9 years ago. Following a comprehensive description of the methods of data collection and quality control and an overview of the characteristics of the study population at baseline, an attempt will be made in this report to answer questions regarding

- the changes over time of the prevalence of newly diagnosed HIV-infections per year;
- the effect of transient viraemia on the outcome of treatment and the incidence of resistance among patients failing on HAART;
- the possible differences between outcomes of initial HAART regimes and a description of the efficacy of second-line regimens;
- the various HAART outcome patterns, including results of HAART interruption;
- frequently registered adverse events and
- the changes in the HIV-related morbidity and mortality.

In addition to the regular HMF registration and research programme, a number of separate research projects using ATHENA-HMF data have started since 2001. An overview of these projects will be presented in this report as well.

Studies using observational data obtained from prospectively followed patients do contribute to the knowledge of the (long-term) efficacy of HAART regimens, the changes in outcome patterns and in morbidity and mortality. However, interpretation of findings from those studies is not always straightforward, as serious biases can be present[1]. To overcome the inherent difficulties with observational data, relatively large numbers of patients need to be included. In addition, it is of importance to systematically define items to be collected and structure the data collection process as clear as possible.

The HMF participates in a number of international collaborations in order to share knowledge and to merge data from the ATHENA cohort with other observational cohorts. The AntiReTroviral (ART) cohort collaboration and the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) collaboration are of vital importance, especially with respect to the analysis of clinical data merged from a large numbers of cohorts. The longstanding collaboration between the HMF and the Department of Infectious Disease Epidemiology (DIDE) at Imperial College in London has resulted in a number of joint studies combining three large datasets for analysis. Together, the HMF and DIDE invest in new research methodology and the development of mathematical and analytical models to be applied to observational data.

Such collaborative studies established, for instance, prognostic factors for clinical outcome of HAART: CD4 cell count and high levels of HIV replication at baseline, older age, a history of AIDS and infection through intravenous drug use but also the initial response to HAART[2] were found to be associated with increased rates of clinical progression[3]. Differences in the residual reproductive capacity of virus (R(0)) in the average patient in a treatment group and, therefore, between different regimens could be estimated by fitting a mathematical model of the interaction among CD4+ T cells, HIV-1, and antiretroviral drugs to the viral load decline following initiation of combination therapy[4].

Efficacy of different initial HAART regimens was studied and survival and progression to AIDS after starting HAART was examined, showing an advantage of treatment in an early phase of the infection[5]. The DAD study revealed that use of the NNRTI and PI drug classes (alone and especially in combination), particularly among older subjects with normalised CD4 cell counts and suppressed HIV replication, was associated with a lipid profile known to increase the risk of coronary heart disease[6].

The work of the HMF essentially depends on the collaboration between AIDS treating physicians in the HIV Treatment Centres throughout the country and the staff specifically appointed to permanently collect the data on site and add these data to the national database. The quality of the data is subsequently controlled for by the data monitors. The HMF analysis unit is essential in the execution of HMF's registration and research programme and its support of scientific research groups that have approval to use data from the ATHENA-HMF dataset. HMF working groups and its Advisory Board meet regularly, advising the HMF governing board and director on policy matters as well as on the usage of the data collected.

As of August 1, 2004, the total number of HIV infected patients included in the monitoring is 9732. Their number is still increasing although at a somewhat slower pace. HIV infected children and an increasing number of pregnant women are now also included in the monitoring. Almost 80 percent of all patients are treated with HAART. With this high precentage of the monitored population on HAART, specific attention is needed to the collection of data regarding adverse events and toxicity (including laboratory data). Moreover, in order to discern between HIV-related, non-related and treatment related morbidity and mortality, event registration, especially of the reason of death require ongoing attention. A specific programme for improvement of such event registrations will be developed in the near future.

Summary

Frank de Wolf

Study population

The HIV Monitoring Foundation (HMF) is one of the very few organisations in the world that represent an observational clinical cohort that is truly nation wide, with 22 participating HIV Treatment Centres that form an efficient framework for applied clinical research not only able to collect substantial amounts of relevant data and maintain a large observational clinical cohort, but also to produce relevant scientific output.

At present, the HMF is monitoring 9732 HIV infected patients in the Netherlands, with a total follow-up of 60769 person years. A majority of these patients are treated with HAART. Since 2003, the total number of HIV infected patients registered and monitored through data collection in the HIV Treatment Centres increased by 1236. Our figures for 2004 indicate a further increase of HIV in the Netherlands, albeit at a somewhat slower pace.

The fraction of patients in the HIV infected Dutch population who were infected through heterosexual contact is still increasing. A significant proportion of these newly diagnosed patients originates from sub-Saharan Africa and, to a lesser extent, from Latin America and the Caribbean. Despite these changes in the population, homosexual men still form the largest HIV infected group. Our data suggests that homosexual men are diagnosed sooner after infection and are infected at older ages than heterosexuals.

Women and children with HIV

After a 10-year period of steady increase, the annual proportion of newly diagnosed women with an HIV infection in the Netherlands appears to be stabilising. At the same time, the number of pregnancies among HIV infected women is increasing.

While currently available antiretroviral medication can in most cases prevent mother-to-child infection, in about 8% of the pregnant women with an HIV infection, resistance associated mutations have been found.

Efficacy of HAART

Faster declines in viral load were found in patients commencing HAART treatment with a combination of AZT+3TC+NVP and AZT+3TC+EFV than in patients commencing with a PI based initial regimen. Except for AZT+3TC+NFV, HAART regimens did not differ with respect to the duration of maintaining virological suppression. No significant differences in the initial CD4 increase were observed between regimens.

Discontinuous HAART

The level of virological suppression and immunological improvement after continuous HAART was better than after discontinuous HAART. A larger increase in CD4 cell counts was found in patients who were on HAART continuously than in patients who were treated discontinuously. We found no differences in mortality between the continuously or discontinuously HAART treated groups.

Temporal interruption of HAART was a common phenomenon among patients who initiated therapy without prior anti-retroviral treatment. The most frequently stated reasons for such interruptions were drug-related toxicity and the patient's personal wish, which suggests that strict dosing protocols and treatment side effects are still major obstacles to long-term adherence.

Therapy interruption was associated with a lower level of therapy success and a greater likelihood of an adverse therapy outcome. The proportion of patients with a continuously low viral load was smaller in the group who interrupted HAART and there was less increase of CD4 cells among patients who had interrupted HAART. We also found that interruptions were associated with an increased risk of a new AIDS diagnosis and a greater hazard of death.

These effects remained apparent even after reinitiating HAART: patients who had interrupted therapy still had an increased hazard for an adverse outcome when compared to patients who had been on HAART continuously.

Second line HAART

Virological outcome was better or comparable with those starting in 1996-1997: the majority of patients on second-line HAART reached plasma viral load levels ≤500 copies/ml within 6 months. Toxicity was the major reason for discontinuation of the initial HAART regime.

The d4T+3TC+NVP regimen was more frequently stopped due to adverse events than other first line regimens. The proportion of patients failing due to toxicity was higher in patients starting in the early years of HAART, which is probably due to the more toxic drug combinations used in those years.

Viral blips

We did not find substantial differences in the clinical course of the infection between patients with sustained viral load suppression and patients who experienced occasional low-level transient viraemia. We did however observe a similar increase in the absolute and relative number of CD4 cells over the first three years of HAART therapy, a similar rate of virological failure and a comparable hazard of new AIDS diagnoses.

Rates of viral blips within our cohort of patients treated with HAART varied strongly, depending on the definitions used. In this study, we found no evidence of an inferior prognosis among patients who had viral blips during treatment as compared to patients who maintained a viral load below 50 copies/ml within three years after start of HAART. More long-term data are needed to confirm these findings.

Morbidity and mortality

The annual decline in the incidence of AIDS in the HAART-treated population that has been observed since 1996 is still observed in 2003 and 2004. After mortality in the HAART-treated population dropped between 1996 and 2002 there seems to be a rise in mortality thereafter. While the underlying cause of this rise remains unclear, it can partly be explained by the increase in expected mortality reflecting the increasing age of the pre-treated HIV infected population.

Mortality was modestly higher in HAART treated patients with CD4 counts above 600×10^6 cells/l than in the age and gender matched general population. However, only a minority of the study population had CD4 counts at 24 weeks above 600×10^6 cells/l. Although mortality rates in successfully treated HIV infected patients and especially younger patients were still higher than in the general population, excess mortality amongst successfully treated HIV infected patients is comparable to those observed in patients with a chronic disease such as diabetes mellitus.

Excess mortality in HAART treated patients relative to the general population is independent of age. It should be noted, however, that the majority of the patients in this study was younger than 45 years of age at 24 weeks after starting HAART.

Resistance

Since the registration of the protease inhibitors saquinavir, ritonavir and indinavir in 1996, new and less

toxic antiretroviral drug classes have been introduced. As a result, the incidence of adverse events has declined. The reverse side is that a higher percentage of patients failing in later years turned out to be resistant to at least two drug classes. Resistance to antiretroviral drugs was found in 75% of patients who failed after being treated with HAART continuously for a longer period.

Transmission of drug-resistant HIV-1 virus strains was observed in 6.5% of the recently infected patients who were diagnosed after 1996. Similar percentages were found amongst newly diagnosed patients. There was no evidence that the frequency of resistant transmissions was changing over time after 1996. The percentage of transmissions of resistant virus differed between risk groups and was higher in homosexual men than in the heterosexual population.

Samenvatting

Frank de Wolf

De Stichting HIV Monitoring (SHM) is een van de weinige organisaties ter wereld die een nationaal observationeel klinisch HIV-cohort vertegenwoordigen. Samen met de 22 deelnemende HIV Behandelcentra vormt zij een efficiënte infrastructuur voor toegepast klinisch onderzoek dat niet alleen in staat is, een substantiële hoeveelheid klinische data te verzamelen en een grootschalig observationeel klinisch cohort te onderhouden, maar ook relevante wetenschappelijke publicaties te produceren.

Momenteel zijn van 9732 patiënten met een HIV-infectie in Nederland gegevens opgenomen in de SHM-registratie, met een totale follow-up van 60769 persoonsjaren. De meerderheid van deze patiënten wordt behandeld met HAART. Sinds 2003 is het totale aantal patiënten dat in de HIV Behandelcentra wordt gevolgd met 1236 toegenomen. De verdere toename van het aantal geregistreerde HIV-infecties in Nederland volstrekt zich in een iets langzamer tempo dan in de voorgaande jaren.

Het aantal patiënten in de met HIV geïnfecteerde populatie in Nederland dat door heteroseksueel contact werd besmet neemt nog steeds toe. Een beduidend aantal van deze nieuw gediagnosticeerde patiënten is afkomstig uit sub-Sahara Afrika en, in mindere mate, uit Latijns Amerika en het Caribisch gebied. Ondanks deze veranderingen in de populatie vormen homoseksuele mannen nog steeds de grootste met HIV geïnfecteerde groep. Onze data wijzen er op dat de diagnose bij homoseksuele mannen na infectie sneller dan voorheen wordt gesteld en dat zij op hogere leeftijd worden geïnfecteerd dan via heteroseksueel contact geïnfecteerde personen.

Vrouwen en kinderen met HIV

Na een periode van gestadige toename gedurende de laatste 10 jaar lijkt het jaarlijkse percentage nieuw gediagnosticeerde vrouwen met een HIV-infectie in Nederland zich te stabiliseren. Het aantal zwangerschappen onder vrouwen met een HIV-infectie neemt toe.

Verticale transmissie kan door de momenteel beschikbare antiretrovirale behandeling in de meeste gevallen worden voorkomen. Resistentie wordt bij 8% van de zwangere vrouwen met een HIV-infectie gevonden.

Effectiviteit van HAART

De hoeveelheid virusdeeltjes daalde sneller in patiënten die startten met een AZT+3TC+NVP of AZT+3TC+EFV combinatie dan in patiënten die startten met een op een proteaseremmer gebaseerde combinatie. Met uitzondering van de combinatie AZT+3TC+NFV werden er in de vergelijking van verschillende HAART regimes geen significante verschillen gevonden in de duur van onderdrukking van de productie van het virus. Er werden ook geen significante verschillen gevonden in de initiële stijging van CD4 cellen bij verschillende Highly Active Antiretroviral Therapy (HAART) combinaties.

Interruptie van HAART

Het percentage patiënten met een goede onderdrukking van de virusvermenigvuldiging was hoger in patiënten die 3 jaar lang aaneengesloten met HAART werden behandeld in vergelijking met patiënten die HAART (tijdelijk) onderbraken. De toename in CD4 cellen was groter in patiënten die zonder onderbreking met HAART werden behandeld. Er waren geen significante verschillen in mortaliteit tussen de groepen patiënten die ononderbroken met HAART werden behandeld gebruikten en diegenen die HAART onderbraken.

In de groep patiënten die HAART begonnen zonder ooit eerder met antiretrovirale middelen te zijn behandeld

kwamen tijdelijke onderbrekingen van HAART veelvuldig voor. De toxiciteit van de middelen en de persoonlijke wens van de patiënt waren de meest voorkomende redenen om HAART te stoppen. Dit zou kunnen betekenen dat therapietrouw op de lange termijn nog steeds wordt bemoeilijkt door strenge doseringsvoorschriften en bijwerkingen van de middelen.

Interrupties van HAART werden geassocieerd met suboptimale onderdrukking van virusproductie en aantal CD4 cellen en een grotere kans op een ongunstige uitkomst van de behandeling. Het percentage patiënten met een continu lage virusconcentratie in het bloed was geringer in de groep waarin HAART tijdelijk werd onderbroken en de toename in CD4 cellen was minder groot dan in de groep waarin geen interrupties voorkwamen. Bovendien werden interrupties van HAART geassocieerd met een groter risico op een hernieuwde AIDS diagnose en een hoger risico op overlijden.

Deze verschillen bleven ook aanwezig nadat HAART opnieuw werd gestart. Patiënten die HAART onderbraken hadden, nadat ze weer met de therapie waren begonnen, nog steeds een grotere kans op een ongunstig therapieverloop dan patiënten die wèl continu met HAART werden behandeld.

Tweedelijns HAART

De meeste patiënten die na het afbreken van het eerste HAART-regime vanwege virologsich falen met een tweede combinatie begonnen bereikten binnen 6 maanden een virusconcentratie in plasma ≤500 kopieën/ml. Toxiciteit was de belangrijkste reden om het eerstelijns HAART regime te stoppen.

De combinatie d4t+3TC+NVP werd vaker gestopt vanwege bijwerkingen dan andere recenter voorgeschreven eerstelijns HAART combinaties. Het percentage patiënten dat door bijwerkingen faalde was groter in de groep die in 1996-1997 op HAART startte, waarschijnlijk ten gevolge van de relatief hoge toxiciteit van de HAART combinaties die in die tijd werden voorgeschreven.

Virale blips

Wij vonden geen significante verschillen in het klinische beloop van de infectie tussen patiënten met een continu lage virusconcentratie en patiënten met een tijdelijke geringe stijging van de virusconcentratie in het bloed ('blip'). De stijging van het absolute en relatieve aantal CD4 cellen gedurende de eerste drie jaar na start van HAART, het percentage virologische falers na drie jaar en het risico van een nieuwe AIDS diagnose bleken vergelijkbaar.

Morbiditeit en mortaliteit

De sinds 1996 waargenomen jaarlijkse afname van de incidentie van AIDS in de met HAART behandelde populatie zette zich ook in 2003 en in 2004 voort. Na een aanvankelijke daling van de mortaliteit in de met HAART behandelde populatie tussen 1996 en 2002 lijkt deze nu weer licht aan te stijgen. De oorzaak hiervan is nog onduidelijk, maar kan gedeeltelijk worden verklaard door de stijging van de verwachte mortaliteit door de hogere leeftijd van de voorbehandelde HIV-geïnfecteerde populatie.

De mortaliteit onder met HAART behandelde patiënten met CD4 aantallen boven $600x10^6$ cellen/l bleek slechts iets hoger dan in de qua leeftijd en geslacht vergelijkbare niet-geïnfecteerde populatie. Slechts een minderheid van de patiënten bereikte echter al na 24 weken CD4 aantallen boven $600x10^6$ cellen/l. Hoewel de mortaliteitsratio in met succes behandelde met HIV geïnfecteerde patiënten nog steeds iets hoger

lag dan in de niet-geïnfecteerde populatie bleek deze vergelijkbaar met de mortaliteit onder patiënten met een chronische ziekte zoals diabetes mellitus.

Resistentie

Sinds de registratie van de proteaseremmers saquinavir, ritonavir and indinavir in 1996 zijn nieuwe, mogelijk minder giftige antivirale middelen geïntroduceerd. De incidentie van bijwerkingen met nadelige gevolgen voor de patiënt daalde. De keerzijde is echter dat patiënten langer met hetzelfde HAART-regime werden behandeld en een hoger percentage in een latere fase van de therapie faalde. Resistentie tegen antiretrovirale middelen kon worden aangetoond in 75% van de patiënten die faalden na langere tijd ononderbroken met HAART te zijn behandeld.

Transmissie van resistente HIV-1 virusstammen kon worden vastgesteld in 6.5% van de patiënten met een recente HIV-infectie die na 1996 waren gediagnosticeerd. Vergelijkbare percentages werden gevonden in patiënten met een recente HIV-diagnose. Wij vonden geen indicatie dat de transmissiefrequentie van resistent HIV sinds 1996 is veranderd. Procentueel varieerde de transmissie van resistent virus per risicogroep. Dit percentage bleek hoger te zijn in homoseksuele mannen dan in de heteroseksuele populatie.

Data quality

Improving the quality of HIV monitoring data

Sima Zaheri

Introduction

With the increase of the number of included patients and, consequently, a steady increase in data, preserving and improving the quality of the data collected and stored in the HIV Monitoring Foundation database is an ongoing concern. Analysis of the observational data in order to answer questions regarding morbidity and mortality of treated and non-treated HIV infections, tolerability and efficacy of drug regimens, their possible toxicity and the occurrence of resistance requires the most efficient collection and storage of the data along with a well-balanced quality control structure. To achieve and maintain high data quality, their validity and reliability has to be maximised[7,8].

Data collection

Patient data (see appendix) are collected in 24 hospitals that are part of 22 specifically appointed HIV Treatment Centres by the Dutch Minister of Health. Data are stored in a database developed in Oracle Clinical® (OC) which was specifically designed for the data management of clinical trials and complies with GCP and FDA guidelines. Its security is of outstanding quality as it consolidates the management of all remote users and enhances the security of the network. OC provides highly sophisticated tracking and data crosschecking options and discrepancy checks for a quick resolution of queries, along with the possibility to export data to analysis software packages such as SAS[9].

Data quality

Key to accurate data collection is simplification of data abstraction methods and avoidance of data interpretation or assumption[7,8]. Efforts made in order to improve data validity are summarised as follows:

- Use of categorical variables instead of free-text variables in the database[7]. Every category contains a refined pick list, which is updated on a regular basis;
- a refined registration of negative information, which distinguishes between 'not performed', 'unknown whether or not it was performed' and 'has been performed, but the date or value is unknown';
- data entry checks: both single-item checks and complex queries for consistency checks are programmed into the database;
- an on-line available co-medication list, including generic and trade names of every medication required for data collection. The list is alphabetically sorted and contains quick codes for data entry in Oracle Clinical database. Since new medications are continuously being introduced, the list is updated on a regular basis;
- an ARV medication list, which is available on-line and has the same alphabetic structure as the co-medication list. Additionally, this list contains standardised and alternative prescription dosages;
- an on-line list of all HIV related clinical trails in the Netherlands, containing start and stop dates and other available information about the trails;
- an on-line Microsoft Access database, which contains reports, graphics and overviews of collected data in each HIV Treatment Centre. The use of reports and overviews simplifies the logistics of data collection in each centre. This Access database also enables query generation for simple on-the-spot data analysis;
- regular and customised training of data collectors by data monitors;
- a training program for data collectors, data monitors and physicians for learning how to perform simple analysis on their own dataset;
- an option for scheduling regional investigator meetings. Such meetings enable data collectors, data monitors, physicians and other parties involved to discuss data abstraction difficulties that may arise and to develop tools to further improve the data abstraction methods;
- an option for uploading laboratory results directly from local laboratory data systems into the central database as an alternative for manual entry. This approach is currently under construction and will be implemented at the end of 2004 in the largest participating centre (AMC).

Monitoring of data quality: results

Data monitors of the HIV Monitoring Foundation compare the data added to the national database against the source document, i.e. the patient's medical file. Possible discrepancies between source documents and data in the database are clarified and, if needed, instantly corrected. At present, quality control procedures are restricted to the follow-up data of a random selection of 10% of the patients and to the retrospectively collected data of a random selection of 10% of the newly admitted patients per year. A data monitor visits each HIV Treatment Centre at least twice a year, depending on the number of patients monitored.

Data monitors can identify missing data and data entry errors and review and resolve discrepancies on-line. So far, a total number of 206 discrepancies, which could not be resolved by the data collectors, were forwarded to the data monitors to be resolved. Data monitors report the results of their source data verification in descriptive terms in monitoring reports. These results suggest that a significant proportion of data collection errors are made during collection of data regarding co-medication and adverse events. Furthermore, data collection seems to be more accurate in those centres where a single data collector is responsible for the data collection. A major problem in data collection of events is that these data are often recorded in a patient's medical file in an inconsistent and ambiguous manner. Therefore, continuous monitoring and subsequent customised training are imperative to protect data quality.

In addition to source data verification, other markers are being used to monitor data quality. All data changes, discrepancies and their corresponding reasons are registered in the database. Analysis of these registered data illustrates the pattern of data entry errors and, consequently, is indicative of data quality. From May 2003 until the time of writing, 224.963 data points were entered into the OC database. 162.102 Discrepancies were raised, of which 160.102 were resolved, 286 were forwarded to the right party (data monitor, data manager or physician) and 1284 are pending for review. Figure 4.1 gives an overview of the percentage of each type of discrepancy per category and figure 4.2 illustrates the proportion of discrepancies in each category as a factor of the total number of discrepancies.

Discussion

The overall error rate of data collected in the OC database is 2,24% (0-5,52%) and relatively low. This may lead to two conclusions: either it suggests that the data collection is proceeding on a satisfactory level or that the number of checks in the OC database should be extended. In order to consolidate the presented results, an extension of the number of checks should give rise to similar error rates.

However, these results are limited to data in the OC database and the programmed checks at data entry level. In order to achieve optimal data quality, the results of source data verification by data monitors should be taken into account. These source data verification results contain additional information about the Microsoft Access database that was previously used. To analyse these results, they should be quantified and incorporated into the OC database. The feasibility of this approach is currently being investigated.

Descriptive results of data monitoring by source data verification confirm the complexity of data collecting directly from the patient's medical file. The variability of data documentation in the medical file[7,8,8] inevitably leads to data interpretation and sheer assumption. To avoid these pitfalls, a more refined data collecting protocol is required. Such a protocol should contain specific guidelines to standardise documentation of diagnosis and data extraction from medical files[10-13]. We are currently working on a more refined protocol for CDC and adverse events.

Appendix: data

Upon entry into the HIV Monitoring Foundation database, the following information is collected:

Items collected upon initial enrolment for HIV infected adults		
Demographic data	Date of birth, gender, first and second nationality, country of birth, height	
History of HIV infection	Date of the last negative HIV-1 and HIV-2 test Date of the first positive HIV-1 and HIV-2 test Risk of infection with non-B HIV-1 subtype	
HIV transmission	The most likely transmission route: homosexual heterosexual IDU blood and blood products during pregnancy/partus via breastfeeding other and unknown	For sexual transmission, the most likely transmission route is entered: either a steady sexual partner or multiple sexual contacts Country where the patient became infected
Additional data for HIV infected children		
Demographic data	Nationality and country of birth of patient's parents	
Family data	HIV status of patient's mother, father, brothers and sisters	
Antenatal data	Pregnancy duration, way of birth, weight at birth, Apgar scores, cogenital defects, antenatal exposure to ARV therapy and co-medication, antenatal complications	

Table 4.1: Items collected upon initial enrolment for HIV infected adults and children.

After enrolment, clinical data are collected on a continuous basis every time the patient is seen by his or her treating physician. These data contain the following information:

Items collected at every follow up visit for HIV infected adults		
Clinical examination	Weight, blood pressure	
CDC events Start and stop date and the status of event at current visit (ongoing: yes or no).	HIV related events according to CDC classification. Definition of diagnosis (possible, presumptive or definitive) are recorded using standard protocol	
Adverse events Start and stop date and the status of event at current visit (ongoing: yes or no).	Every event that results in a change of antiretroviral treatment is collected. In addition, the following events are always recorded:	
	Peripheral neuropathy	Sexual dysfunction (loss of libido, erection failure)
	Myopathy	Alcohol or drug abuse
	Lactate acidosis	Non-CDC malignancies
	Hepatic cirrhosis	Diabetes mellitus
	Osteopenia / Osteoporosis	Myocardial infarction
	Hepatic steathosis	Hypertension
	Hepatic encephalopathy	Arrhythmia
	Pancreatitis	Stroke
	Nephrolithiasis	Coronary artery by-pass grafting
	Renal failure	Coronary angioplasty / stenting
	Lipodystrophy, fat loss of extremities	Carotic endarterectomy
	Lipodystrophy, central fat accumulation	Pregnancy
	Rash	Hospital admission
Antiretroviral therapy Start and stop date, dosage and units, route of admission,reason for stop and the status of medication at current visit (ongoing: yes or no)	The list of standard stop reasons is as follows:	
	Virological failure	Modification of the regimen
	Immunological failure	Drug levels related
	Patient's decision	Structured treatment interruption
	Toxicity	Newly available medication
	New CDC-B and or CDC-C events	Other
	Interaction with co-medication	Unknown
Co-medication Start and stop date and the medication status at current visit (ongoing: yes or no)	CDC events prophylaxis	Anti-diabetic agents
	CDC events treatment	Insulin and its derivatives
	Anti-epileptic agents	Anabolic steroids and appetite stimulants
	Anti-coagulant agents	Hepatitis B treatment
	Platelet aggregation inhibitors	Hepatitis C treatment
	Anti-hypertensive agents	Medication that interacts with antiretroviral therapy
	Anti-arrhythmic agents	Miscellaneous: megestrol acetate, dranabinol and methadone
	Lipid lowering agents	

Table 4.2: Items collected at every follow up visit for HIV infected adults.

Items collected at every follow up visit for HIV infected adults	
Lab results	**Lab results HIV virology: RNA**
	Value (copies/ml), laboratory, sample date, VL assay type, sample material, cut-off and undetectable: yes or no
	Immunology
	Value, units, laboratory and sample date for the following determinates:
	CD4 count, CD8 count, CD4 percentage,
	CD8 percentage, CD4/CD8 ratio
	Chemistry
	Value, units, sample date and laboratory for the following determinates:
	Glucose >N*
	Amylase >250 mmol/l
	ALAT/SGPT>3 x N*
	ASAT/SGOT>3 x N*
	Alkaline phosphates>3 x N*
	Gamma GT >3 x N*
	Lactate>N*
	Triglycerides always collected
	Cholesterol always collected
	Cholesterol HDL always collected
	*: N is normal value; this value can vary for different laboratories.
	Haematology
	Value, units, sample date and laboratory for the following determinates:
	Haemoglobin <5.5 mmol/l
	Leukocytes <2.0 10e9/l
	Thrombocytes <75 10e9/l
	Other viral infections
	Value (positive or negative), laboratory, sample date for the following determinates:
	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV-DNA,
	HCV-Ab, HCV-RNA, CMV-IgG, CMV-IgM
Patient's participation in clinical trials	Trial name, start and stop date

Table 4.2: Items collected at every follow up visit for HIV infected adults.

Additional data for HIV infected children	
Clinical examination	Skull circumference, puberty stage
Adverse events	Pathologic and traumatic fractures, abnormalities of psychological development, abnormalities of motorial development, abnormalities of puberty development
Additional treatment	Psychologist, pedagogue, psychiatrist, speech therapist, physiotherapist, rehabilitation, social worker
Start and stop date, status at current visit	
Care and education	Care by: Mother, father, parents, family, foster family, care institute, other and unknown
	Education: Nursery school, playgroup, primary school, secondary school (VMBO, HVO, VWO), other and unknown
Vaccinations - Date	DKTP1, DKTP2, DKTP3, DKTP4, HIB1, HIB2, HIB3, HIB4, BMR, BCG, PNCV, influenza, meningitis C, pneumovax, other
Lab results	**HIV virology: DNA**
	Value (positive or negative), laboratory, sample date for the following determinates:
	HIV-1 DNA, HIV-2 DNA, HIV-1 antibodies, HIV-2 antibodies
	Chemistry:
	The following determinates are always collected: Glucose, Amylase, ALAT/SGPT,ASAT/SGOT, Alkaline phosphates, Gamma GT, Lactate, Triglycerides, Cholesterol, Cholesterol, HBA1c
	Haematology:
	The following determinates are always collected: Haemoglobin, Leukocytes, Thrombocytes, MCV

Table 4.3: Additional data for HIV infected children.

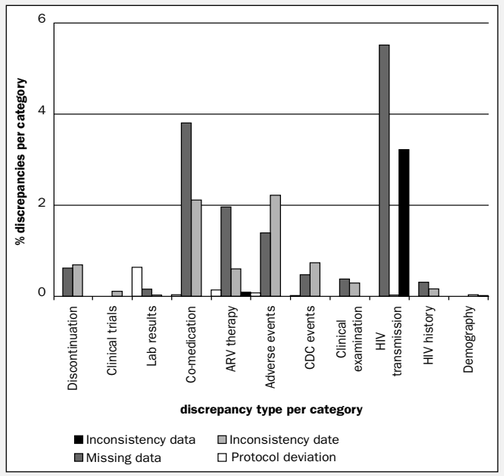


Figure 4.1: Discrepancies= total number of discrepancies in each category /total number of data points collected in each category X 100.

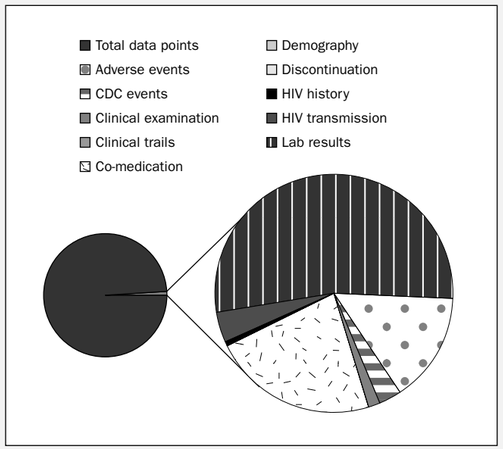


Figure 4.2: Left circle: proportion of all discrepancies on the total number of data points entered into the OC database, right circle: discrepancy proportion of each category.

Study population

Baseline characteristics of the population included in the ATHENA national observational cohort

Frank de Wolf

Introduction

More than 1230 HIV infected patients have been included additionally since publication of our scientific report 2003[9] in December 2003. In the present scientific report 2004, we show data and analyses with regard to demographic changes of the population registered through the HMF monitoring system, the differences in the virological, immunological and clinical effects of various frequently used combinations of antiretroviral drugs, several important issues on treatment strategies, as well as the occurrence of resistance and changes in resistance patterns.

Entry of HIV infected patients in the ATHENA national observational cohort is unrestricted and patients are registered and monitored by default as part of the clinical care provided. Patients can opt out, e.g. object to inclusion of information about the course of their infection into the registration and monitoring system, of course without any consequences for care and treatment. Data obtained from patients are stored anonymously in the firmly secured national ATHENA database in order to safeguard the privacy of patients. The data collection procedure and the database are described more extensively in chapter 4 and in the scientific report 2003.[9]

The importance of the baseline characteristics for predicting the clinical outcome in both the untreated or treated infection was described previously.[14-23] Prognosis is strongly correlated with CD4 cell count and HIV RNA plasma level at baseline as with older age, a history of AIDS and transmission through intravenous drug use (IDU). In this chapter, the characteristics at baseline of the patients registered are described with the aim to provide a comprehensive overview of the composition of the HIV infected population.

Inclusion, median follow-up and geographic distribution of patients

Data were available as of the 1st of August 2004, the date of the merger and freeze of database. The total number included in the population used for the present 2004 scientific report encompassed 9732 patients with a total follow-up of 60769 person years.

Of the study population used for the present report, 7474 (77%) were men and 2172 (22%) women. In addition, 86 (1%) patients were younger than 13 year at the time of HIV diagnosis. The median follow-up of the study population was 5.4 (IQR 2.3–9.3) years, 5.8 (2.6-9.7) years for men and 4.0 (1.7-8.0) for women. The median time between visits was 91 days; follow-up frequency increased when patients participated in a clinical trial. Demographic characteristics influencing follow-up frequency were gender with a time between visits being 1.08 (95% C.I. 1.03-1.13) times longer for men, and route of transmission with a time between visits for IDUs being 1.11 (1.03-1.19) times longer than for homosexual men. Follow-up frequency was not significantly different with respect to region of origin or age. Lower CD4 cell count and a higher plasma viral load were associated with shorter and asymptomatic HIV with longer between visit times. A more recent calendar year of registration and of visit independently resulted in a lower follow-up frequency. In newly registered patients, the median time between visits was 0.57 times shorter in 1999 than in 2003. Finally, there were differences between individual HIV Treatment Centres.

The geographic distribution of the study population in the Netherlands is summarised in Table 5.1, showing that the West of the country, i.e. Amsterdam and the densely populated Western provinces North Holland, South Holland and Utrecht were still the most affected.

HIV diagnosis

Prevalence of the HIV-1, HIV-2 and the HIV-1/HIV-2 double infection are summarised in Table 5.2. The large majority of 94.7% of the patients was tested HIV-1 antibody positive while only a small percentage of the population (0.5%) was tested HIV-2 positive. Antibody reactivity to both HIV-1 and HIV-2 was found in 1.39% of the patients. Infection with HIV is usually diagnosed using an anti HIV-1/HIV-2 antibody combined with a HIV-1 p24 antigen assay[24] followed by Western Blot confirmation of either an antibody response specific for HIV-1, HIV-2 or both. When considering HIV RNA results as well, part of the HIV diagnostic data available remained inconclusive. From 10 patients diagnosed as HIV-1 but not HIV-2 antibody positive, HIV-2 RNA results were registered as positive and in only 5 of the HIV-1 and HIV-2 antibody positive patients, HIV-2 RNA was found. Twenty-five of the HIV-2 antibody positive diagnoses could be confirmed by detection of HIV-2 RNA. For the present report, the analyses were performed only in the HIV-1 infected patient population.

Trends in baselines over time

The absolute number per year of HIV diagnoses is depicted in figure 5.1. From 151 patients the date of HIV-1 diagnosis was missing. 935 Patients were diagnosed before 1990. A steady increase of new HIV diagnoses was seen between 1990 and 2002, starting with 267 new diagnoses in 1990 up to 954 in 2002, reflecting in part the intake procedure of the cohort, but also the course of the HIV epidemic. From 2002 on the number of new HIV diagnoses entering the cohort seems to stabilise. The relative distribution of HIV infected men and women per year of diagnosis changed from 85% men and 15% women in 1990 to 70% men and 30% women in the year 2000 and remained stable since.

Age at the time of HIV diagnosis did not change substantially over time. For the whole group of 9251 HIV infected individuals, 15% were found in the age group 0-25 year, 42% were diagnosed when between 26 and 35 years of age, 28% were between 36 and 45 and 15% more than 45 years old. Women were median 30 years (IQR 24.9–36.0) at diagnosis and therefore significantly ($p<0.0001$) younger than men who were median 35.8 (30.3-42.9) years.

HIV RNA was measured at diagnosis in 4802 (50%) patients. In only 205 (4.3%) patients levels below either 500 or 50 copies/ml were found, depending on the lower quantification limit of the assay used. The median HIV RNA plasma level at diagnosis remained stable around 4.8 log HIV RNA copies/ml plasma per year of diagnosis. Levels measured in women were median 4.4 log copies/ml (IQR 3.5–5.0) and significantly ($p<0.0001$) lower as compared to men, with levels of 5.0 log copies/ml (4.3-5.3).

When taking the whole group at diagnosis, the median CD4 cell number was 280 (IQR 100–490) cells/mm^3, for women 298 (126-500) and men 280 (100-488) cells /mm^3. Median CD4 T cell count at HIV diagnosis did improve over time from 238 cells/mm^3 in 1996 to 305 cells/mm^3 in 2004 ($p=0{,}004$). In male heterosexually infected patients, the CD4 cell count at diagnoses was median 194 cells/mm^3 (60-380), significantly ($p<0.0001$) lower than in male homosexual patients with counts at diagnosis of 320 (120-510) cells/mm^3.

HIV infected children

The registration of children - patients below 13 years of age at diagnosis - in the ATHENA national observational cohort started by the end of 2003; collection of monitoring data subsequently started late in 2004. At present 86 children are registered, 46 boys and 40 girls. Year of diagnosis, transmission route, age at diagnosis and the median HIV RNA level and CD4 cell count at diagnosis are summarised in table 5.3.

The collection of data of the children is far from complete as might be clear from the incomplete data on birth date and year of HIV diagnosis. Main route of transmission of HIV is from mother to child. All children registered as being infected through sexual contact were girls.

Pregnant women

Among 534 of the women diagnosed with HIV, a number of 667 pregnancies was registered. HIV was diagnosed in 510 (96%) women before or maximum 9 months after pregnancy was diagnosed. In the remaining 24 (4%) women, HIV was diagnosed more than 9 months after the date pregnancy was first registered. Women were 27 (IQR 23–31) years of age at HIV diagnosis and had a median HIV RNA level of 3.9 (3.2-4.7) log copies/ml and CD4 cell count of 340 (200-520) cells/mm^3. In 220 (41%) women, HAART was initiated before, in 140 (26%) during and in 129 (24%) after pregnancy. In 89 women (13%), the duration of pregnancy was less than 26 weeks. Transmission of HIV in this group was predominantly (93%) heterosexual. Sixty percent of the women were from sub-Sahara African and only 16% of Dutch origin.

HIV-2

In total 49 patients were infected with HIV-2, 26 men and 23 women. Over time since 1996, the number of patients diagnosed per year ranged between 2 and 9 per year. In total, there were 268 person years of follow-up. Median age at diagnosis was 40.8 (IQR 35.8–50.0) years, with no significant differences between men and women. A substantial fraction of HIV-2 infected patients were of other than Dutch origin: 32 from sub-Saharan African countries versus 13 patients from the Netherlands. Median CD4 cell count measured at HIV-2 diagnosis was 164 (60-445) cells/mm^3 and HIV-2 load, when detectable, median 4.5 (4.1-5.0) log RNA copies/ml. Ten patients were classified as CDC-C and five as CDC-B at HIV-2 diagnosis.

Antiretroviral treatment

Antiretroviral treatment of HIV infected patients began in 1987/1988, first in clinical trials and subsequently as a regular part of patient care.[25,26] From the mid 1980s until 1996, a growing number of patients were treated with mono or dual antiretroviral combination therapy. A large fraction of this so-called therapy experienced or pre-treated patients changed their therapy regimen to HAART combinations in 1996-1998.

In the ATHENA observational cohort, 79.6% of the adult patients were registered to date as being treated with HAART; 56.7% without and 22.9% with pre-HAART antiretroviral drug experience. A small fraction of 1.5% was still using antiretroviral drug combinations that did not fit the definition of HAART, e.g. did not use a combination of at least three antiretroviral drugs from two different drug classes or a combination of three nucleoside reverse transcriptase inhibitors, including tenofovir and abacavir. The remaining 18.9% of the patients were not treated with any antiretroviral drug.

Between 1996 and 2004, the number of patients starting HAART without prior experience with antiretroviral treatment rapidly increased (Figure 5.2). Pre-treated patients also frequently switched to HAART between 1996 and 1999. A relatively constant number of patients started treatment with non-HAART regimens over time since 1990. Finally, non-treated patients were largely diagnosed from 2000 on, corresponding with the start of the registration of these patients.

Finally, as can been seen from table 5.4, there were differences between the four treatment groups with regards to the characteristics at diagnosis, start of non-HAART and start of HAART, indicating that both the group of non-treated patients and the patient group still on ART were clinically well. Compared to CD4 cell numbers and RNA levels found at diagnosis among the HAART and non-HAART treated patients, non treated patients had high CD4 cell numbers at diagnosis and low HIV RNA levels.

As per the 31st of July 2003, 40.2% of the 6455 HAART treated patients had AZT+3TC as backbone. D4T+3TC was given as backbone of the HAART regimen in 7.2% of the patients, while TDF+3TC in 9.3%. The HAART regimens most frequently administered are summarised in table 5.5. Nevirapine was added to various backbones of the HAART regimens given to 26.4% of the treated patients.

Co-infections

Since the introduction of HAART there has been a significant reduction in HIV-related mortality and morbidity in the Netherlands[27]. Consequently, morbidity and mortality from other infections may become apparent. For example, hepatitis C (HCV) is a major cause of death in HIV infected patients[28,29]. Although HCV co-infection is associated with an increased mortality, this association disappears in some studies when adjusting for other covariates[30-32]. No significant influence of HCV co-infection in virological or immunological responses to antiretroviral treatment were found[28,33-36].

Co-infection with cytomegalovirus (CMV) is associated with a more rapid disease progression[37-39]. Conversely, the rise in CD4 cells in CMV-negative patients after initiation of HAART is more rapid than in CMV-positive patients although eventually CD4 counts reach similar levels[40].

In 9270 HIV-1 positive patients, CMV-positive and CMV-negative patients were distinguished by the presence or absence of anti-CMV IgG antibodies as were HCV-positive and HCV-negative patients based on anti-HCV antibodies. For 5943 (61.1%) patients the CMV status could be determined and 5261 (88.5%), were CMV-positive. 162 (68.4%) out of 237 male intravenous drug users patients were CMV positive ($p<0.001$), but for female intravenous drug users no difference was observed with the average population. The prevalence of CMV was 46 (70.8%) out of 65 patients amongst male patients infected with HIV through blood or blood contact.

The HCV status was known for 7131 (73.4%) patients. In this population, 780 (10.9%) were HCV-positive. HCV prevalence was highest amongst intravenous drug users, 388 (92.6%) out of 419 patients ($p<0.001$), and did not differ between male and female drug users. In the population infected through heterosexual contact, the HCV prevalence was 5.4% and was the same for men and women. Prevalence was higher ($p<0.001$) than amongst homosexual men where only 112 (2.9%) of 3836 patients were HCV-positive. HCV was more prevalent amongst men infected through blood-blood contact, 38/84 (45.2%), and amongst men and women from whom the infection route was unknown; 77/454 (17.0%) for men and 43/79 (54.4%) for women, respectively.

Discussion

Since 2003, the total number of HIV infected patients registered and monitored through data collection in 22 HIV Treatment Centres increased by 1236 to a total of 9732 patients. These patients have a follow-up of more than 60000 person years with a median follow-up period of 5.4 years. Median between visit time was approximately 3 months.

In the 2003 report[9] we discussed the increasing trend in numbers of registered HIV infected patients and the increase in the number of newly diagnosed HIV infections. Preliminary figures for 2004 again show a further increase, although at a somewhat slower pace. This might reflect a slowly diminishing reservoir of HIV infected patients awaiting registration. At the same time, the National Institute for Public Health and

the Environment reported a slow-down of the number of sexually transmitted disease as well (Fact sheet June 2004, RIVM, Bilthoven, The Netherlands), indicating that the strong increase seen in 2002 and 2003 might be temporary. New HIV infections might follow this trend, which could explain partly the lower increase in 2004 of newly diagnosed HIV infections. Finally, the expected increase in import of HIV into the Netherlands based on the 2002/2003 figures does not seem to materialise, which might also contribute to the reduced increase of new infections found.

The number of HIV infected women seems to be stabilising as well. As found for 2002/2003 after a period of steady increase since 1993, the fraction of women amongst the registered HIV infected patients is 30%. On average, women are still six years younger than men at HIV diagnosis. The number of pregnancies among HIV infected women is increasing. Apparently, the effect of HAART and the reduced risk of transmission of HIV from mother to child due to antiretroviral treatment encourage women to become pregnant, which, together with the increasing number of HIV positive pregnant women from HIV endemic areas could have contributed to the increase found.

A majority of almost 80% of the patients registered are treated with HAART. Only very few are on an antiretroviral drug regimen that cannot be classified as being HAART while 18.5% of the patients are not treated with antiretroviral agents at all. The majority of untreated patients were diagnosed with HIV during or after 2000. Together with the relative high CD4 cell numbers and low HIV RNA plasma concentrations, this indicates that these patients have only recently become infected and are therefore not eligible for HAART according to current treatment guidelines[41].

In concordance with findings by others[42–44], a high prevalence of HCV co-infection was found amongst HIV infected intravenous drug users. A study into the effect of HCV co-infection on patient's response to HAART is currently conducted.

Region	Total		Male		Female		Child	
	N	%	N	%	N	%	N	%
Amsterdam	4321	44.4	3535	47.3	748	34.4	41	47.7
Western provinces	3029	31.1	2205	29.5	785	36.1	39	45.4
Northern provinces	614	6.3	433	5.8	180	8.3	1	1.1
Eastern provinces	757	7.8	566	7.5	191	8.7	0	0
Southern provinces	1008	10.4	735	9.8	268	12.3	5	5.8
Total	**9732**		**7474**		**2172**		**86**	

Table 5.1: Distribution of HIV infected patients registered in the Netherlands.

	RNA				
HIV-Ab	**Unknown**	**HIV-1 +**	**HIV-2 +**	**HIV-1/2 +**	**Total**
Unknown	208	124	0	0	332
HIV-1 positive	373	8833	0	10	9216
HIV-2 positive	15	5	25	4	49
HIV-1/2 positive	13	116	1	5	135
Total	**609**	**9078**	**26**	**19**	**9732**

Table 5.2: Prevalence of HIV-1 and HIV-2.

Characteristic	N	%
Total	86	
Gender		
Male	46	53
Female	40	47
Year of HIV diagnosis		
Before 1990	11	13
1990-1995	12	14
1996-2000	21	24
2001-2004	16	19
Unknown	26	30
Transmission group		
Blood products	8	9
Mother to child	29	34
Sex	11	13
Other	38	44
At HIV diagnosis	Median	IQR
Age (months)	10.6	3.4 – 68.4
CD4 cells/mm^3	950	272 – 2120
Log HIV RNA copies/ml	5.2	4.5 – 5.8

Table 5.3: Baseline characteristics of 86 HIV infected children.

Characteristic	HAART naïve patients		HAART pre-treated patients		Non-HAART treated patients		Non-treated patients	
N Total	5462		2203		142		1826	
Median (IQR) age:								
at start HAART	37	31-44	38	33-45				
at start non-HAART			36	31-43	35	31-43		
at diagnosis	35	29-42	33	28-41	33	27-39	34	28-40
N (%) Gender:								
Male	4165	76.3	1826	82.9	111	78.2	1360	74.5
Female	1297	23.7	377	17.1	31	21.8	466	25.5
N (%) CDC-C event:								
at start HAART	1190	11.8	259	11.8				
at start non-HAART			191	8.7	9	6.3		
at diagnosis	889	16.3	127	5.8	3	2.1	61	3.3
Median (IQR) CD4 cells/mm^3								
at start HAART	N=4864		N=1932					
	200	80-330	178	70-310				
at start non-HAART			N=1256		N=88			
			190	98-300	240	125-365		
at diagnosis	N=3685		N=872		N=60		N=1094	
	210	70-400	220	90-408	351	145-545	526	380-690
N (%) HIV RNA <500 copies/ml								
at start HAART	72	1.3	183	8.3				
at start non-HAART			16	0.7	4	2.8		
at diagnosis	199	3.6	14	0.6	2	1.4	110	6.0
Median (IQR) log HIV RNA copies/ml								
at start HAART	N=4674		N=1516					
	5.0	4.4-5.4	4.4	3.3-5.0				
at start non-HAART			N=454		N=50			
			4.8	4.3—5.2	4.3	3.1-4.9		
at diagnosis	N=3385		N=306		N=32		N=1052	
	5.0	4.3-5.4	4.8	4.0-5.3	4.6	4.2-5.0	4.2	3.6-4.8

Table 5.4: Baseline characteristics HAART, non-HAART and non-treated patients.

HAART regimen	N	%
AZT 3TC NVP	1152	17.8
AZT 3TC ABC	534	8.3
AZT 3TC EFV	387	6.0
AZT 3TC LPV/r	320	5.0
TDF 3TC NVP	255	4.0
TDF 3TC EFV	230	3.6
AZT 3TC NFV	204	3.2
d4T 3TC NVP	203	3.1
ddI 3TC NVP	95	1.5

Table 5.5: Most frequent HAART regimens given to patients in 2003.

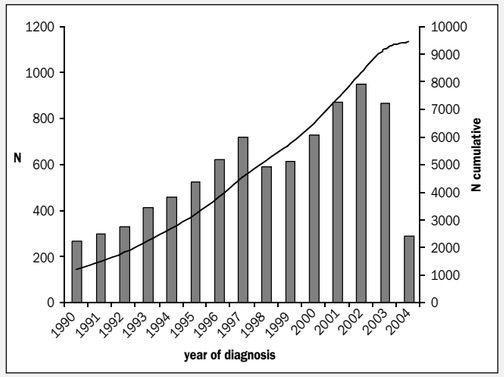


Figure 5.1: Number of new HIV diagnosis per year of diagnosis.

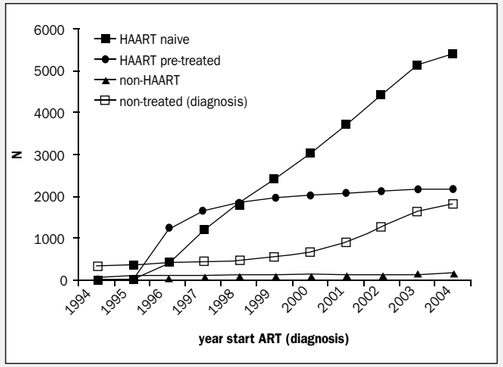


Figure 5.2: Cumulative numbers of patients commencing antiretroviral therapy per year of start HAART (naïve and pre-treated patients), of non-HAART and per year of HIV diagnosis in non-treated patients.

Trends over time

Trends over time in the HIV infected population

Ard van Sighem

Introduction

The HIV infected population in the Netherlands is evolving from a population dominated by the classical risk groups of homosexual men and intravenous drug users to a population of which heterosexuals and patients of a non-Dutch origin form a substantial part[9]. This is also reflected in an increasing proportion of infections with non-B HIV-1 subtypes, suggesting that part of the HIV infections in the Netherlands is imported from endemic areas.

This chapter will focus on the changes over time in risk groups, the origin of HIV-1 infected patients and the differences between these groups at diagnosis. Together with data on HIV-1 subtype and country of infection, the import of HIV-1 infections into the Netherlands will be subject of study.

Study population and methods

The study population consisted of 9348 HIV-1 infected patients of whom the year of diagnosis was known. Transmission risk group and gender were combined into five groups: men infected through homosexual contact, men and women infected via heterosexual contact and men and women infected via other or unknown transmission routes. Patients who were infected via intravenous drug use or blood or blood products were added to the 'other or unknown transmissions' group. Countries of origin or infection were combined in 12 regions: the Netherlands, Western Europe excl. the Netherlands, Central Europe, Eastern Europe, South (East) Asia, North Africa and Middle East, sub-Saharan Africa, North America, Latin America, the Caribbean, Australia and the Pacific.

HIV-1 subtypes were determined using the nucleotide sequences of protease and RT. Sequences were available from four different virology laboratories: AMC-UvA in Amsterdam (Suzanne Jurriaans, Nicole Back, Lia van der Hoek and Ben Berkhout), EMC-Dijkzigt in Rotterdam (Martin Schutten and Ab Osterhaus), UMCU in Utrecht (Rob Schuurman and Charles Boucher) and LUMC in Leiden (Eric Claas and Louis Kroes). Subtypes were determined separately for every sequence available for each patient. Sequences were compared pair-wise using the Kimura 2-parameter model for distances[45]. A representative set of reference sequences was obtained from the Los Alamos sequence database – http://www.hiv-web.lanl.gov – and was included in the distance calculations. Sequences were clustered using the neighbour-joining method; they were assigned a specific subtype when the bootstrap value of the cluster containing the sequences and a reference sequence exceeded 85%[46]. Sequences that could not be classified in this way as a specific non-B subtype or a circulating recombinant form (CRF) were labelled 'non-B'. The CRFs CRF01_AE and CRF02_AG will be referred to as AE and AG in brief.

Changes over time were assessed by studying changes in the patient's characteristics at time of diagnosis. Proportions were compared via a χ^2-test or Fisher's exact test if sample sizes were small. Differences in age, CD4 count and RNA levels were tested using Wilcoxon Mann-Whitney and χ^2 non-parametric tests. The significance of proportional changes over time was assessed with the Cochran-Armitage test for trend or with logistic regression modelling. Changes over time in continuous variables were studied using analysis of variance. For continuous variables, medians are reported together with the inter-quartile range (IQR).

Results

Figure 6.1 shows the proportions of male and female patients per year of diagnosis infected via homosexual or heterosexual contact or through other or unknown transmission routes. The proportion of homosexual transmissions contributing to the annual number of diagnoses declined from 60.0% in 1996 to 46.9% in 2004 ($p<0.001$). This decrease was compensated for by an increase in heterosexual transmissions, from 11.1% to 18.8% for men ($p=0.002$) and from 13.3% to 23.1% for women ($p<0.001$). However, between 2000 and 2004, the proportions did not change with year of diagnosis. They were 45.5% for homosexual men, 17.6% and 26.6% for heterosexual men and women and 9.0% and 1.4% for men and women, respectively, infected via other or unknown transmission routes.

The HIV-1 subtype could be determined for 1801 (19.3%) patients (Table 6.1). The country of infection was known for 1237 (68.7%) infections with a known subtype. In all regions of infection, except sub-Saharan Africa and South (East) Asia, the majority of the infections were with a subtype B strain. Amongst the 172 infections in sub-Saharan Africa, subtype B accounted for only 8 (4.7%) cases. Most prevalent subtypes from this region were A (22, 12.9%), C (54, 31.8%), AG (38, 22.4%) and D (16, 9.4%). Amongst the 28 reported infections in South (East) Asia, 11 (39.3%) were with subtype B and 15 (53.6%) with subtype AE. Of these subtype B infections, 9 (82%) occurred amongst homosexual men, whilst of the subtype AE infections, 11 (73%) were amongst heterosexuals.

Homosexual men

For 4978 (53.3%) men in the study population, the reported mode of transmission was homosexual contact. Of those, 2992 (60.1%) were diagnosed in or after 1996. The majority of homosexual men, 3693 (74.2%), were of Dutch origin. Regions of origin with high prevalence were the rest of Western Europe (7.8%), Latin America (5.9%), the Caribbean (2.8%) and South Asia (2.7%). These proportions did not significantly change across the years of diagnosis.

Median HIV-1 RNA plasma levels and CD4 cell counts at diagnosis were 4.9 (4.3–5.3) $\log_{10}$ copies/ml and 310 (120–499) $\times$ 10^6 cells/l, respectively, and did not differ between patients from different regions. CD4 cell counts increased from 250 (90–400) $\times$ 10^6 cells/l to 350 (157–548) $\times$ 10^6 cells/l in 2004. The median age at diagnosis of patients of Dutch origin, 38.5 (33.1–46.1) years, was higher than in patients from other regions, 33.8 (29.0–39.5) years ($p<0.001$) and increased over time from 36.8 (31.8–45.6) years in 1996 to 38.9 (32.5–46.4) years in 2004 ($p=0.002$).

For 1107 (22.2%) men in the study population, the subtype could be determined. Of these, 1082 were infected with subtype B (97.9%). Between 1996 and 2004, the annual proportion of diagnosed men infected through homosexual contact with a non-B subtype tended to increase ($p=0.06$). In 2003, 10 (9%) out of 109 patients were infected with a non-B subtype.

For 3398 (68.3%) homosexual men, the country of infection was known (Table 6.2). A majority of 3013 (88.7%) patients were infected in the Netherlands. Of the 2687 patients originating from the Netherlands, 2601 (96.8%) were infected in the Netherlands, whilst the remaining 86 patients were mostly infected in the rest of Western Europe, in South Asia or in North America. Of the 711 patients born outside the Netherlands, 412 (57.9%) were infected in the Netherlands and 265 (37.3%) in the region from which they originated.

Intravenous drug users

The group of patients infected via intravenous drug use (IDU) consisted of 376 men and 145 women. The majority of these patients (352 patients, 67.6%) was diagnosed in or before 1995 and originated from the Netherlands (359 patients, 68.9%), the rest of Western Europe (91 patients, 17.5%) and Latin America (18 patients, 3.5%). For 357 (68.5%) patients, the country of infection was known; the majority of these patients were infected in the Netherlands (317 patients, 88.8%) or in the rest of Western Europe (26 patients, 7.3%).

In the group of patients infected via IDU and diagnosed in or after 1996, the median age at diagnosis was 37.3 (33.2–42.7) years. The median CD4 cell counts and HIV-1 RNA plasma levels at diagnosis were 275 (87–423) × 10^6 cells/l and 4.9 (4.3–5.4) $\log_{10}$ copies/ml. No differences were observed between men and women, except that women tended to have higher viral loads, 4.7 versus 5.2 $\log_{10}$ copies/ml. In addition, drug users originating from outside the Netherlands were generally younger, 34.2 versus 38.6 years at diagnosis, compared to those of Dutch origin.

Thirteen patients (2.5%) were born in Central and Eastern Europe. Six of these patients were diagnosed in or before 1995, of which three were infected in the Netherlands and one in Poland. The other seven patients were diagnosed in or after 2000. Four of these patients originated from Russia (also infected there), one from Azerbaijan (also infected there), one from Georgia (country of infection unknown), and one from Yugoslavia (infected in the Netherlands).

For the first time, transmissions of non-B subtypes were observed amongst intravenous drug users: two were infected with subtype A, one with subtype AE and one with subtype G. One subtype A was found in a patient originating from and infected in Russia; the subtype G strain was found in a patient born and infected in Portugal. The other two subtypes were found among Dutch patients who were infected in the Netherlands.

Heterosexuals

The group of patients infected via heterosexual contact consisted of 1236 men and 1760 women. The majority of the male population originated from the Netherlands (460 patients, 37.2%) and sub-Saharan Africa (449 patients, 36.3%), whilst 115 patients (9.3%) originated from Latin America and 68 (5.5%) from the Caribbean. In the female population, the most frequent region of origin was sub-Saharan Africa (855 patients, 48.5%), whilst only 455 (25.9%) of the patients originated from the Netherlands. The proportions of patients from Latin America and the Caribbean were similar to those in the male heterosexual population, 8.9% (157 patients) and 5.9% (104 patients), respectively. The distribution over region of origin for the entire heterosexual population is shown in figure 6.2.

From the year 2000 onwards, the proportions of annually diagnosed heterosexual patients categorised by region of origin were 55.9% for patients from sub-Saharan Africa, 20.7% for the Netherlands, 8.5% for Latin America, 4.7% for the Caribbean, 4.1% for South and South-East Asia and 6.1% for the other regions. These proportions did not change with time.

Table 6.3 shows the age, CD4 counts and RNA plasma levels at diagnosis for heterosexual men and women. In general, regardless the regions of origin, men were older at diagnosis than women and had lower CD4 counts and higher viral loads. When comparing characteristics between men and women from different regions of origin, there was no difference between Dutch patients and patients from other Western European countries. On the other hand, men and women from sub-Saharan Africa were generally younger and had lower CD4 counts compared to Dutch patients. Patients from Latin America and the Caribbean also had lower CD4 counts than Dutch patients, although this was not statistically significant for women from the Caribbean (p=0.3).

Table 6.2 shows that the majority of the heterosexual population (60.5%; men 58.0%, women 62.1%) consists of imported infections, i.e. infections in patients who were infected outside the Netherlands. Only 42.0% of the men and 37.9% of the women were infected in the Netherlands. Of patients born outside the Netherlands and infected through heterosexual transmission, 385 (71.2%) of the 541 men and 771 (77.6%) of the 994 women were infected in the region from which they originated.

In the male population originating from the Netherlands (325 patients), 226 (69.5%) were infected in the Netherlands, 39 (12.0%) in sub-Saharan Africa and 39 (12.0%) in South and South-East Asia. For the 369 women originating from the Netherlands, 320 (86.7%) were infected in the Netherlands, whilst 24 (6.5%) were infected in sub-Saharan Africa.

Of the 1015 patients (676 women and 339 men) originating from sub-Saharan Africa of which the country of infection is known, 89.1% was infected in sub-Saharan Africa and only 9.7% in the Netherlands. These percentages did not differ between men and women. Amongst the 176 patients originating from Latin America, 71 (40.3%) were infected in that region whilst 98 (55.7%) were infected in the Netherlands. Amongst patients from the Caribbean (126), 81 (64.3%) were infected locally whilst 39 (31.0%) were infected in the Netherlands.

Figure 6.3 shows the distribution of subtypes in the 207 patients originating from sub-Saharan Africa and in the 281 patients originating from other regions for whom the subtype could be determined. The most prevalent subtype in the latter group was B (73%), whilst subtype B only accounts for 3% of the infections amongst heterosexuals from sub-Saharan Africa. The most prevalent subtypes amongst heterosexuals from sub-Saharan Africa are C (29%), AG (27%) and A (14%). Over time, the proportion of diagnosed infection with a non-B strain in the heterosexual group increased from 42% in 1996 to 62% in 2004 (Figure 6.4).

Discussion

Our study shows that from 1996 onwards, an increasing proportion of the newly diagnosed patients is infected via heterosexual contact and originates from sub-Saharan Africa[47]. However, since the year 2000, the proportions of risk groups and country of origin have stabilised at a level where the annual number of new diagnoses amongst individuals infected via heterosexual contact is similar to the number of newly diagnosed individuals infected via homosexual contact.

Despite these changes in the newly diagnosed population, homosexual men still form the largest HIV infected group. This group is mainly of Dutch origin and infected in the Netherlands with a subtype B strain. The population is getting older at diagnosis, whilst CD4 counts at diagnosis increase with calendar time. This suggests that homosexual men are diagnosed sooner after infection and are infected at older ages. Assuming that most homosexuals are likely to have sexual contact with men of approximately the same age, it should be expected that the probability of infection is smaller for young homosexual men than for their elderly peers.

In contrast to the homosexual population, infections amongst heterosexuals are mainly imported from sub-Saharan Africa and, to a lesser extent, from Latin America and the Caribbean. The majority of patients of Dutch origin are infected in the Netherlands and in sub-Saharan Africa, although 12% of the male population has been infected in South (East) Asia, mainly in Thailand.

Heterosexual men generally are diagnosed at older age and in a later stage of infection than women. This indicates that men are tested later after infection than women. A partial explanation for this might be that in the Netherlands, women are offered an HIV test during pregnancy by default although the number of women diagnosed in this way appears to be limited[48]. In addition, it has been shown that women have a greater susceptibility to infection then men, so women might be infected at younger ages[49].

Although the majority of the infected heterosexual population is of sub-Saharan origin, the proportion infected in the Netherlands is only about 5%, which is the same order of magnitude as the percentage of individuals originating from Latin America and the Caribbean who are infected in the Netherlands. However, it is not known to what extent foreign individuals living in the Netherlands who visit their country of origin import infections. At the moment, a study is being conducted in the group of patients originating from Suriname and the Netherlands Antilles that aims at unravelling the dynamics of infections in these two groups.

Intravenous drug users form only a small minority of the HIV infected population in the Netherlands. Consequently, the import of infections in this population from outside Western Europe is very limited. However, it was recently reported that in Eastern Europe the rate of new HIV-infections – mainly amongst intravenous drug users but emerging in the heterosexual population – is amongst the highest in the world[50]. Since several of these countries in Eastern Europe are now part of the European Union, infections might more easily migrate to Western Europe. So far, however, there are hardly any indications that this is already happening in the Netherlands.

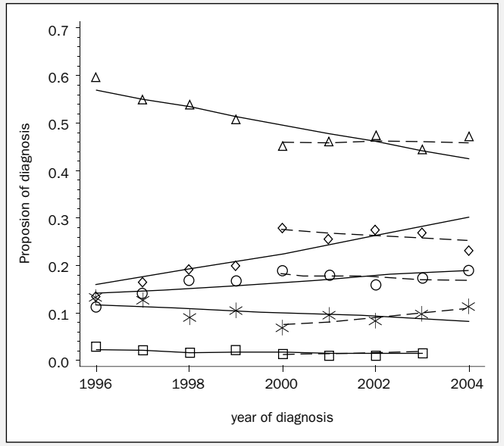


Figure 6.1: Annual proportions of diagnoses per gender-transmission group. Symbols indicate the observed proportions, whilst the lines show the results of logistic regression on these proportions, taking into account all data between 1996 and 2004 (full lines) or only data between 2000 and 2004 (dashed lines). Triangles: homosexual men; circles: heterosexual men; stars: men infected via other or unknown transmission routes; diamonds: heterosexual women; squares: women infected via other or unknown transmission routes.

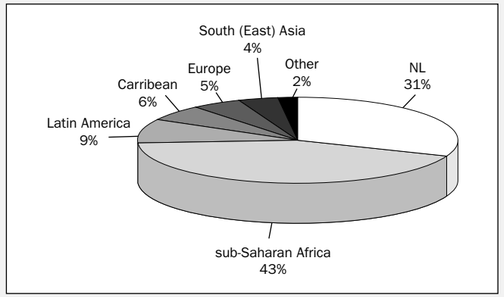


Figure 6.2: Distribution of regions of origin for the heterosexual HIV infected population. NL: the Netherlands; Europe: combined Western Europe excluding NL, Central Europe and Eastern Europe.

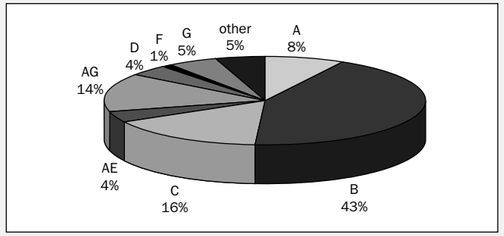


Figure 6.3: Distribution of the 488 known subtypes in the HIV infected heterosexual population.

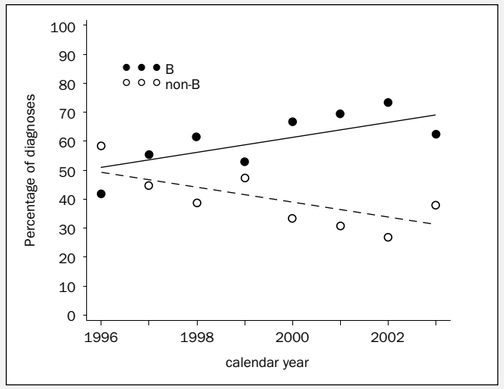


Figure 6.4: Proportion of B and non-B HIV-1 subtypes in the HIV infected heterosexual population per year of diagnosis. The dots represent the data, whilst the lines are the results of a logistic fit.

	Male										Female							
	Homosexual		Heterosexual		IVD		Blood		Unknown		Heterosexual		IVD		Blood		Unknown	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
A	2	0.2	13	6.7	2	3.6			4	4.5	27	9.2					1	5.6
AE	11	1.0	11	5.7	1	1.8	1	5.0	1	1.1	8	2.7			1	11.1		
AG	2	0.2	25	12.9			1	5.0	11	12.4	43	14.6			1	11.1	2	11.1
B	1082	97.9	94	48.5	51	92.7	18	90.0	59	66.3	118	40.1	17	100	3	33.3	11	61.1
C	6	0.5	29	15.0					6	6.7	47	16.0			3	33.3	3	16.7
D			4	2.1					4	4.5	16	5.4			1	11.1		
F			2	1.0							4	1.4					1	5.6
G			6	3.1	1	1.8			1	1.1	16	5.4						
Non-B	2	0.2	10	5.2					3	3.3	15	5.1						
	1105		**194**		**55**		**20**		**89**		**294**		**17**		**9**		**18**	

Table 6.1: HIV-1 subtypes by gender and mode of transmission. IVD: intravenous drug users.

	Total population	Country of infection known		Born in NL Infected in NL		Born in NL Infected outside NL		Not born in NL Infected in NL		Not born in NL Not infected in NL	
	N	N	%	N	%	N	%	N	%	N	%
Men											
Homosexual	4978	3398	68.3	2601	76.6	86	2.5	412	12.1	299	8.8
Heterosexual	1236	866	70.1	226	26.1	99	11.4	138	15.9	403	46.5
IVD	376	256	68.1	194	75.8	4	1.6	35	13.7	23	9.0
Blood	110	91	82.7	50	55.0	11	12.1	7	7.7	23	25.3
Unknown	599	312	52.1	150	48.1	10	3.2	47	15.1	105	33.7
Women											
Heterosexual	1760	1363	77.4	320	23.5	49	3.6	197	14.5	797	58.5
IVD	145	101	69.7	57	56.4	2	2.0	31	30.7	11	10.9
Blood	46	39	84.8	8	20.5	3	7.7	3	7.7	25	64.1
Unknown	98	55	56.1	37	67.3	3	5.5	10	18.2	5	9.1

Table 6.2: Number of patients infected in the Netherlands (NL) or elsewhere, stratified by gender and mode of transmission. IVD: intravenous drug users.

	Men			Women		
	Age (year)	CD4 (x 10^6 cells/l)	RNA (log_{10} copies/ml)	Age (year)	CD4 (x 10^6 cells/l)	RNA (log_{10} copies/ml)
The Netherlands	40.9	270	5.0	34.2	406	4.4
	33.4-49.8	50-480	4.3-5.4	28.5-44.5	160-620	3.5-5.0
Western Europe	41.2*	260*	4.7*	32.7*	400*	4.2*
	34.5-51.3	80-420	4.4-5.3	30.2-44.3	250-630	3.1-5.1
Sub-Saharan Africa	33.6	166	4.9	28.3	260	4.3
	28.0-38.1	77-320	4.3-5.3	23.5-33.6	130-426	3.5-5.0
Latin America	38.8	130	4.9	31.1	300	4.4
	33.5-46.7	30-330	4.2-5.3	26.3-38.0	100-440	3.6-5.0
The Caribbean	36.8	105	4.7*	31.4	352	4.4*
	32.2-43.5	25-258	4.1-5.4	23.6-38.6	105-565	3.9-5.0
South (East) Asia	45.3	170*	3.8*	30.7	93*	4.9*
	33.5-55.7	70-316	3.0-5.3	27.8-36.0	28-280	4.1-5.1
Total	**36.2**	**181**	**4.9**	**30.3**	**290**	**4.4**
	30.9-44.3	**52-370**	**4.3-5.3**	**25.0-36.3**	**120-484**	**3.5-5.0**

Table 6.3: Median age, CD4 count and RNA plasma level at diagnosis for heterosexual men and women from the most prevalent regions of origin; *p>0.01 men vs. women, all other men-women comparisons have p<0.01.

Initial HAART

Comparison of initial HAART regimens
in antiretroviral drugs naive patients

Luuk Gras

Introduction

Highly active antiretroviral therapy (HAART) aims at long-term suppression of HIV-1 replication. In order to achieve this, antiretroviral treatment has to be administered daily and probably for life. Since the number of different classes of antiretroviral drugs currently available is still limited, it is of importance to assess the efficacy of currently prescribed initial HAART combinations in the treatment of HIV infection. The choice of the initial HAART combination is critical because it determines options for 2nd and subsequent combinations[51-54] in case resistance occurs[55-57]. In addition, side effects or adverse events, followed by suboptimal adherence, may limit the magnitude and duration of the antiretroviral response[58,59]. This chapter describes differences in immunological and virological efficacy and toxicity between initial HAART regimens that are currently most frequently used for treatment of patients participating in the ATHENA national observational cohort.

Methods

Study population

Data were used from antiretroviral therapy naive patients commencing AZT+3TC+EFV, AZT+3TC+NVP, AZT+3TC+ABC, AZT+3TC+LOP/r, AZT+3TC+NFV, d4T+3TC+NVP or TDF+3TC+EFV from 1998 onwards. Only data from patients who were 12 years or older at diagnosis and had at least 10 weeks of follow-up after start of HAART and did not participate in a clinical trial were used.

Outcome measures

Three measures of efficacy and one measure of toxicity were considered. Time to the first of two consecutive HIV RNA plasma level measurements <500 copies/ml was used as a marker for the ability of therapy to suppress viral production. The second outcome measure was the time to the first of two consecutive viral load measurements ≥500 copies/ml for those patients who were still on their initial regimen and had achieved viral suppression within one year. This outcome measure was used as an indicator of the longer-term potency of HAART regimens to suppress viral production.

Time to the first CD4 cell count showing an increase from baseline of ≥100 cells/mm^3 was used as a marker for boosting the immune system. Time to toxicity related stop, interruption (for more than 1 day) or change of HAART was used as a marker for the toxicity of HAART.

All four endpoints were measured during the first regimen. In case a patient did not reach one of these endpoints before change, stop or interruption of the first HAART regimen, time was censored at the time of therapy stop in an 'as treated' approach.

Statistical analysis

Categorical baseline variables were compared using Pearson's chi-square statistic and continuous variables using the Wilcoxon Mann-Whitney test. Kaplan-Meier (KM) estimates for each endpoint were constructed. Accelerated failure time models accounting for interval censoring of the virological and immunological measurements were used to compare HAART regimens. Potential confounders included in the models were baseline CD4 cell count and HIV RNA concentration in plasma, occurrence of a CDC-C event in the 24 weeks prior to start of HAART, gender, transmission risk group, region of origin and age.

Treatment regimens were compared by means of the acceleration factor (AF) obtained using accelerated failure time models rather than hazard ratios obtained from standard Cox regression. The AF is the factor by which the time to an endpoint of an individual in the treatment group is accelerated (or slowed down) compared to a patient in the control group. It can also be interpreted in terms of median event times of patients. In case of an AF of 1.6, the median time to an event is 1.6 times that of the comparison group. Rather than splitting the combination up into an NRTI backbone part and a PI/NNRTI part, regimens were compared directly with each other. While this procedure had the disadvantage of a smaller sample size in each therapy group, we did not have to assume that the NRTI backbone had the same effect on the outcome variable irrespective of which PI/NNRTI was added to it. Further, certain NRTI backbones are not commonly used in combination with certain PI/NNRTIs (TDF+3TC is mainly used in combination with EFV).

Results

Patient characteristics and first line HAART regimens

Of all patients who started HAART between January 1998 and June 2004, 784 (18%) commenced with AZT+3TC+NVP. This was the most frequently used first line HAART regimen. Other frequently used combinations were AZT+3TC+LOP/r, d4T+3TC+NVP, AZT+3TC+NFV, AZT+3TC+EFV, AZT+3TC+ABC and TDF+3TC+EFV. Table 7.1 summarises the demographical and clinical status of the 2468 eligible pre-HAART antiretroviral naive patients.

Significant differences in the use of the PI/NNRTI component of HAART were observed by transmission risk group, age and gender with a higher proportion of AZT+3TC+NFV-containing regimens administered to women and younger patients. The most significant differences were observed in the clinical status of patients. Patients starting AZT+3TC+LPV/r had significantly lower baseline CD4+ T-cell counts ($p<0.0001$) and higher baseline HIV RNA levels ($p<0.0001$) compared to the other regimens while patients starting AZT+3TC+ABC had lower viral load levels compared to the other regimens ($p<0.0001$).

Time to virological success

Baseline HIV RNA levels above 500 copies/ml plasma were found in 2349 (95%) of the 2468 patients. This included 290 (10.6%) patients with missing baseline viral load measurement who were assumed to be above 500 copies/ml at start HAART. In 84% of the patients, viral load levels below 500 copies/ml were found within 6 months and in 89% within one year after initiation of HAART.

In the adjusted multivariate models, in patients starting on AZT+3TC+EFV or AZT+3TC+NVP viral load declined to levels below 500 copies/ml significantly faster than in those starting on d4T+3TC+NVP, AZT+3TC+LOP/r or AZT+3TC+NFV (see Figure 7.1a). Also, in patients starting on AZT+3TC+EFV, viral loads declined significantly faster to levels below 500 copies/ml than patients starting on trizivir or TDF+3TC+EFV. Finally, in patients starting on trizivir, time to viral loads <500 copies/ml did not differ from patients starting on AZT+3TC+LOP/r. Apart from lower baseline viral load, IDU was the only other significant baseline factor for predicting slower virological suppression with an AF compared to homosexually infected patients of 0.45 (95% CI 0.31, 0.64).

Time to first virological failure

Within one year after initiation of HAART, suppression of virus production was achieved in 1871 (76%) patients. Two percent of the patients had a viral rebound within six months of suppression and 9% within one year of suppression. Patients on AZT+3TC+NFV regained viral load levels to >500 copies/ml significantly faster than those starting on AZT+3TC+EFV, AZT+3TC+NVP, AZT+3TC+LOP/r or AZT+3TC+ABC (see Figure 7.1b). Finally, older age at start HAART was associated with a

longer time to virological failure (AF with each 10 year increase 0.73, 95% CI: 0.60, 0.89).

Time to immunological success

Baseline CD4+ T-cell measurements were available for 2231 (90%) patients. An increase of ≥100 CD4 T-cells/mm^3 was found in 69% of patients within 6 months and 79% within the first year after start of HAART. This increase was fastest in patients commencing HAART with AZT+3TC+LOP/r and slowest in patients on AZT+3TC+ABC. However, none of the differences between regimens were statistically significant.

CD4+ T-cell counts rose slower in older patients (AF per 10 year increase 0.85; 95% CI 0.78-0.93, p=0.0005). In addition, female patients were more likely to achieve a timely increase of ≥100 CD4 T-cells/mm^3 than male patients (AF 1.42; 1.10-1.83, p=0.007) as were MSM patients (AF compared to heterosexually infected patients 1.36; 1.06-1.76, p=0.02) and patients born in the Netherlands (AF compared with patients not born in the Netherlands 1.29; 1.06-1.58). Higher baseline viral load and a CDC-C event in the year prior to start of HAART were associated with shorter time to immunological success. Patients with a baseline CD4 cell count between 200-350 or 350-500 cells/mm^3 had a significantly faster rise in CD4 cells than patients with a baseline CD4 cell count of less than 200 cells/mm^3 or more than 500 cells/mm^3 (AF compared to 50-200 cells/mm^3 1.67; 1.38-2.07, p<0.0001 and 1.56; 1.18-2.06, p=0.002, respectively).

Toxicity of first line HAART regimens

Toxicity was the most frequently recorded reason to stop the first line HAART regimen. Table 7.2 shows the most frequently recorded adverse events by HAART regimen. A total of 553 (22,4%) patients stopped (part of) the initial regimen because of adverse events. For 90 (16%) patients, the type of adverse event could not be linked to the regimen. Anaemia was the most frequently recorded type of adverse event in patients stopping and was highest in patients using AZT+3TC+NVP. Lipodistrophy was the most frequently recorded adverse event in those stopping d4T+AZT+NVP. The distinction between peripheral fat loss and central fat accumulation in the data collection was made from July 2000 onwards and therefore occurred less frequently as lipodistrophy. The percentage of patients with neurological symptoms was higher in those starting AZT+3TC+EFV compared to any other regimen. Gastrointestinal side effects were more frequently recorded in patients starting HAART including a PI than a NNRTI. Seven out of 14 patients (50%) stopped because of rash occurring on a TDF+3TC+EFV regimen.

Eighteen percent of the patients stopped the initial HAART regimen for reason of toxicity within 6 months and 21% within 12 months. Patients commencing HAART with AZT+3TC+NFV (p=0.0006) AZT+3TC+ABC (p=0.004) or AZT+3TC+NVP (p=0.006) had a significantly longer time to a toxicity driven regimen stop than those starting on d4T+3TC+NVP. In addition, those starting on AZT+3TC+NFV were significantly less likely to stop due to adverse events than those starting on AZT+3TC+LOP/r (p=0.01) or AZT+3TC+EFV (p=0.02). Independent of the regimen patients were on, we found that women were more likely to stop due to adverse events (AF compared with men 2.48; 1.47, 4.18, p=0.007) as were patients of older age (AF for every 10 year increase in age at start HAART 1.23; 1.02-1.48, p=0.0005).

Discussion

The efficacy of seven frequently used first line HAART regimens were compared. This analysis is based on observational data and patients were not randomly assigned to a particular HAART regimen. For instance, the possibility that patients who were expected to encounter adherence difficulties were prescribed to more sustainable regimens cannot be ruled out. Thus, the results presented should be interpreted with caution.

A shorter time to virological suppression was found in patients commencing AZT+3TC+NVP or AZT+3TC+EFV than in patients starting on a PI based regimen, AZT+3TC+ABC or on d4T+AZT+NVP. Similar trends have been reported in other observational studies[60,61].

In agreement with results from other studies, we found that patients starting on AZT+3TC+EFV had a faster viral load decline than patients on AZT+3TC+NVP[62-66]. Efavirenz is also found to be more virologically effective than nevirapine in the 2NN study, although not significantly[63]. Current guidelines recommend efavirenz as part of an initial HAART regimen based on the results of several clinical trials[67,68].

Trizivir (AZT+3TC+ABC) is not recommended as a starting regimen[68,69] because of inferior virological efficacy clinical trials[70-72]. In our study, AZT+3TC+EFV performed significantly better in initially suppressing viral load than trizivir, but there was no significant difference between AZT+3TC+EFV and trizivir in maintaining viral suppression. Moreover, in a recent observational study no difference in viral rebound was observed in therapy naive patients starting AZT+3TC+EFV or trizivir[73]. Trizivir was well tolerated and virological efficacy of trizivir did not seem to be different from most other starting regimens in our study.

Compared to the NNRTI regimens, AZT+3TC+NFV appeared to be the only regimen performing less well, both with regard to the initial viral load decline and the maintenance of HIV RNA levels <500 copies/ml. The AZT+3TC+LOP/r combination was less effective in that time to initial virological success was longer when compared to patients starting AZT+3TC+EFV or AZT+3TC+NVP. However, patients starting AZT+3TC+LOP/r were in a more advanced state of the disease than patients starting on other regimens. Although the results were adjusted for several baseline variables, residual confounding might explain the poor virological outcome for LOP/r. There was no significant difference in maintaining viral suppression below 500 copies/ml between LOP/r and EFV based regimens.

No significant differences were observed between the different regimens in the initial CD4+ T-cell response. In contrast, there was a strong association between the baseline HIV RNA levels and the increase in CD4+T-cells, with those with higher baseline HIV RNA levels experiencing faster responses. This association might be explained by the initial redistribution of CD4+ T-cells in response to HAART rather than longer-term immune reconstitution[74,75].

The d4T+3TC+NVP regimen was more frequently stopped due to adverse events than other first line regimens. While d4T is initially better tolerated than AZT, it has been associated with longer term toxicity symptoms such as lipoatrophy and other metabolic abnormalities[76]. The level of suppression of viral replication and the gain in CD4 cell number was also less when compared to AZT+3TC+NVP, which is why d4T+3TC+NVP is hardly used anymore as an initial HAART regimen in the Netherlands.

In summary, in patients commencing HAART treatment with a combination of AZT+3TC+NVP and in particular AZT+3TC+EFV, significantly faster declines in viral load were found than in patients commencing with a PI based initial regimen. Except for AZT+3TC+NFV, HAART regimens did not differ with respect to the duration of maintaining virological suppression. No significant differences in the initial CD4 increase were observed between regimens. In view

of this, an NNRTI based regimen might be the obvious choice as first line HAART, although factors such as convenience of the regimen, drug-drug interactions, potential salvageability and individual patient characteristics should also be taken into account.

List of abbreviations

Antiretroviral drug	Generic name	Commercial name
AZT	zidovudine	Retrovir
d4T	stavudine	Zerit
3TC	lamivudine	Epivir
ABC	abacavir	Ziagen
TDF	tenofovir	Viread
NFV	nelfinavir	Viracept
LOP/r	lopinavir/ritonavir	Kaletra
NVP	nevirapine	Viramune
EFV	efavirenz	Sustiva, Stocrin

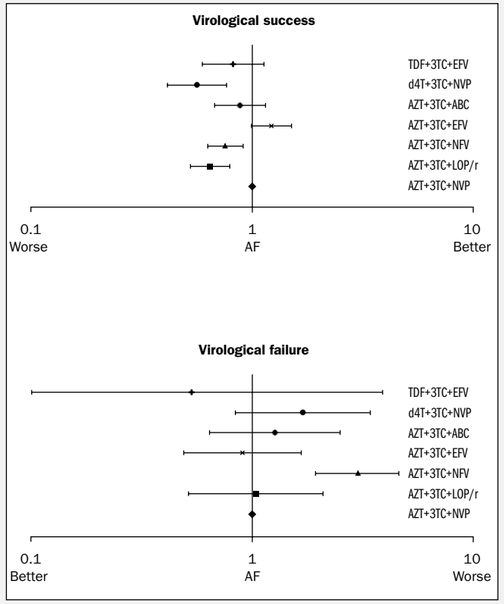


Figure 7.1a+b: Adjusted acceleration factor estimates and 95% confidence intervals of a) time to viral suppression (<500 copies/ml) and b) time to loss of viral suppression (≥500 copies/ml after initial suppression.

		AZT+3TC +NFV, N=539	AZT+3TC +LOP/r, N=349	AZT+3TC +EFV, N=339	AZT+3TC +NVP, N=784	d4T+3TC +NVP N=129	TDF+3TC +EFV, N=116	AZT+3TC +ABC, N=212	
		N(%)/ median(IQR)	N(%) median(IQR)	N(%)/ median(IQR)	N(%)/ median(IQR)	N(%)/ median(IQR)	N(%)/ median(IQR)	N(%)/ median(IQR)	p-value
Gender	**(male)**	293 (54.4)	272 (77.9)	255 (75.2)	553 (70.5)	87 (67.4)	80 (69.0)	155 (73.1)	<0.0001
Age at	**<35**	311 (57.7)	131 (37.5)	133 (39.2)	336 (42.9)	48 (37.2)	38 (32.8)	93 (43.9)	<0.0001
start HAART	**35-45**	154 (28.6)	137 (39.3)	128 (37.8)	289 (36.9)	48 (37.2)	48 (41.4)	74 (34.9)	
	>=45	74 (13.7)	81 (23.2)	78 (23.0)	159 (20.3)	33 (25.6)	30 (25.9)	45 (21.2)	
Risk group	**MSM**	172 (31.9)	153 (43.8)	157 (46.3)	349 (44.5)	55 (42.6)	49 (42.2)	85 (40.1)	<0.0001
	IDU	21 (3.9)	10 (2.9)	6 (1.8)	40 (5.1)	8 (6.2)	2 (1.7)	22 (10.4)	
	Heterosexual	320 (59.4)	147 (42.1)	142 (41.9)	323 (41.2)	59 (45.7)	45 (38.8)	72 (34.0)	
	Other	26 (4.8)	39 (11.2)	34 (10.0)	72 (9.2)	7 (5.4)	20 (17.2)	33 (15.6)	
Year of	**1998**	94 (17.4)		1 (0.3)	72 (9.2)	26 (20.2)			<0.0001
start HAART	**1999**	183 (34.0)		3 (0.9)	167 (21.3)	34 (26.4)		1 (0.5)	
	2000	100 (18.6)	2 (0.6)	48 (14.2)	169 (21.6)	31 (24.0)		21 (9.9)	
	2001	74 (13.7)	77 (22.1)	94 (27.7)	169 (21.6)	20 (15.5)		70 (33.0)	
	2002	43 (8.0)	152 (43.6)	100 (29.5)	105 (13.4)	11 (8.5)	15 (12.9)	77 (36.3)	
	2003	35 (6.5)	101 (28.9)	78 (23.0)	84 (10.7)	6 (4.7)	80 (69.0)	43 (20.3)	
	2004	10 (1.9)	17 (4.9)	15 (4.4)	18 (2.3)	1 (0.8)	21 (18.1)		
CD4 count	**N**	477	334	303	704	109	113	193	
at start HAART	**(copies/mm³)**	260 (103-430)	114 (40-220)	180 (70-279)	240 (140-258)	220 (100-380)	180 (80-270)	250 (170-380)	<0.0001
HIV-1 RNA	**N**	468	317	301	709	108	107	195	
at start HAART	**(copies/ml)**	4.7 (4.0-5.3)	5.2 (5.0-5.6)	5.0 (4.5-5.3)	4.7 (4.2-5.1)	4.7 (4.1-5.3)	5.0 (4.6-5.0)	4.5 (3.9-4.9)	<0.0001
AIDS		98 (18.2)	90 (25.8)	78 (23.0)	81 (10.3)	31 (24.0)	16 (13.8)	22 (10.4)	<0.0001
at start HAART									
Region of origin	**(Netherlands)**	218 (40.4)	170 (48.7)	156 (46.0)	377 (48.1)	59 (45.7)	54 (46.6)	114 (53.8)	0.03

Table 7.1: Demographic and baseline characteristics of 2468 patients starting on recent HAART combinations.

		AZT+3TC+NVP N=784		AZT+3TC+NFV N=539		AZT+3TC+EFV N=339		AZT+3TC+LOP/r N=349		d4T+3TC+NVP N=129		AZT+3TC+ABC N=212		TDF+3TC+EFV N=116		Total N=2468
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N
Patients stopped due to toxicity		183	(33.1)	98	(17.7)	84	(15.2)	78	(14.1)	52	(9.4)	40	(7.2)	18	(3.3)	553
Patients without associated adverse events		22	(24.4)	19	(21.1)	8	(8.9)	18	(20)	10	(11.1)	9	(10)	4	(4.4)	90
Derma-tological	Rash	27	(16.8)	6	(7.6)	10	(13.2)	2	(3.3)	6	(14.3)	2	(6.5)	7	(50.0)	60
	Itchiness	3	(1.9)			2	(2.6)	1	(1.7)					1	(7.1)	7
	Dry skin							1	(1.7)			1	(3.2)			2
	Other	4	(2.5)	1	(1.3)	5	(6.6)	1	(1.7)			2	(6.5)	1	(7.1)	14
Gastero-intestinal	Nausea	31	(19.3)	10	(12.7)	4	(5.3)	12	(20.0)		(0.0)	5	(16.1)			62
	Diarrhoea	1	(0.6)	23	(29.1)			14	(23.3)	2	(4.8)	1	(3.2)			41
	Vomiting	11	(6.8)	9	(11.4)	2	(2.6)	6	(10.0)	4	(9.5)	4	(12.9)			36
	Abdominal pain	2	(1.2)	3	(3.8)			2	(3.3)							7
	Epigastric pain															
	Abdominal distension			3	(3.8)			2	(3.3)							5
	Loss of appetite					1	(1.3)			1	(2.4)					2
	Other	7	(4.3)	3	(3.8)			4	(6.7)							14
Haema-tological	Anaemia	37	(23.0)	17	(21.5)	13	(17.1)	10	(16.7)		(0.0)	6	(19.4)			83
	Leucopenia	7	(4.3)	4	(5.1)	5	(6.6)	3	(5.0)			1	(3.2)			20
	Trombocytopenia	2	(1.2)									1	(3.2)			3
	Pancytopenia					2	(2.6)	1	(1.7)							3
	Neutropenia	1	(0.6)			2	(2.6)									3
Musco-skeletal	Myalgia	2	(1.2)									2	(6.5)			4
	Myopathy, muscle wasting	1	(0.6)	1	(1.3)					1	(2.4)					3
	Other							1	(1.7)	1	(2.4)					2
Urogenital	Renal insufficiency							1	(1.7)					1	(7.1)	2
Blood or liver chemistry	Lipodistrophy	2	(1.2)	1	(1.3)	1	(1.3)	2	(3.3)	11	(26.2)					17
	Central fat accumulation			1	(1.3)			1	(1.7)	3	(7.1)					5
	Peripheral fat loss	1	(0.6)			1	(1.3)	1	(1.7)	5	(11.9)					8
	ALAT (elevated)	7	(4.3)					1	(1.7)	3	(7.1)					11
	ASAT (elevated)	7	(4.3)							2	(4.8)					9
	Gamma-GT (elevated)	4	(2.5)					1	(1.7)	1	(2.4)					6
	Raised alkaline phosphatase (ALP,ALK)	4	(2.5)													4

Table 7.2(1)**:** Adverse events causing stop of part of the initial HAART regimen. Percentages of patients with a particular adverse event divided by the number of patients stopping part of the regimen and adverse events recorded. Only those which were recorded at least twice are listed.

		AZT+3TC+NVP N=784		AZT+3TC+NFV N=539		AZT+3TC+EFV N=339		AZT+3TC+LOP/r N=349		d4T+3TC+NVP N=129		AZT+3TC+ABC N=212		TDF+3TC+EFV N=116		Total N=2468
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N
	(ALP,ALK)															
	Icterus	3	(1.9)									1	(3.2)			4
	Cholesterol (elevated)			1	(1.3)			2	(3.3)							3
	Hyperglucemia			2	(2.5)	1	(1.3)									3
	Triglycerides (elevated)					1	(1.3)	2	(3.3)							3
	Chronic hepatitis	1	(0.6)							1	(2.4)					2
	Hepatitis B					1	(1.3)			1	(2.4)					2
	Diabetes mellitus			2	(2.5)											2
	Pancreatitis	1	(0.6)											1	(7.1)	2
	Lactate acidosis									2	(4.8)					2
	Other	11	(6.8)	1	(1.3)	6	(7.9)	2	(3.3)	2	(4.8)					22
Systemic	Fever	7	(4.3)	2	(2.6)	1	(1.7)	1	(2.4)	3	(9.7)	1	(7.1)			15
	Fatigue	6	(3.7)			1	(1.3)	2	(3.3)			1	(3.2)			10
	General fatigue			1	(1.3)	2	(2.6)	2	(3.3)	3	(7.1)	1	(3.2)			9
	Abacavir hypersensitivity											5	(16.1)			5
Neurological	Peripheral Neuropathy	4	(2.5)					1	(1.7)	9	(21.4)					14
	Headache	4	(2.5)	2	(2.5)	3	(3.9)	3	(5.0)	1	(2.4)	1	(3.2)			14
	Dizziness	2	(1.2)			4	(5.3)	1	(1.7)					2	(14.3)	9
	Mood change	2	(1.2)			3	(3.9)									5
	Depression	1	(0.6)			2	(2.6)	1	(1.7)							4
	Concentration disorders				(0.0)	2	(2.6)							1	(7.1)	3
	Sleeplessness					3	(3.9)									3
	Transient numb-ness or tingling (paraesthesia)									1	(2.4)			1	(7.1)	2
	Dyspnoea			1	(1.3)			1	(1.7)			2	(6.5)			4
	Other					2	(2.6)			2	(4.8)					4

Table 7.2(2)

Second-line HAART

Success and failure of second-line HAART

Luuk Gras

Introduction

While highly active antiretroviral therapy (HAART) has been shown to be effective in initial suppression of plasma HIV-1 RNA load[77,78], subsequent virological suppression is not maintained in all patients[79] due to reasons such as non-adherence, high baseline plasma HIV RNA levels, discontinuation of therapy because of toxicity or infection with a resistant virus strain. Re-suppressing viral load on a second regimen after initial virological failure can be difficult[9,80].

Here we describe the characteristics of patients participating in the ATHENA national observational cohort who were registered as having a virological failure whilst on initial HAART and were subsequently switched to a second-line HAART regimen. We compare a cohort of failing patients starting HAART in 1996-1997, at a time when mainly protease inhibitors were used as an addition to NRTIs, with a cohort of patients failing in the period 1998-2004, when NNRTIs became more frequently prescribed as part of HAART.

Methods

All HIV-1 infected antiretroviral therapy naive patients who had commenced HAART, defined as at least three anti-retroviral drugs from at least 2 drug classes or a triple or quadruple NRTI regimen containing abacavir or tenofovir, from 1996 onwards were selected. Patients were classified into two groups: patients who had initiated first-line HAART during 1996 and 1997 (early HAART) and patients who had initiated first-line HAART between 1998 and 2004 (later HAART). Initial virological success and failure were compared between these groups, as were switches to a second-line HAART regimen after first virological failure. Virological outcome of second-line HAART was used as an endpoint. Time to virological success was defined as the time to the first of two consecutive HIV RNA plasma level measurements <500 copies/ml from start HAART for the first virological success and from start second-line HAART for the second virological success. First and second virological failure were defined as the first of two consecutive HIV RNA viral load measurements >500 copies/ml after first and second virological success, respectively.

Statistical analysis

Differences in continuous variables were tested using the Wilcoxon Mann Whitney test and categorical variables using Pearson's chi-square. Differences in time to events were explored using Kaplan-Meier (KM) estimates and the log-rank test.

Results

Initial virological success on first-line HAART

From 1996 onwards, 5410 patients had started on HAART (1169 patients in 1996-1997 and 4241 in 1998-2004) with in total 19484 person-years of follow-up. The percentage of patients starting on a HAART regimen that included a protease inhibitor declined from 99% in 1996-1997 to 56% in 1998-2004. The percentage of patients in 1998-2004 starting NNRTI including HAART was 42% and 5% started a triple NRTI. On average, the group of 1169 patients who started HAART in 1996-1997 had less advanced disease than the 4241 patients starting in 1998-2004. Median CD4 cell count at start of HAART was 240 cells/mm^3 (IQR 100–364) and HIV-1 RNA level was 4.9 $\log_{10}$ copies/ml plasma (4.4-5.4) for patients starting in 1996-1997 compared to 180 cells/mm^3 (70-310, p<0.0001) and 5.0 $\log_{10}$ copies/ml (4.5-5.4, p=0.06) in patients starting HAART in 1998-2004.

The percentage of patients with initial virological success on first-line HAART was 76% within 6 months and 85% within one year. Seventy-nine percent of the patients starting HAART in 1998-2004 reached HIV-1 RNA plasma levels <500 copies/ml within 6 months compared to 64% in patients starting HAART in 1996-1997 (log-rank p<0.0001). Median time to success was 3.7 months (IQR 1.8–10.6) for those starting in 1996-1997 and 2.5 (1.2–4.9) for those starting in 1998-2004.

Virological failure after initial success

In 1019 (21.4%) of the 4750 HAART treated patients who achieved HIV RNA levels <500 copies/ml plasma before the end of follow-up, a rebound to values >500 copies/ml was measured. Time to virological failure was not significantly different in patients starting HAART in 1996-1997 or 1998-2004 (p=0.07). At the time of viral rebound, 472 (46%) did not use any antiretroviral therapy. Another 71 patients (7%) were on monotherapy or on a non-HAART combination of antiretroviral drugs. Of these non-HAART users, 68% in the 1996-1997 group and 51% in the 1998-2004 group had stopped the last HAART regimen because of toxicity (risk difference 16%; 95% CI 8-25).

Characteristics of the remaining 476 patients are shown in Table 8.1. Patients starting HAART in later years and who had failed on therapy had more advanced HIV disease at start of HAART, as reflected in higher baseline viral load (p=0.03) and lower CD4 cell counts (p<0.0001). The median time on the regimen at time of failure in patients who had initiated HAART in later years was 288 days (IQR 161–492), which was shorter than in patients who initiated HAART in 1996 and 1997 with a median time on the regimen used at the time of failure of 379 days (IQR 173–728, p=0.003).

Most patients were either on an AZT+3TC or a d4T+3TC backbone at the time of virological failure. The composition of the NRTI backbone at the time of failure changed slightly over the years. A higher proportion of patients failed on a triple or quadruple NRTI combination (with or without PI or NNRTI additions) in later years. However, AZT+3TC and d4T+3TC were the most frequently used NRTI combinations at the time of failure in both time periods.

The PI and/or NNRTI drugs used in the HAART combination at time of failure were changed more substantially than the NRTI combinations over the course of the years. In patients starting initial HAART in 1996-1997, a higher proportion of patients used a single PI at the time of failure whilst in patients starting HAART in 1998-2004 LOP/r or a NNRTI was more frequently used.

Three months after virological failure was measured, 48% of the patients who started HAART in 1996-1997 and 46% of those who started HAART in 1998-2004 were still on the same drug regimen. After 12 months, these percentages were 27% and 20% respectively. Patients with lower viral load measured at virological failure were more likely to continue the failing regimen for a longer period of time (HR 1.20; 95% CI 1.07-1.34; p=0.002 for every 1 $\log_{10}$ copies/ml increase in viral load). Sequences were obtained in 81 patients (17%) of the 476 patients who experienced virological failure. 16/17 patients (94%) in the 1996-1997 group were resistant to at least one drug class, and 3/17 (18%) to 2 drug classes. These percentages were 48/64 (75%) and 23/64 (36%), respectively, in those who started HAART during the 1998-2004 period.

Switch to second-line HAART

Eighty patients were still on the same regimen they were using at the time of failure at the end of follow-up and a further 32 patients had stopped the failing regimen but had not started a second-line HAART regimen yet. The remaining 364 patients were started on a second-line HAART regimen.

For 214 patients (59%), both the NRTI combination and the PI/NNRTI component were changed.

For 33 patients (9%), only the NRTI combination and for 117 (32%) only the PI/NNRTI component was changed. A high proportion of patients (77/180) failing on AZT+3TC based HAART did not change their NRTI backbone in the second line HAART (Table 8.2). Most patients who stopped AZT+3TC were switched to another 2 NRTI combination (mainly d4T+ddI) or to a triple NRTI (mainly trizivir).

Of the 152 patients failing on a single PI based HAART, 52 patients (34%) were switched to an RTV boosted PI and 55 patients (36%) were switched to an NNRTI (Table 8.3). The 53 patients who failed using an RTV boosted PI were switched mainly to an NNRTI (26 patients, 49%) based second line HAART. The 100 patients initially failing on an NNRTI based HAART were mostly switched to a LOP/r based second regimen (40%), an RTV boosted PI (15%) or a triple NRTI (14%).

Virological success and failure on second line HAART

Thirty-three out of 152 patients (22%) starting HAART in 1996-1997 and 24 out of 212 patients (11%) starting HAART in 1998-2004 had HIV-1 RNA levels below 500 copies/ml before the start of second-line HAART and were therefore excluded from this analysis (Table 8.4). Of the remaining 307 patients starting second-line HAART upon virological failure of their first-line regimen, 220 patients re-established plasma viral load below 500 copies/ml during follow-up. There was no significant difference in time to virological success between patients who initiated HAART in 1996-1997 and patients who started in the period 1998-2004. Within 6 months after the initiation of second-line HAART, 60% percent of patients reached HIV RNA values below 500 copies/ml, increasing to 71% within one year.

Time to virological failure (plasma viral load >500 copies/ml) after initial suppression to HIV RNA levels <500 copies/ml on second line HAART (including those who had values <500 copies/ml at start of second-line HAART) was longer in patients initiating HAART in 1998-2004 when compared to patients who did so in 1996-1997. However, this difference was not statistically significant (log-rank p=0.10).

Discussion

Toxicity was the major reason for discontinuation of the initial HAART regime. The proportion of patients failing due to toxicity was higher in patients starting in the early years of HAART, which is probably due to the more toxic drug combinations used in those years. A higher percentage of patients failing in later years turned out to be resistant to at least two drug classes. This could be explained by the increased use of NNRTI based regimens in later years and the more rapid emergence of NNRTI resistant mutations compared to PI resistant mutations[81].

Although patients starting in 1998-2004 had more advanced disease, virological outcome was better or comparable with those starting in 1996-1997. This suggests that a higher proportion of patients commencing in 1996-1997 failed because of less effective HAART combinations whilst in later years, a higher proportion failed because HAART was initiated in a later phase of the HIV infection. The majority of patients on second-line HAART reached plasma viral load levels ≤500 copies/ml within 6 months. While time to second virological failure did not significantly differ in patients who had started HAART in 1996-1997 or patients who had started HAART in 1998-2004, differences in virological success and failure may be more pronounced when comparing patients initiating PI vs. NNRTI including HAART combinations. Results of other studies comparing PI and NNRTI including first-line HAART on longer-term outcome suggested that NNRTI based first-line HAART regimens may lead to better long-term viral load suppression and, subsequently, less need for therapy modification[82,83].

Year initial HAART started		1996-1997		1998-2004	
		N=190	%	N=286	%
CDC-C event prior to HAART		28	14.7	74	25.9
Median (IQR) CD4 cell count/mm^3 at start initial HAART			220 (118 – 333)		130 (45 – 287)
Median (IQR) HIV-RNA (log_{10} copies/ml) at start initial HAART			4.9 (4.3 – 5.4)		5.0 (4.7 - 5.4)
Median (IQR) age at start initial HAART			40 (34 – 45)		34 (29 – 42)
NRT backbone at virological rebound	No NRTI			1	0.3
	Single NRTI	11	5.8	8	2.8
	3TC+AZT	103	54.2	143	50.0
	3TC+d4T	34	17.9	46	16.1
	3TC+ddI	1	0.5	12	4.2
	d4T+ddI	16	8.4	8	2.8
	Other 2 NRTI	15	7.9	21	7.3
	3TC+AZT+ABC	7	3.7	23	8.0
	Other 3 NRTI	3	1.6	24	8.4
Addition to backbone at virological rebound	No PI/NNRT	5	2.6	37	12.9
	Single PI	95	50.0	84	29.4
	RTV boosted PI	27	14.2	34	11.9
	LOP/r	1	0.5	21	7.3
	Other 2 PI	7	3.7	4	1.4
	EFV	4	2.1	23	8.0
	NVP	46	24.2	73	25.5
	PI+NNRT combination	5	2.6	10	3.5
Median (IQR) time on current HAART regimen at virological failure			379 (173 – 728)		288 (161- 492)

Table 8.1: Characteristics at time of the first virological failure.

	Second-line NRTI backbone										
NRT backbone at time of first failure	No change in NRTI	No NRTI	1NRT	AZT+3TC	d4T+3TC	ddI+3TC	d4T+ddI	Other 2 NRTI	AZT+3TC+ABC	Other 3 or 4 NRTI	Total
Total	117	1	16	23	10	13	27	81	29	47	364
Single NRTI			1	4	1	3		3	3	2	17
AZT+3TC	77		5		6	3	22	32	16	19	180
d4T+3TC	19		2	9		2	3	17	5	10	67
ddI+3TC	3			1	1			3	1	1	10
d4T+ddI	5			4	1	1	0	7	2	2	22
Other 2 NRTI	6		3	2				5	1	8	25
AZT+3TC+ABC	3	1	1	2		2	2	5	0	2	18
Other 3 or 4 NRTI	4		4	1	1	2	0	9	1	3	23

Table 8.2: Switch from first to second line NRTI backbone.

	Second-line PI/NNRTI									
First-line PI / NNRTI	No change in PI/NNRTI	No PI/NNRTI	Single PI	RTV boosted PI	LOP/r	Other 2 PI	EFV	NVP	PI+NNRTI Combination	Total
Total	33	18	29	70	66	3	35	73	37	364
No PI/NNRT	1		3		4		10	5	7	30
Single PI	7	4	8	52	13	2	12	43	11	152
RTV boosted PI	4	4	5		7		8	18	7	53
LOP/r	3		1				2	2	1	9
Other 2 PI		1	2	1	1			2		7
EFV	3	1		3	7			1	1	16
NVP	11	7	8	12	33	1	2		10	84
PI+NNRT combination	4	1	2	2	1		1	2		13

Table 8.3: Switch from first to second line PI/NNRTI.

Year initial HAART started		**1996-1997** N=152	%	**1998-2004** N=212	%
Second line NRT combination	No NRTI			1	0.5
	Single NRTI	2	1.3	14	6.6
	3TC+AZT	52	34.2	48	22.6
	3TC+d4T	17	11.2	12	5.7
	3TC+ddI	5	3.3	11	5.2
	d4T+ddI	21	13.8	11	5.2
	Other 2 NRTI	25	16.4	62	29.2
	3TC+AZT+ABC	14	9.2	18	8.5
	Other triple or quadruple NRTI	16	10.6	35	16.4
Second line PI/NNRTI component	No PI/NNRTI	10	6.6	9	4.2
	Single PI	21	13.8	15	7.1
	RTV boosted PI	38	25.0	36	17.0
	LOP/r	19	12.5	50	23.6
	Other 2 PI	0	0.0	3	1.4
	EFV	9	5.9	29	13.7
	NVP	45	29.6	39	18.4
	PI+NNRTI combination	10	6.6	31	14.6
Prior AIDS diagnosis		39	25.7	83	39.1
CD4 cell count/mm^3	N measured		146		197
	Median (IQR)		410 (259–590)		270 (180–410)
HIV RNA: log10 copies/ml	HIV RNA: N measured		151		207
	Median (IQR)		3.6 (2.9–4.5)		3.8 (3.2–4.5)
	% <500 copies/ml		21		9

Table 8.4: Characteristics at start of second-line HAART.

Adverse events

Incidence of HAART-related adverse events

Luuk Gras

Introduction

HAART treatment is frequently interrupted or stopped as a result of toxicity[58]. Adverse events and toxicity may also result in diminished adherence and, consequently, sub-optimal therapy and treatment failure[58,59,84,85]. In this chapter, we describe HAART-related adverse events and toxicity within the ATHENA national observational cohort.

Methods

HIV-1 infected patients initiating HAART between January 1996 and July 2004 were selected. Of newly occurring lipodistrophy, nephrolithiasis, rash, hepatic steatosis, pancreatitis, diabetes mellitus (type I and II), peripheral neuropathy or loss of libido, the first date of diagnosis was registered and the time of a patient at risk was calculated. Time at risk was defined as time between start of HAART and first diagnosis, date of death, date of lost-to-follow-up or the 31st December of a year, whichever came first. Reported 95% confidence intervals were determined using the Poisson distribution.

Results

In total 7544 patients had started a HAART regimen between 1996 and July 2004 with 31868 person-years of follow-up. Lipodistrophy (both fat accumulation and fat loss) was the most frequently recorded adverse event, reaching a peak in 2000 of 174 newly affected patients per 1000 person years. Since 2000, newly diagnosed lipodistrophy declined to 52 patients/1000 person-years in 2003, although followed by an increase to 70 new cases/1000 person years in 2004 ($p=0.05$ compared to 2003).

Only from 2000 onwards, the distinction between peripheral fat loss and central fat accumulation was made in the data collection and both showed similar trends, although peripheral fat loss was more frequently recorded than fat accumulation. The declining lipodistrophy incidence coincides with a lower prescription pattern of d4T and protease inhibitors, both assumed to be associated with lipodistrophy[76,86,87].

Self reported loss of libido was higher in men than in women. There was a peak in 1998 of 17 new cases/1000 person years but declined to 7 new cases/1000 person years in the period 2002-2004 (incidence in 1998-2000 vs. 2002-2004 $p<0.0001$).

The incidence of newly diagnosed nephrolithiasis declined from 20/1000 person years at risk in 2000 to 1/1000 person years in 2004 and coincides with reduced prescription of indinavir most commonly associated with nephrolithiasis[76,88].

Since 1999, the incidence of rash after start of HAART has declined. However, after reaching a nadir of 11 new patients/1000 person years at risk in 2002, an increasing trend ($p<0.0001$) was found. Rash is associated with NNRTI use, particularly nevirapine[89] but recently also with PI usage[90].

Hepatic steatosis, associated with NRTI use[91,92], and pancreatitis, associated with the use of ddI, d4T and hydroxyurea[93], are serious and possible life threatening adverse events. The incidence of newly diagnosed cases was 2 and 1 new cases/1000 person years at risk in 2004 for hepatic steatosis and pancreatitis, respectively. The incidence of newly diagnosed diabetes mellitus in the years 2001-2004 is lower than during 1997-2000 ($p=0.002$).

Newly diagnosed peripheral neuropathy decreased from 73 new cases/1000 person-years at risk in 1997 to 7 in 2004. Peripheral neuropathy has been associated with NRTI usage, e.g. ddI and d4T[92,94,95]. Other risk factors include older age, higher viral load and advanced HIV disease[96,97].

Discussion

From the year 2000 onwards, the incidence of lipodystrophy, sexual dysfunction, nephrolithiasis, pancreatitis and peripheral neuropathy declined, most likely because the combination of antiretroviral drugs prescribed for HAART has changed. Since the registration of the protease inhibitors saquinavir, ritonavir and indinavir in 1996, new and less toxic antiretroviral drugs have been introduced, giving physicians a wider choice of drugs to be used in the HAART combination and allowing them to adapt the combination to the characteristics of the patient. One limitation to the data presented in this study is the lack of standardisation of the adverse event. Whether an adverse event is recorded depends on the interpretation of the physician. The importance attributed to symptoms and the chance of a correct diagnosis of the event may differ between physicians and perhaps even within the same physician over time.

The diagnosis of some adverse events depends heavily on the quality of information provided by patients during the clinical visit, which may depend on his or her view on the personal and social implications. A good example of this phenomenon is self-reported loss of libido. Prevalence of low libido in HAART treated homosexuals as high as 48%[98] have been reported. Using self administered questionnaires 71% of HIV infected homosexuals taking PI's reported some degree of sexual dysfunction[99]. This indicates that the real prevalence of loss of libido is likely to be much higher than the 6% prevalence rate in 2003 we found through self reporting.

Discontinuous HAART

Long term immunological and virological outcome in continuous versus discontinuous HAART

Luuk Gras

Introduction

While HAART has been shown to suppress HIV replication and improve the immune status in infected patients[100-102], a substantial percentage of patients followed in the ATHENA national observational cohort was unable to sustain the drug combination and stopped HAART because of toxicity[5]. Temporal discontinuation of HAART might be an option to counteract toxicity as part of a treatment strategy[103]. Here, were compare the effect of cumulative time on HAART on mortality, morbidity and immunological and virological outcomes relative to those patients who have been on HAART continuously.

Methods

Study population

Antiretroviral naive HIV-1 infected adult patients with at least three years of follow-up after the initiation of their first HAART regimen were selected. Patients were classified according to the cumulative time on HAART during three years since initiation into 1) continuous HAART for three years, 2) 2-3 years on HAART or 3) 1-2 years on HAART. Additionally, they were stratified according to their baseline CD4 cell count (<200, 200-350 and ≥350 cells/mm^3) and HIV RNA plasma loads (<5000, 5000-55000 and ≥55000 copies/ml). Patients on HAART for less than 1 year (cumulative time) were excluded from this analysis.

Antiviral effectiveness of HAART was determined by comparing the proportion of patients with a viral load <500 copies/ml and the proportion of patients who had experienced virological failure in the three years since commencing HAART. To study the immunological effectiveness of HAART, absolute CD4 cell counts and changes from baseline over the first three years were compared. Time to virological success was defined as the time from start HAART to the first of two consecutive HIV RNA measurements <500 copies/ml. Virological failure was defined as at least two consecutive HIV RNA measurements >500 copies/ml after initial success within the three-year study period after initiation of HAART.

Statistical analysis

Differences in median values of age, CD4 cells or HIV RNA plasma loads were tested using the Wilcoxon Mann-Whitney test. Categorical variables were tested using the χ^2 test. Differences between therapy groups in virological success, mortality and new CDC-C event rates were explored using Kaplan-Meier analyses, log-rank tests and Cox proportional hazards regression, adjusted for confounders such as age, gender, baseline plasma viral load, CD4 cell count and CDC-C event at start of HAART. Logistic regression was used to assess the effect of baseline CD4 and HIV RNA on the probability of experiencing virological failure.

Results

A total of 2429 patients had at least three years of follow-up from start of HAART. Excluded from the analyses were 387 (15.9%) patients from whom no baseline HIV RNA or CD4 measurement was available. Of the remaining 2042 patients, 1452 (71%) had used HAART regimens continuously for three years, 463 (23%) had used HAART for at least 2 years but less than three years and 127 (6%) had been on HAART for at least 1 year but less than 2 years.

Median time on HAART was 19.4 months (IQR 15.6–21.5) for patients using HAART for 1-2 years and 33.3 (29.8–35.0) for patients using HAART for 2-3 years. Most patients interrupted within the first year after start HAART. Median time to the first HAART interruption was 9.1 months (1.9–20.3) for patients using HAART for 2-3 years and was similar for those using HAART for 1-2 years (10.3 months; 3.0–17.0).

Patients on HAART continuously for at least three years were 37 years (IQR 32–44) at initiation, whereas patients 2-3 years on HAART were 36 years (30–44, p=0.02) and patients 1-2 years on HAART were 36 years (29–40.5, p=0.01). Women were more likely to interrupt HAART for a longer period of time. Of those using HAART continuously, 222/1452 (15%) were women. This was a smaller proportion compared to those using HAART for 2-3 years (26%, p<0.0001) or those using HAART for 1-2 years (23%, p=0.05). There were no significant differences in calendar year of HAART initiation.

Table 10.1 shows baseline CD4 cell counts and HIV RNA levels by cumulative time on HAART. Patients using HAART for 1-2 cumulative years had less advanced disease at start of HAART as reflected in a significantly higher proportion of patients with baseline CD4 ≥350 counts/mm^3 (p<0.0001) and a significantly higher proportion of patients with HIV RNA viral load <55,000 copies/ml (p=0.004).

Changes in CD4 cells

Median CD4+ T cell counts for each CD4 stratum and by cumulative time on HAART are shown in Figure 10.1. In patients with <200 CD4 cells/mm^3 and continuous HAART, the median CD4 cell count increased from 70 cells/mm^3 at baseline to 381 cells/mm^3 significantly different from patients 2-3 years on HAART (from 60 to 310 cells/mm^3, p<0.0001) and 1-2 years on HAART (from 60 to 195 cells/mm^3, p<0.0001).

Although median increases in CD4 cells/mm^3 from baseline during the three year period were highest in those with <200 CD4 cell counts/mm^3, similar trends were found in patients with higher baseline CD4. Increases from baseline in median CD4 cell counts after three years were consistently higher in those treated continuously when compared to those on HAART for 2-3 years or 1-2 years (in patients with 200-350 CD4 cells/mm^3 at baseline p<0.0001 and p=0.002, respectively and in those with >350 CD4 cells/mm^3 p=0.33 and p<0.0001, respectively).

In patients continuously on HAART, the median absolute number of CD4 cells/mm^3 at three years was 381 for patients with a baseline CD4 cell count <200, 560 for patients with a baseline CD4 cell count between 200 and 350, and 770/mm^3 for patients with a baseline CD4 cell count ≥350.

Higher baseline viral load was correlated with significantly larger increases in CD4 cell count in continuously HAART-treated patients (median 340 CD4 cell count/mm^3 increase from baseline in those with baseline HIV RNA ≥55000 copies/ml vs. median increase of 196 cell count/mm^3 in those with <5000 copies/ml, p<0.0001).

Changes in plasma HIV-1 RNA

Plasma HIV-1 RNA for all three groups together declined from median 5.0 $\log_{10}$ copies/ml at baseline to nadir viral load <500 copies/ml in 98% of the patients within the three-year study period. At 36 months, 1275 (86%) of the 1476 patients with an HIV-1 RNA measurement had values below 500 copies/ml. HIV RNA values below 500 copies/ml were strongly correlated with time on HAART (Figure 10.2). At 3 years, 95% of those who were continuously treated had HIV RNA values below 500 copies/ml. These percentages were 78% in patients on HAART for 2-3 years (difference with continuously treated patients 16.4%; 95% CI 11.8-21.3) and 54% in those treated for 1-2 years (difference 41.4%; 29.8- 52.7).

Although almost every patient reached plasma viral load levels below 500 copies/ml within the first three years after HAART initiation, patients on discontinuous HAART reached plasma viral load levels below 500 copies/ml considerably slower than patients on continuous HAART (adjusted HR 0.62; 95% CI 0.56-0.69) and 0.41; 0.34-0.51, for those treated with HAART for 2-3 years and 1-2 years, respectively). After three years, 8% of those continuously on HAART had either

not reached plasma viral load <500 copies/ml or had failed after initial virological success. In patients treated 2-3 years and 1-2 years, this was 42% and 67%, respectively (both p<.0001). There were no significant additional effects to cumulative time on HAART of baseline CD4 and viral load on virological failure within the three-year study period.

Time to CDC-C event or death

After the three-year study period, 39 deaths were recorded in the study population. Six years after HAART initiation 2.7% of the patients had died. There were no significant differences in time to death between patients continuous or discontinuous on HAART (log-rank p=0.66). A new CDC-C event was diagnosed within three years in 6% of patients for those on continuous HAART, 13% of those treated for 2-3 years and 12% of those treated for 1-2 years (log-rank p<0.0001 and p=0.03 compared with continuously treated patients). These differences between treatment groups remained when analysing new CDC-C events beyond the first three years following HAART initiation (results not shown).

Resistance

In total, 122 sequences from 98 patients out of 397 patients who failed (25%) were available (34 of 119 failing patients (29%) in the continuous HAART group, 39/193 (20%) in those treated 2-3 years and 25/85 (29%) in those treated 1-2 years). 26/34 (75%) patients in the continuous HAART group had at least one sequence with resistant mutations to at least one antiretroviral drug class. This percentage was 23/39 (59%) in patients treated with HAART for 2-3 years and 8/25 (32%) in those treated for 1-2 years.

Discussion

We found less immunological improvement in discontinuously HAART treated patients as compared to continuously HAART treated patients. This may explain the higher incidence of CDC-C events found in the discontinuously treated group. Our finding that the majority of patients continued HAART for at least 3 years after initiation is of importance, since the use of HAART is known to correlate strongly with the effective suppression of HIV replication[104-106] and mortality[5,107].

At virological failure, resistance to antiretroviral drugs was found in 75% of patients who were on HAART continuously. This percentage was lower in patients using HAART discontinuously, which indicates that other causes than resistance may play a role. One reason could be poor adherence because of toxicity. Bangsberg and colleagues showed higher resistance levels in patients with almost perfect adherence compared with patients with poor adherence[108]. However, data on adherence are not yet available in the cohort.

A larger increase in CD4 cell counts was found in patients who were on HAART continuously than in patients who were treated discontinuously. However, the absolute number of CD4 cells at the end of the three-year study period was largely determined by baseline CD4 cell count. Although the median increase in CD4 count between start of HAART and at three years was higher in those with lower baseline CD4 cell counts, absolute numbers of CD4 cells after 3 years continuous HAART remained significantly different between baseline CD4 strata.

Recent publications suggest that it might be beneficial to initiate HAART sooner rather than later[104,109]. Restoration of CD4 cell numbers might take a long time in patients with low baseline CD4 cells, if this is feasible at all. In addition to comparing median CD4 cell changes between groups, we recommend to model the slope of the change in CD4 cells for individual patients in future analyses.

We found no differences in mortality between the continuously or discontinuously HAART treated groups. One possible explanation, apart from the small number of deaths, would be the effect of exclusion of patients with less than three years of follow-up after commencing HAART as patients who died or were lost to follow-up within the three-year study period may have been more likely to have used HAART discontinuously.

In conclusion, the level of virological suppression and immunological improvement after three years continuous HAART was better than discontinuous HAART. It is therefore of importance to provide individual patients with a HAART regimen that they are likely to be able to sustain without interruption and therefore might be more effective.

		CD4 cell counts/mm^3 at baseline							
		<200		200-350		≥350		Total	
		N	%	N	%	N	%	N	%
Total		955	46.7	530	26.0	557	27.3	2042	100.0
Time on HAART	Baseline HIV RNA copies/ml								
Continuous HAART	<5000	29	2.0	26	1.8	33	2.3	88	6.1
	5000-55000	133	9.2	133	9.2	168	11.6	434	29.9
	>=55000	538	37.1	218	15.0	174	12.0	930	64.0
	Total	700	48.2	377	26.0	375	25.8	1452	71.1
2-3 years HAART	<5000	12	2.6	17	3.7	9	1.9	38	8.2
	5000-55000	48	10.4	42	9.1	51	11.0	141	30.5
	>=55000	154	33.3	61	13.2	69	14.9	284	61.3
	Total	214	46.2	120	25.9	129	27.9	463	22.7
1-2 year HAART	<5000	4	3.1	7	5.5	3	2.4	14	11.0
	5000-55000	3	2.4	9	7.1	36	28.3	48	37.8
	>=55000	34	26.8	17	13.4	14	11.0	65	51.2
	Total	41	32.3	33	26.0	53	41.7	127	6.2

Table 10.1: Time on HAART during first three years after HAART initiation and baseline CD4 and HIV RNA measurements.

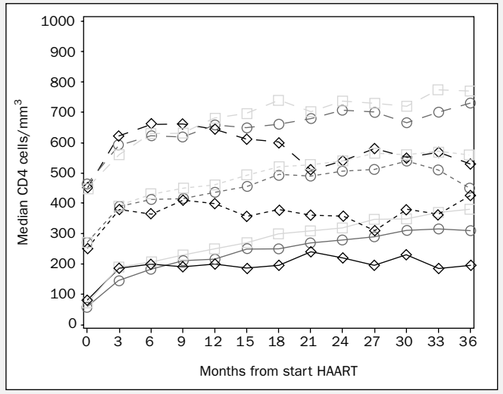


Figure 10.1: Median CD4 cell counts/mm^3 over time according to cumulative time on HAART (continuously on HAART = squares, 2-3 years on HAART = circles, 1-2 years on HAART = diamonds) and baseline CD4 (solid line = less than 200 CD4 cell count/mm^3, dotted line = 200 – 350 counts/mm^3 and dashed line = more than 350 counts/mm^3).

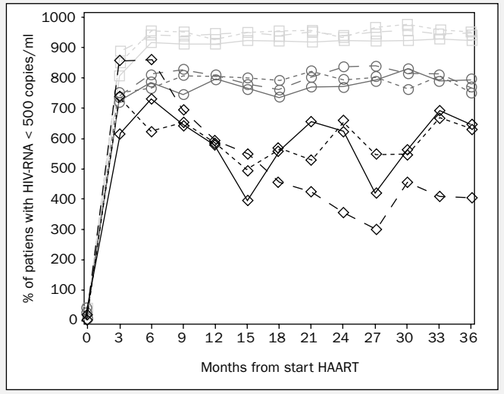


Figure 10.2: Percentage of patients with HIV RNA <500 copies/ml over time according to cumulative time on HAART (continuously on HAART = squares, 2-3 years on HAART = circles, 1-2 years on HAART = diamonds) and baseline CD4 (solid line = less than 200 CD4 cell count/mm^3, dotted line = 200 – 350 counts/mm^3 and dashed line = more than 350 counts/mm^3).

Therapy interruptions

Effect of therapy interruption on the clinical success of HAART

Irene van Valkengoed

Introduction

HAART has led to a decline in morbidity and mortality amongst HIV infected patients[110,111]. In most patients, a decline of HIV RNA levels in plasma and an increase in CD4 cell number are observed shortly after commencing HAART[112-115]. These changes in HIV RNA level and CD4 cell count are directly related to clinical outcome[2,116,117].

Despite the clear benefits associated with HAART, a previous study among patients in the ATHENA national observational cohort found that approximately 10% of the population that initiated HAART was off therapy at any time[5]. Patients may interrupt HAART for a variety of reasons[118]. Firstly, interruption may be prompted by the occurrence of an adverse event or toxicity of the drugs[119,120]. Secondly, therapy may be interrupted due to immunological or virological failure of the current drug combination. Rather than switching to a different combination of drugs, patients may stay off therapy for a certain time in an attempt to preserve remaining treatment options or to enhance the effectiveness of a salvage regimen[121]. Moreover, interruption may occur at the request of the patient. Strict dosing protocols and side-effects of therapy may have a negative impact on the quality of life, particularly in naïve patients starting HAART[122], in the long term leading to a desire to temporarily take a break from therapy, a so called 'drug holiday'.

Several immediate effects of interruption of HAART have been documented. Most patients experience a viral rebound shortly after interrupting treatment, in some instances leading to a viral rebound syndrome[123-125]. In addition, in many patients a rapid loss of CD4 cell counts gained while on HAART was found[106,126]. Nevertheless, several studies reported interruptions to be clinically safe[127,128], especially when CD4 cell counts were high and plasma viral load levels were undetectable at start of the interruption.

A study among patients of the Swiss cohort found no negative effect of occasional interruptions of less than three months duration on morbidity and mortality, although a decreased likelihood of a CD4 cell count increase was reported[129]. In contrast, several other studies have shown the long-term success, both in terms of morbidity and mortality, of discontinuous HAART to be less than continuous HAART[5,130]. However, these studies looked mainly at instantaneous association of HAART interruption with mortality[5], rather than the possible long term consequence of interrupted treatment (i.e. even after HAART is reinitiated). None of these studies were able to determine whether the effect of such interruptions depended on the characteristics of the interruption itself or the particular reason(s) patients may have had for interrupting therapy.

We aimed to study determinants of the duration of interruption of HAART and the association with the reason for stopping therapy. In addition, we sought to determine which factors contributed to the time to (re-)suppression of the virus among patients who had interrupted HAART. Finally, we examined the effects of interruption of HAART on disease progression, as reflected by the course of the CD4 cell count and HIV RNA plasma levels over time and the occurrence of new AIDS events and mortality.

Methods

Study population

Data of 3337 patients, older than 18 years at diagnosis, from the ATHENA national observational cohort were analysed. Patients were only included in the study if they had initiated HAART between 01 January 1997 and 31 July 2003, were therapy naive at start of HAART and had not participated in any drug trials evaluating new treatment strategies. Patients who had been infected through intravenous drug use and patients who had a follow up of less than 365 days after start of HAART were excluded from the analyses.

Data and definitions

The date of HAART initiation was defined as the first date on which a patient started on a combination of at least 3 antiretroviral drugs from at least two different classes or a combination of three nucleoside reverse transcriptase inhibitors (NRTI).

HIV-1 RNA concentration in plasma was measured in each of the participating HIV treatment centres using one of the commercially available quantitative tests. For analysis, a cut-off of 500 HIV RNA copies/ml was used. Absolute numbers of CD4+ T cells were determined using immunofluorescence techniques and flow cytometry. Unless otherwise stated, HIV RNA measurements are reported in $\log_{10}$ copies/ml and CD4+ T cell counts (CD4 count) in cells/mm^3. Baseline values were those measured closest to the time of start of HAART, within 182 days prior to initiation. Cases were defined as patients who had experienced a period of more than 7 subsequent days during which, for whatever reason, no antiviral drugs were taken. Although some patients may have interrupted therapy more than once, only the first interruption was taken into consideration. Disease progression to AIDS (AIDS event) was scored using the Centers of Disease Control classification[131].

Selection of controls: matching procedure

First, determinants of time to interruption of therapy were analysed by means of Cox proportional hazards model, with a stepwise selection of determinants. Only baseline characteristics were taken into account to enable the study of differences between patients who interrupted and patients on continuous HAART in the clinical course of infection over time. Variables considered for this analysis were sex, age, region of origin, time since diagnosis, HIV treatment centre, transmission group, year of start HAART, composition of first HAART regimen, AIDS event prior to start of HAART, baseline CD4 count and log baseline viral load. In addition, various interaction terms were considered.

Subsequently, we calculated a hazard score for each individual patient using the betas obtained from the proportional hazards model as follows[132-134]: Hazard score= var_1*$beta_1$ + var_2*$beta_2$ + …var_k*$beta_k$.

Patients were then stratified into 10 groups based on the 10th-90th percentiles of the calculated hazard score. Weighted dissimilarity scores for each case versus all potential controls within the same stratum as the case were calculated based on the strongest predictors of time to interruption of therapy. Determinants to be included in the dissimilarity score were selected via a 'best subset option' within the Cox proportional hazard's model (PHREG procedure). The dissimilarity score was calculated according to the method suggested by Kaufman and Rousseeuw[135]. Sub-scores for various types of variables were weighted according to the number of variables that contributed to the dissimilarity sub-score. If a sub-score was missing a penalty of 1 point was added to the final score to ensure that matching was, in principle, based on the most complete scores.

Finally, cases were selected in random order and then matched to a control with smallest dissimilarity within the same stratum (i.e. the most similar with regard to the strongest determinants of interruption). This process was continued until no more matches could be made. All successfully matched case-referent pairs were included in subsequent analyses.

Statistical analysis

Characteristics of the total study population and of selected cases and controls at start of HAART are presented. Continuous variables, where necessary, were categorized according to percentiles. For continuous variables, the median and inter-quartile range (IQR) or mean and standard deviation were calculated. For categorical variables, the percentage of the total was calculated. Chi-square tests, t-tests or Wilcoxon tests were used where appropriate to test the baseline differences between groups. Plots were made of the median and inter-quartile CD4 count range and the proportion of patients with a HIV RNA level <500 copies/ml over time in both groups.

Determinants of the time to the various endpoints were assessed using Cox proportional hazards models. The discrete method for handling of tied values was used. Patients were censored at the date of last contact or follow-up, or date of death (if appropriate). The analysis of the outcomes after reinitiating HAART was restricted to patients who had at least one follow-up visit after reinitiating therapy.

Outcomes considered among cases only were time to reinitiating therapy and time to suppression of the HIV RNA concentration to <500 copies/ml plasma after reinitiating HAART. Outcomes considered for both cases and controls were time to a new AIDS event and time to death. No distinction was made between HIV related and non-HIV related death.

Variables taken into account as potential determinants/confounders in the analysis of all endpoints were: gender, risk group, region of origin, age at start of HAART, year of start HAART, CD4 count at start of HAART, HIV RNA plasma level at start of HAART and CDC-C event before start of HAART. In addition, in all analyses concerning duration and effect of the interruption, the reason recorded for the interruption, the HIV RNA level at start of the interruption and the duration of treatment prior to the interruption were evaluated. For the analysis of time to HIV RNA <500 copies/ml, the duration of the interruption was taken into account. In the analyses of morbidity and mortality the CD4 count and HIV RNA level while on HAART, as well as the occurrence of a new AIDS event (analysis of mortality only) were considered as time-dependent factors.

All analyses were performed using the SAS software for Windows, version 8.02 (SAS Institute Inc, USA).

Results

Characteristics

In total, 936 (28.1%) patients in the study group ever interrupted HAART for more than 7 days. Time to interruption of HAART was dependent on gender, region of origin, treatment centre, time between diagnosis and initiation of HAART, year of start HAART, first-line HAART regimen, CD4 count at start HAART, HIV RNA level at start HAART, and AIDS event prior to start HAART (data not shown). After stratification of the population based on the hazard score, an eight-fold difference could be observed between the lowest and highest risk strata in the probability of stopping therapy: 8.4% in lowest stratum to 64.9% in highest stratum. In total, 837 patients (89.4%) who interrupted could be matched to a suitable control. The remaining 99 cases (10.6%) could not be matched, as the number of potential controls in the corresponding (highest) stratum was too limited.

Characteristics of the cases and controls prior to and after the matching procedure are presented in Table 11.1. Prior to matching, significant differences were observed in baseline characteristics between patients who interrupted and potential controls. After matching, no significant differences were found between selected cases and controls, with the exception of age at start of HAART, year of start of HAART and specific HAART components. A higher proportion of patients who interrupted had started HAART prior to or in the year 1998 (37.6% vs. 23.3%) and, consequently, on a protease inhibitor containing regimen (68.5% vs. 61.5%). Of all patients in the final study population, 69.6% were male, 48.7% were of Dutch origin and 87.1% had been infected via sexual contact. The median duration of follow-up in all patients after start of HAART was 46.9 months (range: 12.1-90.9 months).

Interruptions

Patients who interrupted therapy had been on HAART for an average of 10.0 months (IQR: 2.3–24.5) prior to the interruption. During that time, 59.5% had remained on their first regimen, 19.5% had switched therapy once and 21.0% more than once. At interruption, 403 of the 679 (59.4%) of the patients with at least one measurement between start of HAART and interruption had an HIV RNA level below 500 copies/ml.

In total, 679 of the 837 who interrupted HAART reinitiated treatment during follow-up. The main reasons recorded for interruption were toxicity (47.0%), interruption at the request of the patient (22.4%) and therapy failure (5.9%). Other reasons recorded varied from simply running out of pills to hospital admission.

The median duration of the interruption was 3.4 months (IQR: 1.1–13.4). Several determinants of duration of the interruption were identified (Table 11.2). Patients who interrupted at their own request were less likely to reinitiate HAART than patients who interrupted due to toxicity (HR=0.64, CI: 0.52-0.79) Furthermore, patients younger than 25 years (<25 years vs. ≥46 years, HR=0.60, CI: 0.44-0.83) and patients with higher CD4 counts at start of HAART (CD4 count <50 vs. ≥500, HR=2.5, CI=11.6-3.9) and during HAART remained off therapy longer than older patients and patients with lower CD4 counts. Other determinants of a longer duration of the interruption were a low HIV RNA concentration at start of HAART, no prior AIDS event and HIV RNA levels <500 copies/ml within a month on initial HAART (Table 11.2). Finally, patients who interrupted HAART while on their third or later regimen remained off therapy longer than patients who interrupted while on their first regimen (first regimen vs. third regimen or higher, HR=1.3, CI: 1.1-1.6).

Of the 679 patients who reinitiated HAART, 182 (26.8%) continued the regimen used prior to the interruption. Reinitiating the same regimen was associated with the reason recorded for the interruption: 17.2% of patients who interrupted due to toxicity vs. 40.1% of patients who interrupted at their own request vs. 10.0% of patients who interrupted due to failure vs. 41.4% among those with other reasons (p<0.0001). Viral load measurements were available after reinitiating HAART for 664 (97.8%) of the patients who reinitiated.

Within 6 months, 73.5% of these 664 patients had reached a HIV RNA level <500 copies/ml, increasing to 81.2% after 12 months. In total, 607 patients had HIV RNA levels <500 copies/ml during the remainder of their follow-up, with a median time to below 500 of 2.7 months (IQR: 1.2–6.9). Determinants of a longer time to HIV RNA level <500 copies/ml were initiation of HAART prior to or in 1998 (≤1998 vs. ≥2002, HR=0.52, CI: 0.38-0.70), lower CD4 count at start HAART, HIV RNA level >500 copies/ml at interruption and heterosexual transmission (Table 11.3). In addition to these determinants, reinitiating the same regimen as

before interruption (HR=0.83, CI: 0.69-1.0), shorter duration of HAART use and an average duration of the interruption (between 3-12 months) were associated with the time to HIV RNA level <500 copies/ml as well.

CD4 count and plasma viral load

Figure 11.1.A shows the median CD4 count over time in both groups. The median CD4 count at start of HAART was 230 cells/mm^3 (IQR: 79–370) among those who had ever interrupted therapy and 220 cells/mm^3 (IQR: 80–350) among those on continuous HAART. At 24 months, the CD4 counts had risen to 420 cells/mm^3 (IQR: 270–590) and 450 cells/mm^3 (IQR: 310–620), respectively. Figure 11.1.B represents the proportion of patients over time that achieved HIV RNA levels <500 copies per ml. The proportion of patients with a level <500 copies/ml at 24 months was 95.4% for continuous HAART and 68.4% for interrupted HAART. Both remained at that level until 48 months (Figure 11.1.B).

Disease progression

In total, 216 patients were diagnosed with a new AIDS event during follow up. Furthermore, 50 patients died, of whom 34 (68%) had ever interrupted HAART. Patients who interrupted therapy had a higher hazard of disease progression than those who remained on therapy continuously (Table 11.4). The hazard of a new AIDS event was 2.7 (CI: 1.7-4.5) times higher among patients who were off therapy, i.e. during the interruption, than among patients who were on continuous HAART. This effect remained even after reinitiating HAART (reinitiated vs. continuous, HR=3.2, CI: 2.2-4.5). Other factors that affected the hazard of a new AIDS event were having had an AIDS event prior to start of HAART, and the course of the HIV RNA plasma concentration and CD4 count while on HAART.

Analogously, patients who interrupted HAART had a higher hazard of death. After adjustment for CD4 count on HAART, occurrence of a new AIDS event and region of origin of the patient, the hazard ratio for interrupted HAART vs. continued HAART was 7.3 (CI: 3.2-16.5). Patients who reinitiated HAART after an interruption, although not statistically significant, still had a 1.6 times higher hazard of dying (CI: 0.85-3.3) than patients who had remained on HAART continuously.

Discussion

Therapy interruptions

Temporal interruption of HAART was a common phenomenon among patients who initiated therapy without prior anti-retroviral treatment. In the ATHENA-HFM national observational cohort, the main reasons recorded for interruption of HAART were drug-associated toxicity and the patient's request. This suggests that, besides side-effects of treatment, long-term adherence to the strict dosing protocols may play an important part in the decision to temporarily interrupt HAART, although several studies have shown that interruption of treatment does not significantly improve the quality of life[122,136]. In general, those who interrupted therapy had started HAART earlier than patients who had never interrupted.

Regardless of the reason(s) for interruption, 81% of patients re-suppressed HIV replication as has been shown by the HIV RNA plasma levels decreasing to below 500 copies/ml within a year of reinitiating HAART, the time to virological success being shorter among persons with a higher CD4 count and suppressed viral replication at interruption. This is in concordance with the finding of others that interruptions may not pose a direct threat, i.e. lead to acute progression, among patients whose CD4 counts are high and whose viral load remains low while on HAART[127,128]. Previous studies have shown that switches or interruptions for reasons of immediate side-effects, which in this study were found to be shorter than interruptions for other reasons, occur relatively soon after initiation of a regimen[118,119]. Although the reason for interruption was not directly associated with therapy success after reinitiating in our study, the higher rate of success among patients who experienced an interruption of less than one month and among patients who had interrupted after a relatively short episode of HAART does suggest a link with drug-related toxicity.

With regard to the long-term outcome of therapy, we found that interruption of therapy was associated with a lower level of therapy success and a greater likelihood of an adverse therapy outcome. Not only was the proportion of patients with a continuously low viral load smaller in the group who interrupted HAART, but also there was less increase of CD4 cells among patients who had interrupted HAART. Furthermore, we found that interruptions were associated with an increased risk of a new AIDS diagnosis and a greater hazard of death, independent of the CD4 count and HIV RNA plasma concentration after initiation of HAART. These results are in line with previous findings that discontinuous use of HAART leads a to poorer long-term recovery of CD4 cells and higher hazard of disease progression[5,130,137].

The questions remains whether the inferior prognosis of patients who interrupt HAART is indeed the result of the interruption, as it has been described that many patients interrupt therapy prior to death[5]. This would imply that interruption among these patients is a result of the bad prognosis rather than the other way around. In the analyses presented in this paper, we accounted for this by not merely looking at HAART interruption as a time dependent dichotomous determinant, scored as "no" prior to interruption and "yes" immediately after, but by distinguishing between the time off therapy and the time after reinitiating. It was shown that even after reinitiating HAART, patients who had interrupted therapy still had an increased hazard for an adverse outcome when compared to patients who had been on HAART continuously.

Limitations

Several limitations of the analyses presented in this chapter must be mentioned. Firstly, the main analyses did not account for the differences in follow up frequency, which may be closely related to the health status of the patient[138].

Secondly, in the Cox proportional hazards models the assumption is made that drop-out and censoring are neither selective nor informative. This may not always be the case as, for example, drop-out may be associated with a poorer prognosis, e.g. if patients dropped out because they were in such poor physical condition that they could no longer attend scheduled appointments.

Thirdly, in our study we attempted to rule out confounding by using a matching procedure based on the propensity score matching as suggested by Rosenbaum et al[132-134]. Cases and controls were matched based on the hazard of interrupting therapy; matching in a large part eliminated measured differences in baseline characteristics. The limitation of this method, however, is the inability to correct for unmeasured factors[133]. In addition, especially since we accounted for baseline factors only, the method does not consider changes in (unmeasured) determinants over time that may be associated with both the likelihood of interruption and the risk of at the same time simultaneous disease progression.

Moreover, differences in treatment history of the patients were not considered in the analyses although

baseline comparisons showed a difference in the components of the initial HAART regimen, which in turn will have an effect on the options for future drug combinations. In the multivariable analyses, however, including components of initial HAART (at a regimen level and by drug class) had no effect on the outcome. While this is an interesting area for future research, we believe that not accounting for potential differences in effectiveness of different HAART regimens had a negligible effect on our conclusions.

Lastly, we only took the first interruption of HAART into account despite the fact that some patients may have interrupted therapy more than once. The association found might therefore in part be due to multiple interruptions rather than the initial one. However, since only a small number of patients in our study (n=55 (6.6%)) interrupted HAART more than once, this not likely to have had a significant impact on our findings.

Conclusion

Therapy interruptions were associated with a less favourable treatment outcome. After reinitiating HAART, 19% of the patients who had interrupted therapy did not manage to adequately suppress virus production within the next 12 months. Moreover, the level of therapy success among those who interrupted therapy was less than among persons on continuous HAART, i.e.: the proportion of patients with an HIV RNA level <500 copies/ml during the course of treatment was lower, the gain in CD4 cells was lower and the hazard of disease progression was higher among patients who interrupted HAART than among those on continuous HAART. These effects remained apparent even after reinitiating HAART.

		Before			After		
		Stop (n=936)	No stop (n=2401)		Stop (n=837)	No stop (n=837)	
		N(%)/median (IQR)	N(%)/median (IQR)	p	N(%)/median (IQR)	N(%)/median (IQR)	p
Gender	(Male)	591 (63.1)	1922 (80.0)	<0.0001	570 (68.1)	595 (71.1)	0.18
Age at start HAART	(years)	34 (28-41)	37 (31-44)	<0.0001	35 (29-42)	36 (30-44)	0.05
Risk group	MSM	396 (44.0)	1282 (54.1)	<0.0001	384 (47.5)	410 (50.1)	0.63
	Heterosexual	410 (45.5)	857 (36.2)		339 (41.9)	325 (39.7)	
	Other	17 (1.9)	30 (1.3)		15 (1.9)	11 (1.3)	
	Unknown	78 (8.7)	200 (71.9)		71 (8.8)	72 (8.8)	
Region of origin	Netherlands	426 (45.5)	1309 (54.5)	0.0008	402 (48.0)	413 (49.3)	0.87
	European	61 (6.5)	175 (7.3)		59 (7.0)	48 (5.7)	
	Sub-Saharan Africa	239 (25.5)	484 (20.2)		196 (23.4)	206 (24.6)	
	Lat. Am.& Car.	136 (14.5)	260 (10.8)		119 (14.2)	118 (14.1)	
	South-East Asia	35 (3.7)	89 (3.7)		32 (3.8)	25 (3.0)	
	Other	34 (3.6)	73 (3.0)		24 (2.9)	21 (2.5)	
	Unknown	5 (0.53)	11 (0.46)		5 (0. 60)	6 (0.72)	
Time between diagnosis	Unknown	9 (0.96)	28 (1.2)	0.02	8 (0.96)	5 (0.60)	0.24
and start HAART	<12 months	621 (66.4)	1718 (71.6)		553 (66.1)	554 (66.2)	
	12-60 months	177 (18.9)	389 (16.2)		151 (18.0)	174 (20.8)	
	>60 months	129 (32.7)	266 (11.1)		125 (14.9)	104 (12.4)	
Year start HAART	1997-1998	339 (36.2)	630 (26.2)	<0.0001	315 (37.6)	220 (26.3)	<0.0001
	1999-2001	451 (48.2)	1138 (47.4)		402 (48.0)	416 (49.7)	
	>2002	146 (15.6)	633 (26.4)		120 (14.3)	201 (24.0)	
Components of	NRT+PI	649 (69.3)	1421 (59.2)	<0.0001	573 (68.5)	517 (61.8)	0.01
initial HAART*	NRT+NNRT	226 (24.2)	814 (33.9)		213 (25.5)	248 (29.6)	
	Other	61 (6.5)	166 (6.9)		51 (6.1)	72 (8.6)	
CD4 at start HAART	N	785	2048	<0.0001	731	785	0.20
	(cells/ mm3)	250 (90-400)	170 (70-292)		230 (79-370)	220 (80-350)	
pVL at start HAART	N	761	2029	<0.0001	718	732	0.41
	(log copies/ml)	4.9 (4.3-5.3)	4.6 (4.1-5.0)		4.9 (4.4-5.4)	5.0 (4.5-5.3)	
CDC-/C event prior to							
start HAART	(yes)	222 (23.7)	663 (27.6)	0.02	210 (25.1)	204 (24.4)	0.73
Hazard score		-1.3 (-1.7- -0.86)	-0.74 (-1.2- -0.17)	<0.0001	-0.84 (-1.3-0.39)	-0.82 (-1.3- -0.40)	0.74

IQR= inter-quartile range, pVL= plasma viral load, MSM= men who have sex with men, CDC=Centers of Disease Control classification,

*** the hazard score was based on individual drug combinations (i.e. regimens)**

Table 11.1: Baseline characteristics of HIV-1 patients who interrupt therapy and patients on continuous HAART before and after matching based on a hazard score and dissimilarity score.

		HR Adjusted	95%-CI
Age at start	≤25	0.60	0.44-0.83
HAART (years)	26-35	0.97	0.79-1.2
	36-45	0.90	0.72-1.1
	≥46	1.0	-
CDC-C event prior		1.3	1.1-1.6
to start HAART	(yes)		
CD4 count at start	Missing	1.5	0.99-2.2
HAART (cells per mm^3)	<50	2.5	11.6-3.9
	51-200	2.1	1.4-3.1
	201-350	1.7	1.1-2.4
	351-500	1.2	0.82-1.8
	≥ 500	1.0	-
pVL at start HAART	Unknown	0.93	0.73-1.2
(log copies per ml)	≤100,000	0.83	0.69-1.0
	>100,000	1.0	-
Time to pVL <500	Unknown	1.1	0.82-1.4
copies/ml on first	≤1	1.1	0.86-1.5
regimen (months)	>1	1.3	1.0-1.6
	Not <500	1.0	-
Number of regimens	One	1.3	1.1-1.6
prior to interruption	Two	1.2	0.92-1.5
	≥ Third regimen	1.0	-
Reason for interruption	Toxicity	1.0	-
	Patient's request	0.64	0.52-0.79
	Failure	0.82	0.59-1.2
	Other	0.69	0.56-0.86
	Unknown	0.52	0.36-0.74
CD4 count in cells/mm^3#	Unknown	1.1	0.82-1.5
	<50	1.9	1.3-2.8
	50-200	1.7	1.2-2.4
	200-350	1.4	1.1-1.9
	350-500	1.2	0.88-1.6
	≥500 1.9	1.0	-

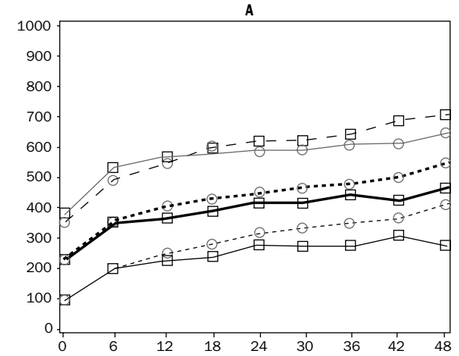
HR= hazard ratio, CI= confidence interval, pVL= plasma viral load, CDC= Centers of Disease Control classification, # time-dependent variable

Table 11.2: Determinants of time to reinitiation of HAART among naïve patients who interrupted HAART (n=837).

		HR Adjusted	95%-CI
Risk group	MSM	1.0	-
	Heterosexual	0.83	0.70-0.99
	Other	1.6	0.80-3.1
	Unknown	0.84	0.64-1.1
Year start HAART	1997-1998	0.52	0.38-0.70
	1999-2001	0.72	0.55-0.95
	≥2002	1.0	-
Duration of HAART use	≤3	0.78	0.61-1.0
(months)	3-12	0.64	0.48-0.84
	12-30	0.91	0.67-1.2
	>30	1.0	-
pVL<500 copies/ml	Unknown	0.44	0.33-0.58
at interruption	Yes	1.0	-
	No	0.55	0.45-0.68
Duration of interruption	0-1	0.96	0.72-1.3
(months)	1-3	0.78	0.60-1.0
	3-12	0.77	0.59-1.0
	≥12	1.0	-
Reinitiation of			
same regimen	(yes)	0.83	0.69-1.0

HR= hazard ratio, CI= confidence interval, pVL= plasma viral load, MSM= men who have sex with men

Table 11.3: Determinants of time to pVL <500 copies/ml plasma after reinitiation among naïve patients who temporarily interrupted HAART (n=664).



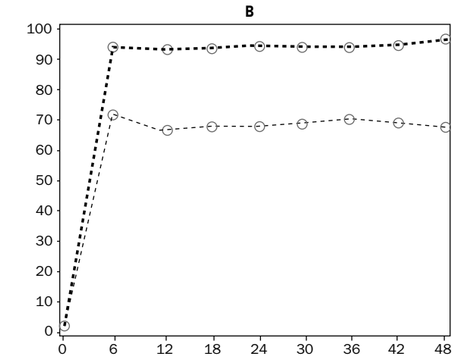


Figure 11.3: Median CD4 count (A: dotted: interrupted HAART, dashed: continuous HAART) and proportion of patients with a viral load (500 copies/ml (B: thin: interrupted HAART, bold: continuous HAART) over time.

		New AIDS event		Death	
		HR Adjusted	95%-CI	HR Adjusted	95%-CI
AIDS events prior					
to start HAART	(yes)	1.3	1.0-1.8	-	-
Region of origin	(Netherlands)	-	-	3.3	1.6-6.7
Age at start	≤25	0.40	0.19-0.86	0.48	0.11-2.2
HAART (years)	26-35	0.94	0.65-1.4	0.46	0.22-0.99
	36-45	0.91	0.62-1.3	0.69	0.35-1.4
	≥46	1.0	-	1.0	-
Interruption#	None	1.0	-	1.0	-
	Off therapy	2.7	1.7-4.5	7.3	3.2-16.5
	Reinitiated HAART	3.2	2.2-4.5	1.0 1.7	0.85-3.3
pVL >100,000	Unknown	3.0	2.0-4.6	-	-
copies/ml#	≤100,000	1.0	-		
	>100,000	2.1	1.4-3.0		
New AIDS event#		Na	na	3.0	1.6-5.8
CD4 count in	Unknown	1.6	0.85-3.0	3.0	1.1-8.1
cells/mm^3#	<50	7.7	4.2-14.3	13.1	3.4-50.4
	50-200	3.4	2.0-5.9	5.3	2.0-13.9
	200-350	1.4	0.77-2.5	2.9	1.0-7.9
	350-500	0.75	0.37-1.5	2.0	0.69-5.7
	≥500	1.0	-	1.0	-

HR= hazard ratio, CI= confidence interval, pVL= plasma viral load, MSM= men who have sex with men, # time-dependent variable, na= not applicable

Table 11.4: Determinants of time to a new AIDS diagnosis and death among patients who interrupted therapy (n=837) and patients who on continuous HAART (n=837).

Viral blips

Effects of viral blips among HIV-1 positive patients

Irene van Valkengoed

Introduction

Highly active antiretroviral therapy (HAART) results in an increase of CD4 cell number and a substantial decrease in HIV production in infected patients[112,113,115,139] and is directly related to long-term clinical outcome[2,116,117]. At present, the goal of treatment is therefore to maintain the HIV RNA plasma concentration to below 50 copies/ml[140]. However, depending on the setting 25-40% of the patients experience viral blips, which is commonly defined as a period of low level (transient) vireamia preceded and followed by a period of suppressed viral replication[141-144].

Viral blips are believed to be a result of abrupt virus release from latent reservoirs in combination with ongoing low-level productive infection[145]. The effect of such temporary increases in virus production on the prognosis is still unclear. While some studies have reported an increased risk of virological failure and an association with viral drug resistance among patients who experienced viral blips[144,146,147], others have failed to confirm these findings[142,148,149]. A recent study found that in addition to a possibly increased risk of virological failure, patients with moderate viraemia (400-20000 copies/ml) had a slightly lower increase in CD4 cells in the first year of therapy than patients with suppressed viral replication[150]. However, the risk of disease progression did not differ between both groups.

The objective of the analyses in this study was to describe the occurrence of viral blips in the ATHENA-HMF cohort. Moreover, we sought to determine what the effects of viral blips are on the course of the HIV infection, such as the gain in CD4 counts, the risk of therapy failure and the risk of disease progression.

Methods

Study population

Data of 8452 patients from the ATHENA-HMF national observational cohort were analysed. All patients selected for the present study were HIV-1 seropositive and older than 18 years at diagnosis. Further criteria for inclusion were HAART initiation between 01 January 1997 and 31 July 2004 and a follow-up of ≥ one year after start of HAART. Patients who had not been tested with an assay with a quantification limit of 50 copies/ml (50-assay) or less after start of HAART and did not achieve a plasma viral load of ≤50 copies/ml within 26 weeks after start of HAART were excluded.

Definitions

A viral blip was defined as a single measurement or several measurements between 50-1000 copies/ml preceded by at least two measurements below 50 copies/ml and followed by at least one measurement below 50 copies/ml. The maximum number of days allowed between measurements was 122 days. The date of HAART initiation was defined as the first date a patient started on a combination of at least 3 antiretroviral drugs from at least two classes or a combination of three nucleoside reverse transcriptase inhibitors (NRTI). HIV-1 RNA concentration in plasma was measured in each of the centres using one of the commercially available quantitative assays with a cut-off of 50 copies/ml or lower. Absolute numbers of CD4+ T cells were determined by using immune-fluorescence techniques and flow cytometry. Unless otherwise stated, viral load measurements were reported in $\log_{10}$ copies/ml and CD4+ T cell counts (CD4 count) in cells/mm^3. Baseline values were those measured closest to the time of start of HAART, within the 182 days prior to initiation. Disease progression to AIDS (AIDS event) was scored using the Centers of Disease Control classification[131].

Selection of cases and controls

For the comparative analyses, cases (blip group) were defined as patients who experienced a viral blip, using the criteria for blips as described above. We included all patients who had a follow-up of at least three years and who had been tested with 50-assays since starting HAART. Potential cases were excluded if their viral load measurements exceeded 1000 copies/ml at any time after initial suppression of the viral load within 26 weeks after start of HAART. Potential controls (suppressed group) were identified by selecting patients from the group tested with 50-assays and who, after suppressing their viral load to <50 copies/ml within 26 weeks, had managed to keep their viral load suppressed until 156 weeks after start of HAART.

Statistical analysis

Rate of blips

The overall rate of blips was calculated by dividing the cumulative number of blips by the cumulative person-years of follow-up. In addition, the rate per year of HAART use was calculated by dividing the number of blips per year by the total person-years on HAART in the first to seventh year of HAART use. To study the effect of the follow-up frequency on the recorded rate of blips, we compared the rate in two groups with a different follow-up frequency. One group had an average follow-up frequency of 1.00-3.25 visits per year in the 3 years after start HAART, with a maximum interval of 270 days between visits. This group will be further referred to as group 2, for two visits per year. The other group had an average follow-up frequency of 3.25-4.75 visits per year in the 3 years after start of HAART, with a maximum interval of 135 days between visits (further referred to as group 4).

For these analyses, follow-up was calculated according to two definitions:
1) Follow up after initiation of HAART (follow-up) was defined as the time between the date when a patient was first tested <50 HIV RNA copies/ml plasma after commencing HAART and the date of the last viral load measurement.
2) Follow–up with virus suppression (follow-up <50) was defined as the total duration of suppression of viral replication after start of HAART, starting from the first measurement below 50 copies/ml with a 50-assay and ending at the date of the last measurement below 50 copies/ml.

Comparative analysis

Characteristics at start of therapy of selected cases and controls are presented. Continuous variables, where necessary, were categorized according to percentiles. For continuous variables, the median and inter-quartile range (IQR) or mean and standard deviation were calculated. For categorical variables, the percentage of the total was calculated. Where appropriate, chi-square test, t-test and Wilcoxon tests were used to test univariate differences between groups. Logistic regression analysis was used to compare the patients who had experienced blips to those who had not. Variables considered as determinants in the analyses were gender, risk group, region of origin, age at start of HAART, time between diagnosis and start of HAART, year of start HAART, pre-treatment with non-HAART regimens, components of first-line HAART, CD4 count at start of HAART, HIV RNA level at start of HAART and AIDS diagnosis before start of HAART.

The course of the CD4 cell count in the blip group and in the suppressed group over the first three years of therapy was described. Mixed effects models were used to test whether there were any differences between groups in the absolute and relative change in the CD4 count during the first three years of therapy. Cox proportional hazards models were used to study the long-term course of the infection, i.e. the occurrence of virological failure and new AIDS-defining events after the required period of three years of sustained viral load suppression (with or without occasional blips). The date of censoring for these analyses was the last date of follow-up.

All analyses were performed using the SAS software for Windows, version 8.02 (SAS Institute Inc, USA).

Results

Of the 5998 HIV-1 positive patients who commenced HAART in the specified period, 5035 had a follow-up of at least 1 year after initiation of HAART. Of these patients, 1730 had been tested solely with 50-assays. In addition, 1816 patients had been tested initially with assays with a quantification limit of 400 or 500 copies/ml, but had since been tested with 50-assays for a period of at least one year. In total, 3546 patients with 9348 person-years of follow-up (HIV RNA measured by using 50-assays) after start of HAART were included, of whom 432 (12.2%) ever experienced a viral blip.

Rate of blips

We identified 587 blips during the 9348 person-years of follow-up, translating to an overall rate of 6.3 blips per 100 person-years of follow up (Figure 12.1.A). The rate of blips was 2.9 per 100 person-years in the first year of HAART, followed by a peak in the second year of 7.6 blips per 100 person-years and a subsequent decrease thereafter to 3.5 blips per 100 person-years in year 7 (Figure 12.1.B). Alternatively, the number of viral blips per person-years of cumulative time with HIV RNA plasma levels <50 copies/ml is shown in figure 12.1.B. The calculated rate of blips is higher in all years of HAART use, with a more pronounced peak at 11.7 blips per 100 person-years in year 2 and a stronger decline to 3.8 per 100 person-years in year 7. The overall rate of blips was 9.0 blips per 100 person-years.

Finally, the rate of registered blips depends on the frequency of follow-up. In group 2, with a follow-up frequency of 1-3.25 visits per year (n=910), the rate was 1.1 blips per 100 person-years (1.5 /<50) and 5.3 blips per 100 person-years (6.6/<50) of follow-up in group 4, with 3.25-4.75 visits per year (n=928) (Figure 12.1.A).

Comparative analysis

Of the 1730 patients who had been tested with 50-assays only, 1123 had viral loads <50 copies/ml within 182 days after start of HAART and 401 had a follow-up of three years or longer. Only 297 of these patients did not have a measurement above 1000 copies/ml during that time.

In total, 88 of these 297 patients were identified as experiencing one or more blips. From the same set of patients 165 were identified who maintained their viral load suppressed for the entire period, i.e. until 3 years after start of HAART. Because of the apparent effect of the follow-up frequency on the ability to identify blips, we excluded 31 patients (all controls) as they had less than 10 viral load measurements over the follow-up period of three years after start of HAART. In addition, one patient (case) was excluded due to having only one CD4 count measurement available during follow-up.

Characteristics of both groups at start of HAART are presented in Table 12.1. There were no significant differences in baseline characteristics between patients who experienced blips and patients who maintained a suppressed viral load. The majority of patients was male and had been infected via sexual contact. Most patients had started HAART in the period 1999-2001 without any prior ARV treatment (Table 12.1). The median follow-up time after start of HAART was 205 weeks (3.9 years, IQR: 181–243 weeks) in patients who experienced blips and 205 weeks (3.9 years; IQR: 177–242) in patients who maintained a suppressed viral load.

As expected, due to the inclusion criteria for the analysis, in the control group the proportion of patients with a viral load below 50 copies/ml in week 26 to week 156 was 100%. In the corresponding period, the proportion for the group with blips varied between 86.5% and 95.6%. Figure 12.2 shows the median CD4 cell count (IQR) over time since start of HAART in both groups. The median CD4 cell count at start of HAART was 140 cells/mm^3 (40-310) among patients who experienced blips and 180 cells/mm^3 (70-300) among patients who maintained a suppressed viral load. After 156 weeks on HAART, the CD4 counts had risen to 430 cells/mm_ (315-615) in the group with blips and 410 cells/mm_ (310-580) in the group without blips. There was no significant difference between both groups in the absolute and relative change in CD4 counts over the 156 weeks (3 years) of therapy.

After three years, during the remainder of follow-up of median 49 weeks, 4 patients (3.0%) who had initially maintained a viral load below 50 copies/ml until 156 weeks after start of HAART and 3 patients (3.5%) who experienced blips had a viral rebound, defined by a viral load measurement above 1000 copies/ml. Of these patients, 3 had stopped therapy prior to the rebound. The hazard of experiencing a rebound was equal in both groups (HR= 0.890; 0.199-3.975). Resistance measurements were available of two patients, one in each group, who rebounded while still on HAART. The case had already been treated with combinations containing AZT 3TC d4T and DDI prior to HAART and had been exposed to HAART combinations containing ABC NVP RTV and IDV. At the time of virological failure, 7 mutations were found, corresponding to resistance to NRTIs and 2 to nNRTIs. The patient from the control group had started on a combination of AZT+3TC+NVP without any prior antiretroviral experience. At the time of the rebound, 2 mutations associated with resistance to NRTIs and 2 to nNRTIs were found.

Among the cases (patients who had experienced blips), 8 (9.2%) new AIDS diagnoses occurred. Fifteen (11.2%) of the controls (patients who maintained plasma viral load <50 copies/ml) were diagnosed with AIDS. There was no difference in the hazard of experiencing a new AIDS diagnosis between groups, even when AIDS events prior to start of HAART and baseline CD4 count were taken into account (HR=1.4, CI:0.60-3.4). All patients were still alive at the time of the present analysis.

Discussion

Rates of viral blips

In this study, we found that 12.2% of patients tested with 50-assays ever experienced a viral blip between 50-1000 copies/ml, which is substantially lower than proportions reported in other studies. Other clinical cohorts have found that 25-35% of patients experienced viral blips[141,151,151]. Differences found might be due to different definitions of a viral blip used in the respective studies, the duration of follow-up or the characteristics of the cohort under observation.

The rates of viral blips among patients in the ATHENA cohort varied between 2.9 and 11.9 per 100 person-years of follow-up, depending on the definition of follow-up and the duration of HAART use. The reported rates might be an underestimation of the true rate of viral blips as the detected rate depends strongly on the availability of viral load measurements. In a large proportion of the population, the follow-up frequency may simply have been insufficient to detect a viral blip. A recent study has suggested that the average duration of a blip is approximately one month[152]. This would imply that in order to detect all viral blips within the population, a higher measurement frequency is required than is currently recommended in most clinical situations[140].

Besides an association with the follow up frequency and the duration of HAART use, we did not evaluate determinants for the occurrence of viral blips. Others have suggested a number of plausible causes of the transient increase in viral production. Viral blips have been linked to intercurrent infection[146,147], pharmacological factors[146,147], including interactions with co-medication and variability in the assay. With regard to the latter, Percus et al have shown that the probability distribution and amplitude of viral blips counteract the notion of simple assay variation[153]. Moreover, it has been suggested that viral blips are associated with limited

adherence to therapy[147,151]. Yet, in a recent study by Miller et al. no association was found with the occurrence of transient viraemia[141]. Drug adherence was however assessed via self-report and electronic monitoring with MEMS caps, which may have contributed to socially desirable reporting. Therefore, further research is needed to uncover whether drug levels and adherence, co-infections or interactions with co-medication are associated with the temporary increase in viral load measured in plasma among patients within the ATHENA cohort.

Comparative analysis

In contrast to previous studies[144,146,147,150], we did not find substantial differences in the clinical course of the infection between patients with a sustained viral load suppression and patients who experienced occasional viral blips. We observed a similar increase in the absolute and relative number of CD4 cells over the first three years of HAART therapy, a similar rate of virological failure and a comparable hazard of new AIDS diagnoses.

This lack of difference between the two groups could not be explained by confounding due to differences in the characteristics of the selected patients, as the two groups were very similar with regards to demographic factors and baseline immunological and virological status. One important point to be noted is the relatively small number of events that occurred during follow-up. Future analyses with longer follow-up may reveal more subtle differences in the long-term prognosis between both groups.

Finally, we looked at resistance mutations among patients who had experienced a viral rebound to determine whether, as was suggested previously, low level replication was associated with emergence of resistant virus[144,146,147,150]. Unfortunately, results of resistance measurements in two patients were available from the time of the viral rebound, but not from blood samples taken at baseline. We aim to study the emergence of resistance in more detail in future work.

In summary, rates of viral blips within our cohort of patients treated with HAART varied strongly, depending on the definitions used. Further research is needed to unravel which factors lead to the sudden increase in viral load levels in plasma. In this study, we found no evidence of an inferior prognosis among patients who had viral blips during treatment as compared to patients who maintained a viral load below 50 copies/ml within three years after start of HAART. More long-term data are needed to confirm these findings.

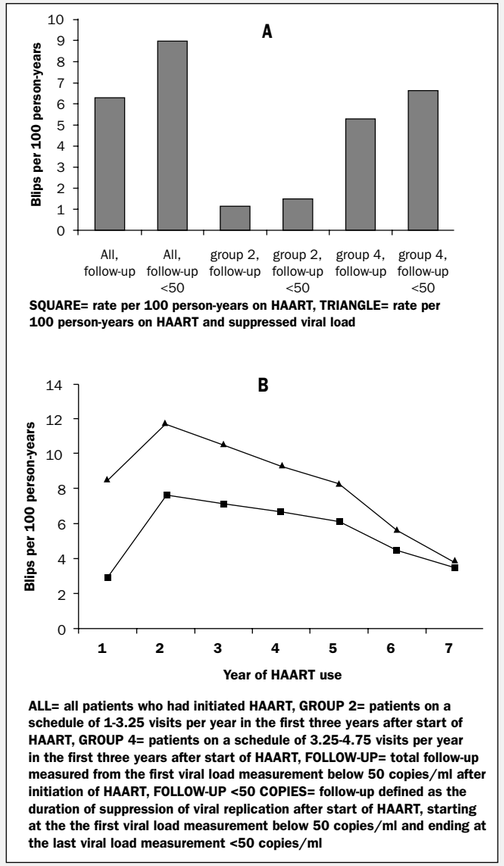


Figure 12.1: Rate of viral blips by frequency of follow-up (A) and rate of viral blips per year of treatment (B)

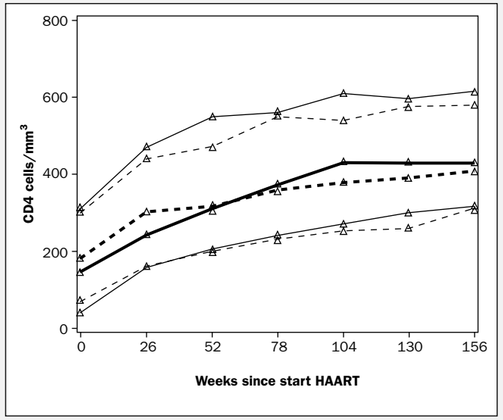


Figure 12.2: Median CD4 count over time among patients who experienced blips after suppression of the viral load to <50 copies/ml (solid line) and patients who remained <50 copies/ml until 3 years after initiation of HAART (dotted line).

Blips after suppression					
		Blips, N=87		Suppressed, N=134	
		N/median	%/IQR	N/median	%/IQR
Gender	(Male)	64	74	112	84
Age at start HAART	(years)	37	30-42	37	31-43
Risk group	MSM	45	52	85	63
	IDU	4	5	4	3
	Heterosexual	30	35	37	28
	Other	7	8	8	6
Region of origin	Netherlands	48	55	76	57
Time between diagnosis and start HAART	≤12 months	58	67	86	65
	12-60 months	13	15	19	14
	>60 months	16	18	28	21
Naive	(yes)	76	87	123	92
Year start HAART	1998	3	3	4	3
	1999	32	36	46	34
	2000	37	43	61	46
	2001	18	21	27	20
CD4 at start HAART	N	78		125	
	(cells/ mm^3)	145	40-310	180	70-300
pVL at start HAART	Undetectable	1	1	3	2
	Detectable	83	99	124	98
	log copies/ml	4.9	4.4-5.2	4.9	4.5-5.3
AIDS diagnosis prior to start HAART	(yes)	29	33	44	33
First HAART regimen	IND+RTV	9	10	20	15
(NRTI backbone: 3TC+AZT)	IND+RTV (D4T)	4	5	8	6
	NVP	24	28	38	28
	NFV	9	10	15	11
	EFV	15	17	15	11
	Other	26	30	38	28

Table 12.1: Baseline characteristics of HIV-1 patients who experience blips after suppression of the viral load to <50 copies/ml and patients who remain <50 copies/ml up to 3 years.

Aids and mortality

Ard van Sighem

Introduction

Treatment of HIV infected patients with HAART slows disease progression and reduces mortality directly attributable to HIV or AIDS[18,110,154,154-156]. However, the incidence of therapy-related and non HIV-related cases of death remains stable over time. This indicates that the adverse effects of HAART are not yet a major cause of death[154,155].

Progression to death and disease outcome are strongly associated with CD4 count and HIV RNA plasma concentration at initiation of HAART[18,21,32]. In a collaborative study, we showed that these predictors are not significantly associated with prognosis, once the initial response to HAART - as reflected in the 6 month CD4 counts and RNA levels - is taken into account[2]. In this chapter, a model will be presented that takes into account patients' initial immunological and virological response to HAART. The model estimates the probability of death for previously antiretroviral therapy naïve patients who have been treated with HAART for at least 24 weeks. It was developed in collaboration with the HIV/AIDS working group of the Dutch Association of Insurers (Verbond van Verzekeraars).

Population and methods

The study population consisted of 7744 HIV-1 infected patients who ever started HAART. All deaths and AIDS cases occurring during follow-up in this population were assessed. AIDS was defined as the first occurrence of a CDC-C event at least four weeks after start of HAART (T_0) as it was assumed that AIDS cases occurring in the first four weeks after initiation of HAART were most likely the result of the patient's condition prior to start of HAART. Follow-up ended at the date of death or AIDS diagnosis. Patients were censored at their last follow-up visit, at closure of the database (31 July 2004) or, for AIDS incidence only, at the time of death, whichever came first. In a separate analysis, the incidence of any CDC-C event after initiation of HAART was studied, allowing for multiple events per patient.

Annual mortality and AIDS incidence were calculated as the number of deaths or AIDS cases per year divided by the total number of person-years of follow-up after initiation of HAART during that year. Poisson's distribution was used to calculate 95% confidence intervals (CI). Significance of changes in mortality over time was subsequently assessed by a χ^2-test.

A subgroup of patients was selected who were antiretroviral therapy naïve at T_0, who had more than 24 weeks of follow-up, had not been infected via intravenous drug-use, and had a viral load and CD4 count measurement at 24 weeks, i.e. between 12 and 36 weeks, after initiation of HAART. In this group, a multivariate hazards model was used to predict the time from 24 weeks after T_0 to death. The hazard of death in this model was calculated as the sum of an expected hazard h_0 and a function containing patient-specific covariates. The expected hazard h_0 depended on the patient's age and gender and was estimated from the annual mortality of the general population in the Netherlands [Actuarial Association, Woerden; 2002, available: http://www.ag-ai.nl.].

Covariates were excluded from the multivariate model via backward elimination if this did not yield a significantly worse model ($p<0.01$, likelihood ratio-test). Wald 95% confidence intervals were calculated for parameters. Interactions between covariates and interactions with time of follow-up were assessed. The standardised mortality ratio (SMR) was defined as the ratio of one-year mortality for HAART-treated patients and one-year mortality for the general population, matched by age and gender. Bootstrapping methods were used to obtain 95% confidence intervals on SMRs.

Results

The total number of AIDS cases registered in the HAART-treated population since 1996 was 879 during 31322 person-years of follow-up, yielding an overall incidence of 2.81 (2.62–3.00) per 100 person-years. The annual AIDS incidence declined dramatically ($p<0.001$) from 15.3 (12.4–18.7) per 100 person-years in 1996 to 1.1 (0.8–1.6) per 100 person-years in 2004 (Figure 13.1a).

In the first year after initiation of HAART, 870 (multiple) CDC-C events were recorded in the HAART-treated population, corresponding with an incidence of 12.2 (11.4–13.0) per 100 person-years. In the second year, the incidence dropped to 3.8 (3.3–4.3) per 100 person-years. In the third and fourth year, the incidence was 3.1 (2.7–3.5), whilst after the fourth year the incidence was 2.6 (2.3–2.9) per 100 person-years. The relative contribution of different CDC-C events to these incidences did not change over time, except for an increase in recurrent pneumonia (3.3% in the first year, 11.7% after four years, $p<0.001$) and esophageal candidiasis (14.0% in the first year, 19.9% after four years, $p=0.008$) along with a decrease in CMV retinitis (6.4% in the first year, 3.9% after four years, $p=0.002$).

Of the 7744 patients initiating HAART, 653 (8.4%) died during 34211 person-years of follow-up. Mortality declined ($p<0.001$) from 4.54 (3.07–6.49) in 1996 to 1.37 (1.08–1.70) per 100 person-years in 2002 (Figure 13.1b). Thereafter, mortality increased slightly by 43% to 1.95 (1.47–2.53) per 100 person-years in 2004. However, this increase was not statistically significant. Between 1996 and 2004, the expected mortality in the age and gender matched general population in the Netherlands rose from 0.21 to 0.32, an annual increase of 7%. Amongst the 5510 patients who initiated HAART without prior exposure to antiretroviral drugs, 268 (4.9%) patients died, yielding an overall mortality of 1.29 (1.14–1.45) per 100 person-years that did not vary with calendar year.

In total, 3520 patients were eligible for inclusion in the survival model, of which 101 (2.9%) died during 11373 person-years from 24 weeks after T_0. The overall mortality was 0.89 (0.72–1.08) per 100 person-years. Figure 13.2 shows that mortality decreased with increasing 24-week CD4 count ($p<0.001$), but still remained higher than in the age and gender matched general Dutch population albeit modestly for CD4 counts exceeding 600×10^6 cells/l. Only log transformed CD4 count (hazard ratio (HR) 0.47; 0.37–0.61, per unit increase) and viral load (HR 0.31; 0.11–0.72, load <100,000 copies/ml versus ≥100,000 copies/ml) measured at 24 weeks were significantly associated with survival. There was no additional effect of age and gender once these were taken into account in the expected hazard h_0.

In total, 570 (16%) patients had a 24-week CD4 count above 600×10^6 cells/l. Of those, 140 (25%) already had a CD4 count above 600×10^6 cells/l at start of HAART, 263 (46%) had CD4 counts between 350 and 600×10^6 cells/l, 103 (18%) between 200 and 350×10^6 cells/l and 17 (3%) below 200×10^6 cells/l at start of HAART. For 47 (8%) patients, CD4 counts at initiation of HAART were unknown. Of the 736 patients with a CD4 count at start of HAART exceeding 350×10^6 cells/l, 403 (55%) had a 24-week CD4 count above 600×10^6 cells/l.

Figure 13.3 show the expected SMR for HIV infected men and women, respectively, as a function of age for various CD4 counts at 24 weeks. The expected SMR in men decreased from 5.3 (3.5–8.4) at 25 years to 1.15 (1.08–1.25) at 65 years. In women, the expected SMR decreased from 10.4 (6.4–17.4) at 25 years to 1.29 (1.16–1.50) at 65 years when CD4 counts were 600×10^6 CD4 cells/l at 24 weeks. For HIV infected patients with 200×10^6 CD4 cells/l at 24 weeks the expected SMRs for men and women ranged from 10.7 (5.6–19.9) and 22.4 (11.9–42.8) for patients 25 years of age to 1.33 (1.17–1.64) and 1.66 (1.33–2.29) for 65 year old patients,

respectively. As a comparison, SMRs are shown for insulin treated diabetes patients.

Discussion

After mortality in the HAART-treated population dropped between 1996 and 2002 there seems to be a rise in mortality thereafter. As yet, the underlying cause of this rise remains unclear. In part, however, it can be explained by the increase in expected mortality reflecting the increasing age of the pre-treated HIV infected population.

In contrast, the annual decline in the incidence of AIDS in the HAART-treated population that has been observed since 1996 is still observed in 2003 and 2004. However, the incidence reported for 2004 might be underestimated, as a backlog in the registration of CDC events cannot be excluded. Compared to our previous report, incidences for 2001 and 2002 increased by 15%, whilst the incidence in 2003 was 81% higher. The incidence of CDC-C events also declined with time after initiation of HAART. The relative contribution of each CDC-C event to the total number of events that were recorded largely remained the same over time.

In the model for progression to death, CD4 counts and HIV RNA plasma levels measured after 24 weeks of HAART are the only strong predictors for progression to death, with lower mortality observed in those with higher CD4 counts. This finding is consistent with recently published results from a large international cohort[2]. Our analyses excluded patients infected via intravenous drug use who usually have a worse prognosis compared to patients infected through sexual contact[28,155,157].

In patients with CD4 counts above 600×10^6 cells/l the mortality was modestly higher than in the age and gender matched general population. However, only a minority of the study population had CD4 counts at 24 weeks above 600×10^6 cells/l. The probability of having a 24-week CD4 count above 600×10^6 cells/l increased with higher CD4 counts at start of HAART[104]. This argues in favour of an early initiation of HAART when CD4 counts are still high[158]. Independent of this, CD4 cell restoration is also related to age with a more complete restoration in younger patients[159,160].

Our study shows that SMRs are higher for women than for men. This is due to the lower annual mortality for women compared to men in the general Dutch population. We emphasise that despite the large difference in SMRs between men and women of the same age, the absolute difference in mortality is small. In addition, the worse prognosis associated with older age that is usually observed[2,155] is, according to our model, fully accounted for by the expected hazard in the non-HIV infected population. In other words, the excess mortality in HAART treated patients relative to the general population is independent of age. It should be noted, however, that the majority of the patients in this study was younger than 45 years of age at 24 weeks after starting HAART. Therefore, the estimation of the SMR at older ages is largely based on extrapolation of results obtained from patients at younger ages.

A proportion of the patients analysed here initiated HAART regimens that are by now obsolete and generally no longer administered. Over time, the composition of first HAART combinations shifted towards regimens without protease inhibitors. Newer regimens are likely to be more potent in terms of their immunological and virological effect, and may also be less toxic and, as a result, easier to adhere to. The current response to HAART is therefore likely to be sustained for a longer time resulting in a better prognosis. Hence, the SMRs are likely to improve further in future.

Although mortality rates in successfully treated HIV infected patients and especially younger patients were still higher than in the general population, they were comparable to those observed in patients with diabetes mellitus[161–163]. Similar patterns were observed in the Swiss HIV Cohort Study, where it was shown that excess mortality amongst successfully treated HIV infected patients is similar to mortality in successfully treated cancer patients[164,165]. As was argued for the Swiss HIV Cohort, our results indicate that, as for many other chronic diseases, insurance for HIV infected patients is possible under specific conditions.

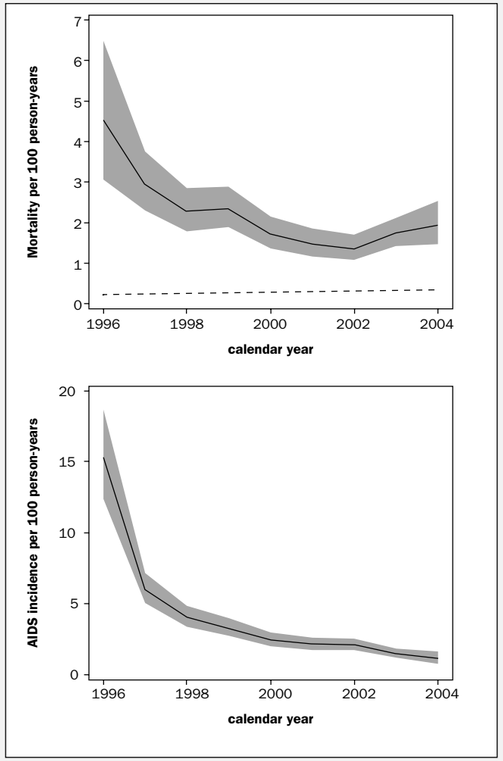


Figure 13.1: Mortality and incidence of AIDS as a function of calendar year. The black line represents the incidence whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality expected in an age and gender matched group from the general Dutch population.

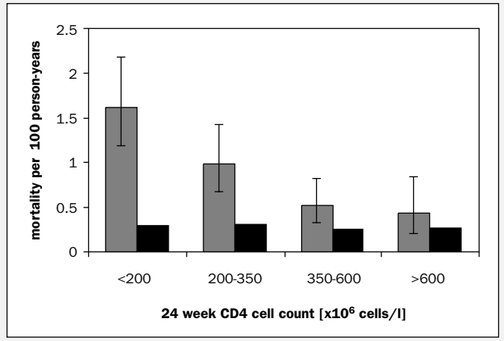


Figure 13.2: Mortality stratified by 24-week CD4 counts with 95% confidence intervals. Grey bars represent overall mortality whilst black bars denote expected mortality in age and gender matched individuals from the general population in the Netherlands.

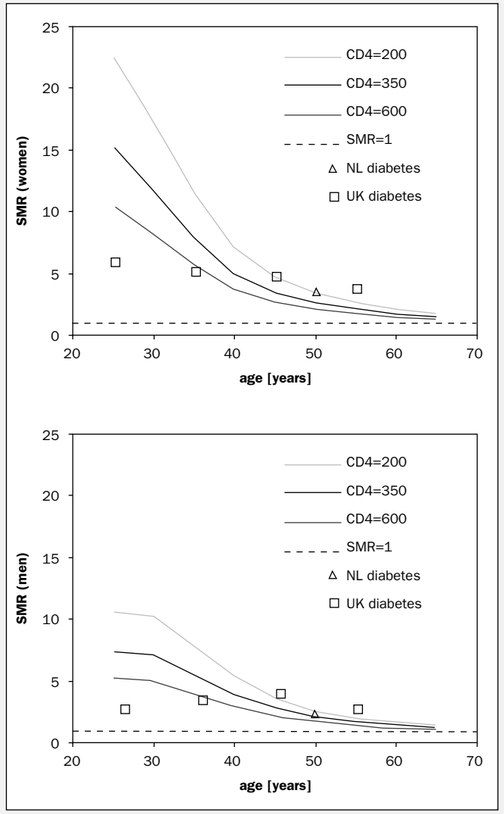


Figure 13.3: Standardised mortality ratio (SMR) as a function of age for HIV infected men and women with 24-week CD4 counts of 600×10^6 cells/l (grey lines), 350×10^6 cells/l and 200×10^6 cells/l. The horizontal dotted lines indicate an SMR of 1. The dots are SMRs for insulin treated diabetes patients from the Netherlands and the United Kingdom.

Resistance

Resistance: Increasing prevalence in the treated population

Ard van Sighem

Introduction

HIV still replicates in patients treated with HAART, albeit at a lower level[166,167]. The strong but not complete suppression of HIV replication achieved with prolonged treatment with HAART, in combination with a non-optimal adherence, might lead to selection of HIV-1 viruses that escape HAART-induced suppression due to resistance. The presence of resistant virus strains limits future therapy options and might lead to a worsened prognosis. The prevalence of resistant virus in patients failing on therapy may be as high as 80%[168-170].

Resistant virus strains might also be transmitted to uninfected patients. In recent years, the prevalence of transmitted drug resistant viruses in newly infected patients varied between 5% and 25% in Europe and the United States[171-178]. Transmission of resistant virus strains was observed in 6% of newly infected participants of the Dutch Amsterdam Cohort Studies after 1998[179].

Resistance to antiretroviral drugs might particularly affect pregnant women. The choice and number of antiretroviral drugs that can be used during pregnancy is limited, given the possible toxic effects of these drugs on the foetus and the mother[180,181]. In addition, if a pregnant woman is in relative good clinical and immunological condition, the first aim of antiretroviral treatment is often at prevention of HIV-transmission from mother to child and not at treatment of the maternal infection. Hence, resistance to one or more drugs in the regimen taken by the mother will increase the risk of infection of the child.

Study population and methods

Resistance measurements were based on isolation of HIV-1 RNA plasma of patients and amplification of the protease and (part of) the RT gene of the virus. Successful amplification was only achieved in patients with a viral load above 1000 copies/ml. HIV-1 RT and protease were genotyped by using the amplified genes in a sequencing procedure. Sequences were obtained in four different virological laboratories: AMC-UvA in Amsterdam (Suzanne Jurriaans, Nicole Back, Lia van der Hoek and Ben Berkhout), EMC-Dijkzigt in Rotterdam (Martin Schutten and Ab Osterhaus), UMCU in Utrecht (Charles Boucher and Rob Schuurman) and LUMC in Leiden (Louis Kroes and Eric Claas).

Sequences were compared to subtype B wild-type virus and scanned for specific mutations at codons known to be associated with drug resistance. Mutations that can occur as natural polymorphisms were excluded, even if they also contribute to resistance when they are present with other resistance associated mutations. Nucleoside RT inhibitor resistance mutations included M41L, E44D, A62V, K65R, D67N, T69D, K70R, L74V, V75T, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, T215D/N/S/C/E (denoted T215X), K219Q and an insertion after position 69. Non-nucleoside RT inhibitor resistance mutations included L100I, K103N, V106A, V108I, Y181C/I, Y188C/L/H, G190S/A, P225H, M230L, P236L. PI resistance mutations that were scanned for included D30N, M46I/L, G48V, I50V, V82A/F/T/S, I84V and L90M. These mutations constitute a canonical set, though some reports included somewhat more or less mutations[172,182,183]. E44D and V118I can also occur as natural polymorphisms. Therefore, we only counted them as resistance associated mutation when they occurred in combination with other nucleoside RT inhibitor resistance related mutations[184].

Transmission of resistant virus strains was studied in the group of patients with either a recent infection or a recent diagnosis. Patients with a recent infection were either diagnosed during acute infection or were tested HIV-1 positive less than two years after their last negative test. All other patients with a known HIV-1 positive test were assigned to the group of recent diagnoses. For both groups, a sequence had to be available within one year after diagnosis and before initiation of antiretroviral treatment. The sequences available from the HMF database were combined with those from the Amsterdam cohort studies (ACS)[179].

Data on viral load measurements were used to define the start and the stop of failures after initiation of antiretroviral treatment. For the present study, failure was defined as at least two consecutive viral load measurements >500 copies/ml. A period of failure started at the midpoint of the interval between the last measurement ≤500 copies/ml and the first one above. Analogously, the period of failure ended at the midpoint of the interval between the last measurement >500 copies/ml and the first one below. It should be noted that this definition of failure did not take into account the use of therapy.

For each calendar year the number of persons failing after initiation of HAART, N_{fail}, and the number of persons in follow-up, N_{total}, in that year were counted. In addition, the total number of person-years of follow-up, PY_{total}, failure, PY_{fail}, and on therapy, $PY_{therapy}$, per year was determined. The number of patients failing whilst on therapy was estimated by reweighing N_{fail} by $PY_{therapy}/PY_{fail}$. In the group of patients failing therapy, we counted the number of sequences obtained per year and the number of sequences with one or more resistance associated mutations. The fraction of patients with a (resistant) sequence was determined by dividing this number by N_{fail}.

Results

Transmission of drug-resistant virus

The group of recently infected patients consisted of 162 individuals (Table 14.1). In 16 (10%) patients resistance associated mutations were found, of which eight were infected in or before 1996. The percentage of resistant virus strains per estimated year of infection dropped from 31% in 1994 to 8% in 1996 and, due to a limited number of recent infections, fluctuated thereafter between 0% and 20% (Figure 14.1). Overall, the percentage was 21% (95% CI: 9–36) in patients infected before or in 1996 and 6.5% (3–12) in patients infected thereafter.

There were no patients with resistance to more than one drug-class. One patient harboured a mixture of wild-type virus and M46I at codon 46 in protease as the only resistance associated mutation. In three patients, mutations conferring resistance to non-nucleoside RT inhibitors were found. One patient harboured a M184V mutation that confers resistance to 3TC[185]. The other 11 patients had one or more mutations associated with resistance to AZT with K70R (4 patients), M41L (4 patients), T215Y/F (3 patients) and T215X (3 patients) the most frequently found mutations[186-188].

In the group of 387 recent diagnoses, resistance was found in 28 (7.2%) patients. The majority of the resistant sequences (20) were obtained in or after 2002. The annual percentage of transmissions of resistant virus strains varied between 0% and 13% (Figure 14.1). In 2003, 11 (out of 161) transmissions of resistant virus were observed, yielding a proportion of 6.8% (95% CI: 3.5–11.9). Amongst homosexual men, 8.9% (21/236) of the newly diagnosed patients were infected with a resistant virus strain, whilst this proportion was 3.4% (4/188) in the population infected via heterosexual contact. Most resistant transmissions were infections with a subtype B virus: 25/290 (8.6%) versus 3/97 (2.3%) for non-B subtypes.

In four patients, mutations associated with resistance to protease inhibitors were found: M46I/L in all four patients and in one of them a L90M mutation. Five patients harboured mutations conferring resistance to nevirapine and efavirenz (K103N: 3 patients; Y181C:

2 patients; G190A: 2 patients)[189,190]. In four other patients the only mutation found was V108I in RT, conferring resistance to nevirapine, but not to efavirenz in the absence of other mutations[191].

In 20 patients, mutations were found conferring resistance to nucleoside RT inhibitors, mainly AZT, d4T and 3TC. In 11 patients, a mutation T215X was found at codon 215, which reflects evolution from a transmitted AZT-resistant virus[192]. Other mutations were the AZT resistance related mutations M41L (10 patients), K219Q (3), D67N (2), T69D (2) and K70R (2). In two patients, the 3TC resistance associated mutation M184V was found.

Resistance to both nucleoside and non-nucleoside RT inhibitors was observed in three of the 28 patients. One patient harboured mutations conferring resistance to all three drug classes.

Resistance during treatment

The fraction of pre-treated patients who failed virologically declined from 59% in 1996 to 38% in 2003 (Figure 14.2). During the same period, the fraction of failures amongst therapy naïve patients increased from 9% in 1996 to 21% in 2003. Correcting for failure due to therapy interruptions yielded fractions of failing patients that were on average 15% lower in pre-treated patients and 38% lower in naïve patients.

In the pre-treated group, the fraction of failing patients in whom a sequence was obtained increased from around 6% in 1996 and 1998 to 20% in 2003. More than 80% of the sequences harboured one or more resistance associated mutations. After 2000, this percentage had increased to more than 90%. In the therapy naïve group, the fraction of failing patients with a sequence increased from a few percent before 1998 to 16% in 2004. In the years after 2000, 60% to 75% of the sequences harboured mutations.

The nature of resistance associated mutations observed per year of sequencing in the population that failed on therapy changed over time. In general, there was a decline in the prevalence of mutations associated with resistance to AZT. Between 1996 and 2003 the prevalence of M41L declined from 59% to 30%, L210W from 45% to 22%, K219Q from 14% to 9% and T215Y/F from 68% to 34%.

In contrast, there was a rise in M184V/I from 48% in 1996 to 65% in 2003. The prevalence of K65R and L74V rose from 0% and 1% to 5% and 10%, respectively. In addition, an increase was observed in non-nucleoside RT inhibitor resistance associated mutations. The prevalence of K103N increased from 0% in 1996 to 24% in 2003, V108I from 1% to 7%, Y181C/I from 1% to 16% and G190S/A from 0% to 13%.

As per July 31, 2004, a total of 8452 patients were still in follow-up. In 888 (10.5%) of these patients, a sequence had been obtained in which resistance associated mutations were found. The cumulative number of patients in whom only one drug class resistance had been found thus far, was 287 (32.3%). Resistance to two drug classes had been found in 401 (45.2%) patients whilst 200 (22.5%) patients turned out to be resistant to all three drug classes.

Pregnant women

In total 534 women were reported as having been pregnant at least once whilst being HIV-1 infected. For 85 (16%) women, the subtype was available. The most prevalent subtypes in this group were B (27 patients, 33%), C (17 patients, 21%), AG (12 patients, 15%) and D (8 patients, 10%). For 22 (4%) of these women, a sequence was available before initiation of therapy. Resistance associated mutations were found in only one of these 22 patients (T251F, Y188L).

In the 85 patients with at least one sequence, the most recent one was selected. Overall, half of these sequences, 43 (51%), harboured one or more resistance associated mutations. In the subgroup of 63 women who had had a sequence after initiation of therapy, resistance was found in 42 (67%) individuals. Resistance to nucleoside RT inhibitors was found in 39 (93%) patients, resistance to non-nucleoside inhibitors in 24 (57%) patients and resistance to protease inhibitors in 13 (31%) patients. Dual drug class resistance was found in 20 (47%) patients, whilst 7 (17%) patients were resistant to all three drug classes.

Discussion

Transmission of drug-resistant HIV-1 virus strains was observed in 6.5% of the recently infected patients who were diagnosed after 1996. Similar percentages were found amongst newly diagnosed patients. This indicates that transmission of resistant virus remains detectable later in the infection[172]. There was no evidence that the frequency of resistant transmissions was changing over time after 1996. The percentages found in this study are comparable with those observed in other European countries[171,193].

Since 2002, it is standard of care in some hospitals to obtain a protease and RT sequence in all newly diagnosed patients. Only since then, the estimates of the percentage of resistant transmissions amongst newly diagnosed patient are accurate. As for patients with a sequence at diagnosis before that time, it is unknown whether the sequence was obtained immediately at diagnosis or retrospectively, e.g., when a therapy regimen failed. Moreover, the number of patients in whom a sequence was obtained at diagnosis was very limited before 2002.

The percentage of transmissions of resistant virus differed between risk groups and was higher in homosexual men than in the heterosexual population. Currently, the Kwaliteitsinstituut voor de Gezondheidszorg CBO is formulating guidelines that will recommend obtaining a sequence at diagnosis only in those populations who have an increased risk of being infected with a resistant virus strain. Whilst this recommendation would reduce the strain put on the available hospital and laboratory resources, it reduces the chances of observing a possible future increase in resistant transmissions in presently low-risk populations.

The fraction of failing patients in whom a sequence was obtained increased over time. Of those patients with a sequence, 65% to more than 90% harboured resistance associated mutations[168-170]. These figures indicate that determining the genotypic resistance profile is becoming an integrated part of routine clinical care for HIV infected patients. Still, the fraction of patients from whom a sequence was obtained in 2003 was only around 20% (or slightly higher when using the therapy corrected number of failing patients), suggesting that the perceived necessity to obtain a sequence was not always pressing.

Our definition of failure does not take into account viral loads that are above 500 copies/ml in the first weeks or months after reinitiating HAART since obtaining a sequence within this period is not a common procedure. In addition, patients might have detectable viral loads because they do not adhere well enough to their drug regimen or do not take their drugs at all. In that case, the chance of developing resistance is low[108].

Presently, 10.5% of the population in follow-up and registered in the HMF database, harbours virus strains that are resistant to one or more drug classes. However, the prevalence of specific resistance associated mutations changed over time. In general, the prevalence of AZT and d4T related mutations declined whilst the prevalence of resistance to 3TC increased. In addition, a rise in the prevalence of K65R and L74V was observed

which confer resistance to abacavir[194]. Moreover, the prevalence of mutations associated with resistance to non-nucleoside RT inhibitors increased. This pattern correlates with the changes in antiretroviral drug use[195]. Initially, only nucleoside analogues were used, whilst after 1996, 3TC became widely used in combination with either AZT or d4T and non-nucleoside RT or protease inhibitors.

Our results suggest that resistance amongst pregnant women is becoming a problem. In about 8% of the pregnant women, resistance associated mutations have been found. The population is, however, too diverse and the number of sequences too limited to draw firm conclusions as yet. Therefore, a study is planned that will assess the development of resistance in pregnant women and the consequence for treatment and transmission to the child.

	recent diagnoses	recent infections
	N=387	N=162
gender, male	306 (79%)	145 (90%)
born in NL	257 (66%)	101 (62%)
transmission category		
homosexual	236 (61%)	92 (57%)
heterosexual	118 (31%)	16 (10%)
IVD	5 (1%)	8 (5%)
other/unknown	28 (7%)	46 (28%)
CD4	256 (90–420)	490 (350–510)
RNA	4.9 (4.4–5.4)	5.0 (4.3–5.4)
age	38.1 (32.0–44.2)	33.8 (31.4–43.4)
non-B subtype	97 (25%)	16 (10%)
resistant	28 (7.2%)	16 (9.9%)

Table 14.1: Characteristics at diagnosis of the newly diagnosed and the recently infected patients.

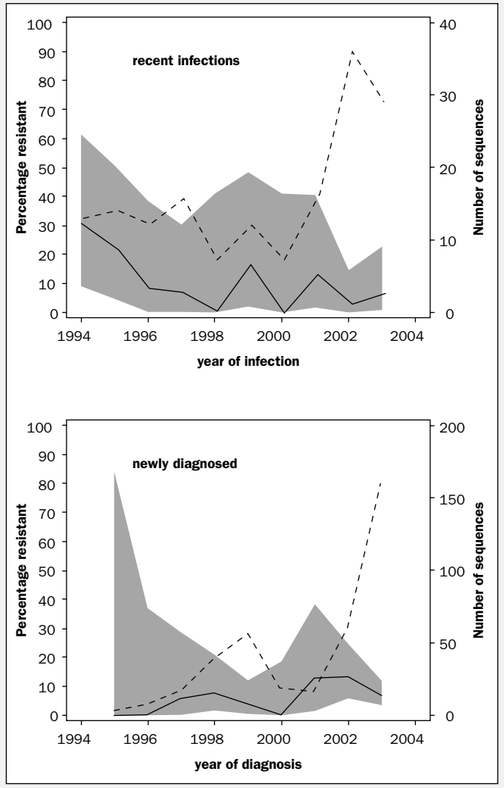


Figure 14.1: Percentage of transmissions of resistant virus as a function of time amongst recently infected and amongst newly diagnosed patients. The black line represents the percentage whilst the grey areas are the 95% confidence intervals. The dotted line is the number of sequences that was obtained in each year (right axis).

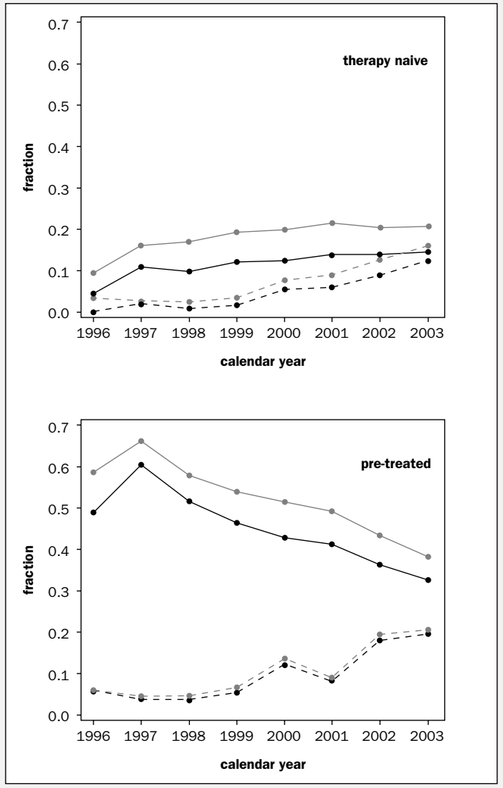


Figure 14.2: Fraction of pre-treated and therapy naïve patients failing per year and the fraction of failing patients in whom a sequence is obtained. The grey line represents the fraction of patients who fail irrespective the usage of therapy. The black line represents the fraction of patients failing whilst on therapy. The grey dotted line indicates the fraction of failing patients in whom a sequence is obtained. The black dotted line indicates the fraction of failing patients in whom a sequence is obtained that harbours resistance associated mutations.

Conclusions and recommendations

Frank de Wolf

Conclusions

Data collection and follow-up

Since 2003, the total number of HIV infected patients registered and monitored through data collection in 22 HIV Treatment Centres has increased by 1236 to a total of 9732 patients, with a total follow-up of more than 60000 person years and a median follow-up period of 5.4 years. Median time between visits is approximately 3 months, although the number of visits per calendar year is decreasing.

The overall error rate of data collected in the newly implemented OC database is relatively low. In part, this follows the more stringent data verification procedures that are built-in. Descriptive results of data monitoring by source data verification confirm the complexity of data collecting directly from the patient's medical file. In addition, complexity increases with time of follow-up. To contain the complexity a more refined data collecting protocol is currently under preparation encompassing specific guidelines to standardise documentation of diagnosis and data extraction from medical files[10-13]. Moreover, better-structured registration of clinical events, such as HIV disease, adverse events and causes of death is needed.

Changes over time of the prevalence of newly diagnosed HIV-infections per year

The figures for 2004 so far show a further increase in number of registered HIV infected patients and the increase in the number of newly diagnosed HIV infections, although at a somewhat slower pace as compared to the previous years. This is partly the result of the way patients are included in the registration and therefore might reflect a slowly diminishing reservoir of HIV infected patients awaiting registration.

However, mid 2004 the National Institute for Public Health and the Environment reported a slow-down of the number of sexually transmitted diseases (Fact sheet June 2004, RIVM, Bilthoven, The Netherlands). New HIV infections might follow this trend, which could explain as well the slower increase observed in 2004. In addition, the import of HIV through migration of patients from endemic area currently seems to slow down.

Homosexual men still form the largest HIV infected group. This group is mainly of Dutch origin and was infected in the Netherlands with a subtype B strain. This population is getting older at diagnosis, whilst CD4 counts at diagnosis increase with calendar time. This suggests that homosexual men are diagnosed sooner after infection and are infected at older ages. Assuming that most homosexual men are likely to have sexual contact with men of approximately the same age, it should be expected that the probability of infection is comparatively smaller for younger homosexual men.

In contrast to the male homosexual population, infections amongst heterosexual men and women are mainly imported from sub-Saharan Africa and, to a lesser extent, from Latin America and the Caribbean. The majority of patients of Dutch origin were infected in the Netherlands and in sub-Saharan Africa, although 12% of the male population was infected in South (East) Asia, especially in Thailand.

After a period of steady increase since 1993, the fraction of women amongst the registered HIV infected patients remained 30%. On average, women are still six years younger than men at HIV diagnosis are. Moreover, heterosexually infected men generally are diagnosed in a later stage of infection than women are. This indicates that men are tested later after infection than women. Cultural influences might be a possible explanation for the latter phenomenon. Another explanation might be that in the Netherlands, women are offered an HIV test during pregnancy by default although the number of women diagnosed in this way appears to be limited[41].

The number of pregnancies among HIV infected women is increasing. Apparently, the effect of HAART treatment and the reduced risk of transmission of HIV from mother to child due to antiretroviral treatment encourage women to become pregnant, which, together with the increasing number of HIV positive pregnant women from HIV endemic areas could have contributed to the increase found.

The proportion of patients of non-Dutch origin that is infected through heterosexual contact in the Netherlands is about 5% and similar per region of origin. However, it is not known to what extent foreign individuals living in the Netherlands who visit their country of origin import infections. Currently, a study is being conducted in the group of patients originating from Suriname and the Netherlands Antilles that aims at unravelling the dynamics of infections in these two groups.

Intravenous drug users are now a minority of the HIV infected population in the Netherlands. It was recently reported that in Eastern Europe the rate of new HIV-infections – mainly amongst intravenous drug users but emerging in the heterosexual population – is amongst the highest in the world[43]. Since several of these countries in Eastern Europe are now part of the European Union, infections might more easily migrate to Western Europe. So far, however, only limited data are available.

A majority of almost 80% of the patients registered are treated with HAART. Only very few are on an antiretroviral drug regimen that cannot be classified as being HAART while 18.5% of the patients are not treated with antiretroviral agents at all. The majority of untreated patients were diagnosed with HIV during or after 2000. Together with the relative high CD4 cell numbers and low HIV RNA plasma concentrations, this indicates that these patients have only recently become infected and are therefore not eligible for HAART according to current treatment guidelines[34].

In concordance with findings by others[35-37], a high prevalence of HCV co-infection was found amongst HIV infected intravenous drug users. A study into the effect of HCV co-infection on patient's response to HAART is currently conducted.

Transmission of drug-resistant HIV-1 virus strains was observed in 6.5% of the recently infected patients who were diagnosed after 1996. Similar percentages were found amongst newly diagnosed patients, indicating that transmission of resistant virus remains detectable later in the infection[164]. There is no evidence that the frequency of resistant transmissions is changing over time after 1996 and percentages found are comparable with those observed in other European countries[163, 185].

The effect of transient viraemia on the outcome of treatment and the incidence of resistance among patients failing on HAART

Transient plasma viraemia with HIV RNA plasma levels between 50 and 1000 copies/ml were found in 12.2% of patients, substantially lower than proportions reported in other studies due to different definitions used, the duration of follow-up or the characteristics of the cohort under observation[135, 137, 138, 141].

The rates of these so-called viral blips among patients varied between 2.9 and 11.9 per 100 person-years of follow-up, which might be an underestimation of the true rate as the detected rate depends strongly on the availability of viral load measurements. In a large proportion of the population, the follow-up frequency may simply have been insufficient to detect a viral blip. A recent study has suggested that the average duration of a blip is approximately one month[143], which would imply that in order to detect all viral blips within the population, a higher measurement frequency is required than is currently recommended in most clinical protocols[131].

No substantial differences in the clinical course of the infection were found between patients with sustained suppressed HIV RNA plasma levels and patients who experienced occasional blips. The increase in the absolute and relative number of CD4 cells over the first three years of HAART therapy, the rate of virological failure and the hazard of new AIDS diagnoses were all comparable. This lack of difference could not be explained by confounding due to differences in the characteristics of the selected patients. Both groups were very similar in terms of demographic factors and baseline immunological and virological status. No relationship could be found with the emergence of resistant virus, although the number of measurements that were available was limited[135, 137, 138, 141].

The fraction of failing patients in whom a sequence was obtained has increased over time. Of those patients with a sequence, 65% to more than 90% harboured resistance associated mutations[160-162]. Presently, 10.5% of the population in follow-up and registered in the HMF database, harbours virus strains that are resistant to one or more drug classes. However, the prevalence of specific resistance associated mutations changed over time and correlates with the changes in antiretroviral drug use[187].

In about 8% of the pregnant women, resistance associated mutations have been found. The population is, however, too diverse and the number of sequences too limited to draw firm conclusions yet. Therefore, a study is planned that will assess the development of resistance in pregnant women and the consequence for treatment and transmission to the child.

Possible differences between outcomes of initial HAART regimes; efficacy of second-line regimens

Comparison of seven frequently used first line HAART regimens revealed that patients commencing with a HAART combination of AZT+3TC+NVP and in particular AZT+3TC+EFV had a significantly faster decline of plasma viral load levels than patients commencing with a PI based initial regimen. Except for AZT+3TC+NFV, HAART regimens did not differ with respect to the duration of maintaining virological suppression. No significant differences in the initial CD4 increase were observed between regimens. In view of this, an NNRTI based regimen might be the obvious choice as first line HAART, although factors such as convenience of the regimen, drug-drug interactions and potential to salvage drugs, together with individual patient characteristics should also be taken into account.

Toxicity was the major reason for discontinuation of the initial HAART regime. The proportion of patients failing due to toxicity was higher in patients starting in the early years of HAART, which is probably due to the more toxic drug combinations used in those years. Although patients starting in 1998-2004 had more advanced disease, virological outcome was better or comparable with those starting in 1996-1997. This suggests that a higher proportion of patients commencing in 1996-1997 failed because of less effective HAART combinations whilst in later years, a higher proportion failed because HAART was initiated in a later phase of the HIV infection. The majority of patients on second-line HAART reached plasma viral load levels ≤500 copies/ml within 6 months. Time to second virological failure did not significantly differ in patients who commenced HAART in 1996-1997 or patients who did so in 1998-2004.

HAART strategies and outcome

Less immunological improvement was found in discontinuously HAART treated patients as compared to continuously HAART treated patients. This may explain the higher incidence of CDC-C events found in the discontinuously treated group. Our finding that the majority of patients continued HAART for at least 3 years after initiation is of importance, since the use of HAART is known to correlate strongly with the effective suppression of HIV replication[95-97] and mortality[5, 98].

Although a larger increase in CD4 cell counts was found in continuously HAART treated patients, the absolute number of CD4 cells at the end of the three-year study period was largely determined by baseline CD4 cell count. The median increase in CD4 count between start of HAART and at three years was higher in those with lower baseline CD4 cell counts, but absolute numbers of CD4 cells at 3 years between baseline CD4 strata remained significantly different.

No differences in mortality were found between the continuously or discontinuously HAART treated groups. One possible explanation, apart from the small number of deaths, would be the effect of exclusion of patients with less than three years of follow-up after commencing HAART as patients who died or were lost to follow-up within the three-year study period may have been more likely to have used HAART discontinuously.

Temporal interruption of HAART was a common phenomenon among patients who initiated therapy without prior anti-retroviral treatment. The main reasons recorded for interruption of HAART were drug-associated toxicity and the patient's request. In general, those who interrupted therapy had started HAART earlier than patients who had never interrupted.

Although therapy interruption does not pose a direct threat, i.e. lead to acute progression among patients with high CD4 cell counts and low HIV RNA plasma levels while on HAART[118, 119], therapy interruptions are associated with a less favourable treatment outcome. After reinitiating HAART, 19% of the patients who had interrupted therapy did not manage to adequately suppress virus production within the next 12 months. Moreover, the proportion of patients with an HIV RNA level <500 copies/ml during the course of treatment was lower, the gain in CD4 cells was lower and the hazard of disease progression was higher among patients who interrupted HAART than among those on continuous HAART. These effects remained apparent even after reinitiating HAART[5, 121, 128].

Previous studies have shown that interruptions for reasons of immediate side-effects are shorter than interruptions for other reasons and occur relatively soon after initiation of a regimen[109, 110]. Although the reason for interruption was not directly associated with therapy success after reinitiating, the higher rate of success among patients who experienced an interruption of less than one month and among patients who had interrupted after a relatively short episode of HAART does suggest a link with drug-related toxicity.

Frequently occurring adverse events

From the year 2000 onwards, the incidence of lipodystrophy, sexual dysfunction, nephrolithiasis, pancreatitis and peripheral neuropathy declined, most likely because the combination of antiretroviral drugs prescribed for HAART has changed. Since the registration of the protease inhibitors saquinavir, ritonavir and indinavir in 1996, new and less toxic antiretroviral drugs have been introduced, giving physicians a wider choice of drugs to be used in the HAART combination and allowing them to adapt the combination to the characteristics of the patient.

Changes in HIV-related morbidity and mortality

Mortality in the HAART treated population seems to rise again since 2002. The underlying cause of this rise remains unclear although it can be partially explained by the increase in expected mortality reflecting the increasing age of specific sub-groups the HIV infected population.

In contrast, the annual decline in the incidence of AIDS in the HAART-treated population that has been observed since 1996 continues in 2003 and 2004. The incidence of CDC-C events also declined with time after initiation of HAART. The relative contribution of

each CDC-C event to the total number of events that were recorded largely remained the same over time. CD4 counts and HIV RNA plasma levels measured after 24 weeks of HAART are the only strong predictors for progression to death, with lower mortality observed in those with higher CD4 counts[2].

After excluding those infected through intravenous drug use[28, 146, 149], mortality was found to be only modesty higher in patients with CD4 counts above 600×10^6 cells/l than in the age and gender matched Dutch general population. However, only a minority of the study population had such CD4 counts at 24 weeks and the probability of reaching counts above 600×10^6 cells/l increased with higher CD4 counts at start of HAART[95]. This argues in favour of an early initiation of HAART when CD4 counts are still high[150]. Independent of this, CD4 cell restoration is also related to age with a more complete restoration in younger patients[151, 152].

Standardised mortality ratios (SMRs) were higher for HIV infected women than for men, due to the lower annual mortality for women compared to men in the general Dutch population. However, the absolute difference in mortality is small. Excess mortality in HAART treated patients relative to the general population is independent of age. Although mortality rates in successfully treated HIV infected patients and especially younger patients were still higher than in the general population, they were comparable to those observed in patients with diabetes mellitus[153-155]. Similar patterns were observed in the Swiss HIV Cohort Study, where it was shown that excess mortality amongst successfully treated HIV infected patients is similar to mortality in successfully treated cancer patients[156, 157]. As was argued for the Swiss HIV Cohort, our results indicate that, as for many other chronic diseases, life insurance for HIV infected patients is possible under specific conditions.

Research recommendations

Based on the descriptions and analyses of the data collected from HIV infected patients monitored in the ATHENA-HMF cohort, we make the following recommendations:

Meaningful interpretation of the data collected on the efficacy of HAART needs fine-tuning of the various protocols that are used to follow patients clinically. Differences in follow-up frequencies between groups of patients and over time influence more refined outcome parameters, such as transient viraemia and the impact of these parameters on clinical outcome. A more standardised follow-up protocol describing the minimum frequencies required for the definition in time of adverse events and toxicity due to antiretroviral drug use, but also CDC-C events and non-HIV related events is of crucial for further clinical research and should be developed.

In addition, it is recommended to standardise definitions of the clinical events mentioned and to add specific guidelines for these events to the data collection protocols. Specific attention must be paid to the registration of causes of death. In collaboration with other cohorts participating in the ART-Cohort collaboration and the DAD study proposals are currently being developed to standardise collection and interpretation of data regarding causes of death and their possible relationship with either the HIV infection or the antiretroviral treatment of that infection or both.

Regarding the specific contribution of the HIV Monitoring Foundation to the collection of HIV surveillance data it is recommended to further to the collection of data on primary HIV infections, to set up a registration of events regarding various primary prophylaxis protocols and to expand the registration programme on the molecular epidemiological characteristics of specific sub-groups. The latter is needed in order to achieve more insight on the import of new HIV infections and the transmission of imported infections into the populations at risk in the Netherlands.

Following the work on primary infections that is currently in progress it is recommended to invest in the development of a specific primary infection data collection protocol. Introducing nation wide resistance testing of all newly diagnosed infections would not only be vital for the timely detection of transmission of resistance and decisions regarding the composition of future HAART regimens, but would also contribute to a more thorough understanding of future changes in the HIV epidemic in the Netherlands.

The registration of co-infections, such as infections with hepatitis C, hepatitis B and cytomegalovirus needs to be improved, both with respect to clinical and laboratory data on the diagnosis of such infections, as well as the clinical follow-up of treatment and outcome. Improved registration and monitoring of co-infections is essential for further investigation - in collaboration with other observational cohorts - their effect on the course of the HIV infection.

A similar recommendation can be made regarding the registration of TBC infections and the clinical follow-up of TBC. Following up on the initiative for a study on TBC in HIV infected patients in the Netherlands, a protocol for a more refined collection of data on TBC should be developed aiming at descriptive analysis of changes in the occurrence of TBC among HIV infected patients and more in depth analyses in collaboration with other cohorts.

The number of HIV infected women being pregnant at, or becoming pregnant after HIV diagnosis is increasing. One of the preliminary findings presented in this report is the high prevalence of resistance amongst pregnant women. Adequate follow-up of these women requires the collection of a specific set of data in addition to the data that are collected regularly. Data collection and entry procedures are currently being developed. It is therefore recommended to develop a specific programme for the registration and monitoring of pregnant women.

Resistance to antiretroviral agents is of growing concern. Although at present the number of patients in whom antiretroviral therapy fails is relatively limited, the fraction of patients at failure that harbours virus strains resistant to at least one of the drug classes is high. Over time, the fraction of therapy failures will increase and so will resistance. The occurrence of multi-drug resistance in the near future is inevitable. One of the crucial factors in the development of resistance is the level to which patients adhere to the drug regimens prescribed. Long-term follow up of patients will provide more insight in the relationship between adherence patterns to combinations of drugs used in the life-long treatment of a chronic infection and disease progression. It is recommended to collect and combine data on these adherence patterns with those on treatment failure, resistance and drug levels in plasma, with the aim to better understand and predict the timeframe within which resistance will develop.

Finally and in view of the above, it is recommended to continue and expand current international collaboration on studies comparing the efficacy, tolerability and toxicity of HAART treatment, especially the studies into more recently prescribed combinations of antiretroviral drugs. Despite the relative large number of patients actively in follow-up in the ATHENA-HMF cohort, studies on currently administered HAART regimens are only feasible in large-scale international collaborations, especially when clinical end-points such as AIDS and death are used.

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Overview

Overview of ongoing research projects

Overview of ongoing research projects

Research proposals using SHM data and approved by the Advisory Board in 2003-2004

Effectiveness of first-line antiretroviral therapy among HIV-infected patients co-infected with hepatitis C virus

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01-08-2004

Objective

To explore the effect of hepatitis C virus (HCV) co-infection on response to antiretroviral therapy (ART) in a large cohort of HIV-infected patients (ATHENA [Netherlands]; HIV Insight™ [USA]; Plum Data Mining LLC [USA])

Methods

The ATHENA database consists of data collected nationally in the Netherlands on all HIV-infected patients being followed in one of the 22 hospitals acknowledged by the Dutch Ministry of Health as HIV treatment centres. The HIV Insight™ and Plum Data Mining LLC (Plum) databases record information collected from HIV-infected patients when they attend one of several clinics throughout the United States. HCV-co-infected patients will be compared with non-coinfected patients in terms of virological and immunology response to ART, time to discontinuation of first-line ART and overall mortality. For the present study, data from previously antiretroviral-naïve HIV-infected patients will be used who initiated ART (defined as therapy with one or more antiretroviral drug) between January 1998 and December 2003. Patients have had at least one serological HCV test at baseline, defined to be before or in the three months following ART initiation.

Four primary outcomes will be studied to measure the success of first-line ART: 1. Time to HIV viral suppression, defined as the time from ART initiation until plasma HIV RNA falls below 500 copies/ml; 2. Time to HIV viral rebound, defined as the time from ART initiation until plasma HIV RNA rebounded above >500 copies/ml confirmed by two consecutive results above 500 copies/ml, after a recorded period with plasma HIV RNA below 500 copies/ml; 3. Time to 50-cell CD4+ T-cell count increase, defined as the time from ART initiation until CD4+ T-cell count increases by 50 cells/mm^3 above its baseline level; 4. Time to discontinuation or modification of the first-line antiretroviral regimen.

Statistical Analysis

For three of the four primary outcomes in each patient, the exact time of the event of interest was not directly observable. Instead, events were only known to have occurred in the interval between two successive clinical visits. Such data are known as and may be analysed using Accelerated life regression models will be uses to analyse interval-censored survival data (when events are only known to have occurred in the interval between two successive clinical visits). The multiple regression models for the four primary outcomes and the subgroup analyses will be fitted simultaneously.

Comparison of the risks of atherosclerotic events versus death from other causes associated with antiretroviral use

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28-05-2004

Introduction

The benefits of highly active antiretroviral therapy (HAART) for HIV infection have been demonstrated by the observed long-term improvement in clinical markers of disease progression, such as HIV-1 RNA measurements and CD4+ T-cell counts, and the associated reduction in HIV-associated morbidity and mortality. However, concern has been raised over the longer-term impact of toxic side effects, in particular metabolic abnormalities such as hyperlipidemia and lipodystrophy which have been associated with antiretroviral agents, and, concomitantly, their potential to induce cardiovascular disease (CVD).

Several studies have investigated a possible association between HAART and CVD through examining cohorts of individuals using a variety of statistical methodologies. All studies noted that these potential risks are outweighed by the benefits of HAART, but none have jointly calculated the relative benefits and drawbacks of ART using competing risk methodologies. Such methods are necessary to study the survival of patients who are at risk from more than one event.

In this setting, the increase in survival associated with ART use makes observation of other serious conditions, such as CVD, more likely. Analyses that do not jointly consider the increase in survival with the risk of CVD could therefore falsely indicate an increased risk associated with ART use (the potential confounding by "aging" was taken into account by the analysis from DAD). We propose therefore to compare the competing risks of atherosclerotic events versus death from other causes and to investigate whether various methodological approaches will influence substantially the result.

Methods

Cohort: to achieve enough power, we would like to do our analyses in a compiled cohort with data from two sources: (a) the HIV InsightTM database which contains information from routine clinical practice in a group of HIV treatment centres throughout the United States from 1983 onwards and (b) the HMF or ATHENA national cohort which includes information on the majority of HIV-infected patients receiving treatment in the Netherlands recorded from 1985 onwards. No restrictions are made on entry to the cohort.

Selection: patients will be selected for this analysis if they have received at least one ART regimen (of 1 or more antiretrovirals), initiated at the age of 18 or over, and have a known ART start date. The analysis of the effect of different types of regimens speaks of comparison with persons who are not on ART in the sense of having stopped ART! Persons stopping ART should not be expected to behave the same as those never having been exposed to ART. Why are persons never having been treated not part of the analysis?

Statistical analyses: time from ART initiation to the first event will be included. Those who do not experience an event will be censored at the earliest of (a) 3 months following their last recorded observation of a clinical measurement or change in ART or (b) the end of the study follow-up. Proportional hazards models will be used to assess the risk associated with protease inhibitors (PI)- or non-nucleoside reverse transcriptase inhibitors (NNRTI)- or PI+NNRTI-containing regimens compared to no ART (stopping therapy) or nucleoside reverse transcriptase inhibitors (NRTI) only regimens, on the first of either a atherosclerosis disease event or death from other causes (competing risks).

Sensitivity analyses: To compare consistency, the results from our competitive model will be compared to those obtained by using a Poisson regression approximation or proportional hazards models. Next to that, sensitivity of the model to the inclusion or exclusion of those experiencing an atherosclerotic disease event prior to the initiation of ART will be analysed, as well as using an MI only as the outcome event and the inclusion/exclusion of HIV disease stage as a fixed covariate.

Protocol voor het onderzoek naar heteroseksuele HIV-transmissie onder migranten afkomstig uit Suriname, Nederlandse Antillen en Aruba: de rol van import van HIV uit het land van herkomst

GG&GD Amsterdam: ir. Merlijn Kramer, dr. Maria Prins. RIVM: dr.ir. Eline Op de Coul
29-04-2004

Achtergrond

In Nederland stijgt de laatste jaren het percentage heteroseksueel geïnfecteerde HIV-positieve personen, waarvan een groot deel van Surinaamse, Antilliaanse of Arubaanse herkomst is. Onderzoek suggereert een toenemende instroom van HIV uit Suriname, de Antillen en Aruba naar Nederland. Tot op heden ontbreken echter gedetailleerde gegevens over het risico van HIV door seksueel contact in het land van herkomst.

Dit project bestaat uit twee studies: een algemeen en een moleculair epidemiologisch onderzoek. Het heeft als doel om bij personen afkomstig uit Suriname en de Antillen te onderzoeken: 1. het risico van een HIV-infectie bij bezoeken aan het land van herkomst en 2. de import en verspreiding van HIV in deze populatie uit Suriname en de Antillen, door het vergelijken van HIV stammen in deze migrantengroepen in Nederland met de HIV-stammen die circuleren bij heteroseksuelen in Suriname en de Antillen.

Specifieke onderzoeksvragen

Wat zijn de kenmerken van personen afkomstig uit Suriname, de Nederlandse Antillen en Aruba, die het land van herkomst bezoeken. Wat is het seksuele (risico)gedrag tijdens het bezoek en wat zijn hiervan de determinanten?
In hoeverre is bij deze migrantengroepen sprake van risicovolle seksuele contacten in Nederland en wat zijn de seksuele netwerken? Welke HIV-1 subtypen circuleren er bij heteroseksuelen in Suriname, de Antillen en Aruba?

Eindpunten

HIV-1 subtypen (bepaald op basis van env, gag en pol-sequenties) die circuleren bij 1. HIV positieve heteroseksuelen in Suriname en de Nederlandse Antillen, 2. Surinamers en Antillianen die in Nederland wonen en 3. autochtone Nederlanders. Overeenkomsten tussen de HIV-stammen uit deze 3 groepen worden vergeleken op basis van fylogenetische analyse. Uiteindelijk zal inzicht verkregen worden in de epidemiologische relatie tussen de HIV-epidemieën in Suriname/Antillen en Nederland.

Het Genotypic Inhibitory Quotient (GIQ) van lopinavir

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01-03-2004

Inleiding

Uit onderzoek bleek dat GIQ de beste voorspeller was voor een virologische respons op een amprenavir bevattend regime in een groep van PI-voorbehandelde patiënten. Voortbordurend op dit gegeven is er een behoefte om het GIQ vast te stellen van de proteaseremmer die in Nederland het meest gebruikt wordt bij patiënten met resistent virus: lopinavir. Het is ons voorstel om dit in een grotere Nederlandse groep te gaan onderzoeken.

Uitvoering

Voor deze exercitie zijn een 3-tal verschillende datasets nodig: 1. uitslagen van genotypische resistentiebepalingen die geleid hebben tot een start van een lopinavir bevattend regime; 2. uitslagen van lopinavir plasmaspiegels; 3. klinische follow-up data (m.n. viral load). Daarnaast moet dit onderzoeksvoorstel ook gezien worden als een test case voor het combineren van onderzoeksgegevens uit de verschillende datasets, wat ook voor toekomstige vraagstellingen relevant kan zijn.

Rol van 3-NRTI therapie tijdens initiële- en vervolgbehandeling

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02-02-2004

Inleiding

In meerdere studies werd al aangetoond dat 3-NRTI combinaties als initiële therapie bij naïeve patiënten inferieur is aan combinaties van 2NRTI met hetzij een PI dan wel een NNRTI. Dit geldt met name bij patiënten met een hoge baseline viral load (>100.000 copies/ml). Toch is het succespercentage

van 3-NRTI als initiële therapie niet nihil en voor bepaalde patiënten categorieën wellicht de enige kans op haalbare compliantie.

De rol van 3-NRTI als onderhoudstherapie lijkt gunstiger, vermits in eerdere behandelfases geen resistentie-inductie heeft plaats gevonden, zoals in de periode dat 2NRTI nog gebruikelijk was of tijdens perioden van incompliantie van in principe effectieve triple/quadruple therapie. Het is daarbij wel belangrijk goed op de samenstelling van de 3-NRTIs te letten, waarbij combinaties als b.v.ABC-3TC-TDF ook in deze fase opvallend veel falers laat zien. Een combinatie van AZT-3TC-ABC gedraagt zich in dat opzicht voordeliger.

Doel van het onderzoek

1. Binnen SHM/ATHENA te evalueren in welke mate 3-NRTI werd toegepast als initiële therapie en wat daarbij de kans op duurzaam virologisch succes is geweest, verder uitgesplitst naar mogelijke risico factoren op virologisch falen (zoals baseline viral load en CD4, duur infectie, risicogroepen etc);
2. evalueren in welke mate 3 NRTI werd toegepast in onderhoudsfase en in welke mate virologisch succes langdurig kon worden bereikt.

Onderzoek zal beschrijvend van aard moeten zijn, waarbij de grootte van de groepen vermoedelijk toch groot genoeg zal zijn om betrouwbare statistische analyses uit te voeren. Zelfs moet het mogelijk zijn case control studies binnen SHM te doen, waarbij vergeleken kan worden met bijvoorbeeld PI en NNRTI bevattende ART, zowel in de initiële- als in de onderhoudsfase. Met 3 NRTI worden alle combinaties NRTI bedoeld, waaronder ook NTRTI (TDF).

HIV-TBC co-infection in the Netherlands

J.G. den Hollander, G.C. Heerdink, M. Bakker, S. de Marie en M.E. van de Ende
28-11-2003

Background

Tuberculosis is one of the most important causes of morbidity and mortality in the developing world. Due to the progression of the HIV epidemic tuberculosis has been re-introduced into the western world. Along with the immigration of people from the developing countries, the incidence of patients with HIV-TBC co-infection is increasing.

Aim of the study

To compare the incidence of adverse events attributed to tuberculostatics and/or HAART in patients with a HIV-TBC co-infection. To compare the outcome in patients concurrently treated with tuberculostatics and HAART with the outcome in patients in whom the start of HAART is postponed to the end of tuberculostatic therapy.

Study population

Patients participating in the SHM data set from 1997 until 2004 will be identified for co-infection with TBC. Data on patient characteristics, antiretroviral drugs, co-medication, HBV or HCV co-infection, and localization of tuberculosis at the time of entry in the study will be collected. Follow-up on ASAT, ALAT, GGT, AF, bili, CD4, CD8, HIV-RNA, mortality and opportunistic infections, treatment interruptions due to toxicity, starting or changing of HAART from baseline to the end of therapy for TBC, will be notified. Survival after starting tuberculostatics will also be recorded until January 1st 2004.

HIV-1 and HIV-2 infection in West African residents in The Netherlands: epidemiology and missed diagnosis

Martin Schutten, Marchina E van der Ende, Frank de Wolf, Ab Osterhaus
09-07-2003

Background

At present there are no reported data on the prevalence of HIV-2 infection in The Netherlands. Diagnosis of HIV-2 may be missed due to false positive HIV-1 RNA assays, caused by cross reactivity. HIV-2 has been found in many parts of the world, especially in countries that have links with Western Africa. Due to the increasing number of West African immigrants the number of HIV-2 infected patients in the Netherlands may be increasing. This has implications for subjects sexually infected by West Africans.

Objectives

To obtain a list of HIV infected individuals from selected West African countries (Senegal, the Gambia, Guinea Bissau, Guinea, Sierra Leone, Liberia, Côte d'Ivoire, Ghana, Togo, Burkina Faso, Mali) with low plasma HIV-1 RNA and low CD4 cell counts in order to assess possible missed double HIV-1/HIV-2 infection or HIV-2 mono-infection.

Methods

From 1997 until September 2004, all HIV infected individuals from selected West African countries participating in the SHM will be identified. Data on plasma HIV-1 RNA and CD4 cells will be collected. From patients with plasma HIV-1 RNA $<$ 10.000 c/ml and CD4 $<$ 200/mm^3 plasma samples will be obtained to perform HIV-2 diagnostics.

Clinical, immunological and virological parameters in a cohort of HIV-2 infected patients in the Netherlands on or off therapy with different antiretroviral regimens

Marchina E van der Ende, Martin Schutten, Albert D.M.E. Osterhaus
09-07-2003

Background

At present, there are few reported data on the treatment of HIV-2 infection. HIV-2 has been found in many parts of the world, especially in countries that have links with Western Africa. The number of HIV-2 infected patients in the Netherlands may be increasing. We propose to study clinical, immunological and virological parameters in HIV-2 infected patients on or of treatment.

Objectives

1. To obtain a list of HIV infected individuals from selected West African countries (Senegal, the Gambia, Guinea Bissau, Guinea, Sierra Leone, Liberia, Côte d'Ivoire, Ghana, Togo, Burkina Faso, Mali) for epidemiological studies; 2. To observe clinical, immunological and virological parameters in HIV-2 and infected patients not on antiretroviral therapy; 3. To assess the clinical, immunological and virological response and the emergence of resistance towards antiretroviral therapy (ART) in HIV-2 infected patients.

Study population

From 1997 until September 2004, data on all HIV-2 infected patients and all HIV infected individuals from selected West African countries participating in the SHM will be collected. Patients will be studied from the start of the study period until death or the end of the study period, whichever is earliest.

Clinical, virological and immunological outcome

Data of patient characteristics (i.e. age, gender, origin, nationality, route of HIV-transmission), co-morbidity (i.e. HBV or HCV infection), treatment, and parameters of HIV-infection (clinical stage, CD4-cell count, HIV-2 RNA, sequence analysis) will be retrieved from the SHM.

Protease inhibitor containing therapy as a driving force of in vivo HIV-1 evolution

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16-05-2003

Introduction and background

In clinical practice many patients on highly active antiretroviral therapy (HAART) are only partially adherent to their drug regimen. Regardless of the reason of this non-adherence, the sub-optimal therapy jeopardises the likelihood of maintaining viral suppression, which in turn may lead to therapy failure and drug resistance. The development of resistance in patients treated with HAART is usually studied by assessing the changes in the virus population at specific nucleotide positions in RT or protease that are known to be associated with resistance to RT or protease inhibitors. In this proposal we describe a study that will assess the development of resistance by looking at the rate of nucleotide substitutions over time of follow-up.

Pilot study

A pilot analysis has been performed on data presently available in the ATHENA cohort. Around 600 of the patients in ATHENA were included in a core group. For those patients RT and protease sequences were obtained at baseline and at therapy failures. The final number of protease and RT sequences was 1154 and 1166, respectively. The Nei-Gojobori p-distance was used to calculate synonymous and non-synonymous pair wise distances between sequences. The p-distances were corrected to account for multiple substitutions at the same site (Jukes-Cantor correction). All distances calculations were done with MEGA 2.1.

Conclusions and proposal

A more sophisticated analysis of growth rates of synonymous and non-synonymous distances requires more sequences. Therefore, we would like to use sequences obtained from patients registered in the HMF database since 2000/2001 in addition to those that were collected during the ATHENA project. In addition, with a larger set of sequences we hope to extend the group of patients who discontinue PI containing therapy and who were sequenced several times before and after the discontinuation. A third analysis we hope to do is to compare growth rates before starting any therapy and after initiating therapy. A further issue that we want to address is the viral replication rate, which determines the growth rates of the synonymous and non-synonymous distances.

TRIESTAN: TReatment Interruption in Early STArters

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Academic Medical Centre, Amsterdam and Leiden University Medical Centre
02-04-2003

Study design

A non-randomised, two-armed, prospective, observational study to evaluate the efficacy and safety of discontinuing successful antiretroviral combination therapy in patients who initiated antiretroviral therapy with CD4+ T-cell counts above 350 cells/mm^3.

Methodology

This is a non-randomised prospective multi-centre, two-armed study with approximately 180 subjects. The target population of this study consists of patients who initiated HAART with CD4+ T-cell counts above 350 cells/mm^3. At the time of inclusion into the study these patients need to have CD4+ T-cell counts of more than 500 cells/mm^3, and their plasma HIV-1 RNA levels need to be undetectable ($<$ 50 copies/ml) for more than 6 months.

In eligible patients who wish to participate in the study, HAART will be discontinued (Group A) or continued (Group B). Both groups will be closely monitored according to a predefined schedule for 48 weeks. As soon as one of the study endpoints is reached that meets the criteria for initiating HAART, antiretroviral therapy will be restarted. Both the visit schedule as well as the reinitiation of HAART is based on current treatment practice. The virological and immunological response will be carefully documented.

Objectives

The primary objectives of the study are to determine the safety and efficacy of discontinuing HAART in patients who initiated HAART too early according to current guidelines.

Verschillen in therapie respons bij patiënten op AZT of d4T bevattende eerstelijns HAART regimes

Ferdinand Wit, Joep Lange
Academisch Medisch Centrum, Amsterdam
27-03-03

Achtergrond
Vrijwel alle eerstelijns HAART regimes van in Nederland behandelde HIV-geïnfecteerden bevatten óf AZT óf d4T. Tot nu toe hebben gerandomiseerde klinische studies niet overtuigend laten zien dat HAART met één van deze middelen duidelijk beter behandelresultaten oplevert.

Doel van de analyse
De tot nu toe gepubliceerde cohort studies waarbij AZT en d4T bevattende HAART regimenes met elkaar vergeleken werden, waren met name gericht op het onderzoeken van de prevalentie van mitochondriale toxiciteit.
Wij willen een systematische vergelijking doen van de verdraagbaarheid, en klinische, virologische en immunologische effectiviteit van AZT en d4T bevattende HAART regimenes in de klinische praktijk.

Methodologie
Verdraagbaarheid zal worden onderzocht door het optreden te vergelijken van bijwerkingen, waardoor het gebruik van AZT of d4T gestaakt moet worden. De klinische effectiviteit wordt onderzocht door het verschil in ziekteprogressie tussen de groepen te vergelijken. De virologische effectiviteit wordt vergeleken door het bepalen van zowel de korte als lange termijn respons van het plasma HIV-1 RNA. De immunologische effectiviteit wordt vergeleken door de veranderingen in CD4-getal en CD4-percentage te vergelijken. Alle effectiviteitanalyses zullen zowel op 'as treated' als 'intent to treat' basis uitgevoerd worden.

Patiëntengroep en haalbaarheid
Voor deze analyse hebben wij gegevens nodig van alle patiënten die therapie-naïef met HAART zijn begonnen. Momenteel bevat de SHM database gegevens van enkele duizenden van dergelijke patiënten. Deze aantallen zijn ruim afdoende voor het doel van deze analyse.

In hoeverre verschillen het beloop van de HIV-infectie en de behandelresultaten van allochtone patiënten van die van de autochtone patiënten?

Dr. M.M.E. Schneider, Dr. M.E. van der Ende, Dr. J.M. Prins
UMC, Utrecht, Erasmus MC, Rotterdam, Academisch Medisch Centrum, Amsterdam
24-09-2002

Recent hebben wij de behandelresultaten geanalyseerd van alle 1773 patiënten die sinds 1996 de AMC HIV-polikliniek hebben bezocht. Hierbij bleek een onduidelijk verschil in stadium van presentatie, moment van begin therapie en behandelresultaten tussen autochtone Nederlandse en (subgroepen) van allochtone patiënten. Met name het verschil in behandelresultaten is nog niet eerder (inter)nationaal gerapporteerd, en behoeft bevestiging uit een grotere database.

Ons inziens zouden drie analyses gedaan kunnen worden met als vraagstellingen: is er verschil tussen onbehandelde autochtone en allochtone patiënten, bijvoorbeeld in ziektestadium op moment van presentatie, aantal en aard van opportunistische infecties, respons op behandeling van eventuele OI's? Is er verschil tussen autochtone en allochtone patiënten in behandelresultaten van ARV therapie? Wat is de effectiviteit en veiligheid van ARVT bij zwangere vrouwen?

Analyseplan: de patiënten in de SHM worden onderverdeeld naar land van herkomst c.q. landenregio van herkomst. In de SHM is dit gegeven verzameld. Demografische gegevens, transmissieroute, klinische HIV-gerelateerde gegevens, behandeling, bijwerkingen medicatie en virologische/immunologische data worden in de SHM database verzameld.

Wat zijn de behandelresultaten van patiënten bij wie behandeling gestart wordt tijdens een primo-HIV infectie?

Jan Prins, Frank Kroon, Academisch Medisch Centrum Amsterdam, Leids Universitair Medisch Centrum.
24-09-2002

Op zich wordt primo-HIV infectie door velen beschouwd als een behandelindicatie, waarbij het doel van de behandeling is een betere HIV-specifieke CD4-helper functie te verwerven, iets wat tijdens behandeling in de chronische fase van de infectie niet meer mogelijk is (data van Rosenberg/Walker). Een substantieel deel van zulke patiënten houdt na staken van de behandeling ook zonder therapie een lage viral load. Volstrekt onduidelijk is na hoeveel tijd bij zulke patiënten de behandeling gestopt kan worden.

Concrete vragen zijn derhalve: hoeveel patiënten worden of werden er voor hun primaire HIV infectie in de afgelopen jaren behandeld? Welke acute bijwerkingen en bijwerkingen op langere termijn worden er gerapporteerd? Wat is de virologische/immunologische respons bij patiënten met een primo-HIV infectie die starten met ARVT in vergelijking met chronische patiënten met vergelijkbare regimes? Is er verschil in klinisch, virologisch en immunologisch beloop tussen patiënten die wel en patiënten die niet tijdens de primo-fase ARVT krijgen? Is er verband tussen duur en de samenstelling van ARVT en snelheid optreden/hoogte viral rebound na staken therapie?

Verschillen in CD4+ T-lymfocyten respons bij patiënten op eerstelijns HAART therapie met een proteaseremmer, nevirapine, evavirenz of triple-NRTI

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15-09-2002

Achtergrond
Deze aanvraag voor data van de Stichting HIV Monitoring is een vervolg op onze vorige aanvraag betreffende hetzelfde thema. In deze vorige analyse bevestigden wij de resultaten van de 96-weekse data van de Atlantic studie en enkele kleine andere studies. Het blijkt inderdaad dat er een geringere CD4 stijging is bij patiënten die een nevirapine (NVP) bevattend HAART regime gebruiken in vergelijking met patiënten die een proteaseremmer (PI) bevattend HAART regime gebruiken. Dit terwijl het verloop van het CD4 percentage en de CD4-CD8 ratio in beide groepen patiënten vergelijkbaar is.

Doel van de 2e analyse
Het uitbreiden van de analyse met een groep patiënten die EFV plus 2 NRTI gebruiken en met een groep patiënten die triple-NRTI regimes gebruiken geeft mogelijk meer inzicht in de pathogenese van het geobserveerde verschil in CD4 respons tussen de PI en NVP groepen. Voor deze nieuwe analyse zouden wij graag gebruik willen maken van de gegevens uit de database van de Stichting HIV Monitoring.

Methodologie
De methodologie is exact gelijk aan de vorige analyse, alleen met 2 additionele groepen patiënten. Om het therapie-effect zo zuiver mogelijk te analyseren zal er gekozen worden voor patiënten die geheel therapie naïef zijn bij het begin van een HAART regime. HAART wordt gedefinieerd als 3 of 4 middelen waarvan exact 2 NRTI's. De overige middelen zijn of een PI of NVP of EFV of een derde NRTI. De data van de patiënten wordt geanalyseerd tot aan het moment dat er sprake is van een ongeoorloofde medicatie verandering, van virologisch falen (>1000 copies/ml) of het bereiken van de maximale follow-up van 96 weken.

Prevalentie van resistentie onder nieuwe patiënten met de diagnose HIV infectie en het effect van resistentie bij aanvang van antiretrovirale therapie op het uiteindelijke behandelresultaat

Frank de Wolf en Rob Schuurman
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04-09-2002

Inleiding
Er is een toename in het aantal nieuwe infecties waarbij resistente HIV een rol speelt. In Nederland is over het voorkomen van resistentie bij nieuwe HIV infecties en over de invloed van pre-existente resistentie op het behandelresultaat weinig bekend. Ons voorstel is om bij nieuw aangemelde HIV infecties routinematig RT en protease te genotyperen en zo zowel resistentie te meten als het HIV-1 subtype te bepalen. Door tegelijkertijd te subtyperen kan inzicht worden gekregen in het voorkomen van andere subtypes dan B en de invloed daarvan op de prevalentie van resistentie. Het therapie-effect van tweede en derdelijns combinatietherapie en tenslotte ook van zogenaamde 'salvage' therapie zal worden gerapporteerd.

Vraagstelling
Drie vragen zouden beantwoord moeten worden: a. wat is de prevalentie van HIV resistentie onder nieuwe HIV geïnfecteerden in Nederland sinds de introductie van de behandeling met HAART; b. wat is het effect van preëxistente resistentie op het resultaat van behandeling met HAART; en c. wat is het effect van introductie van andere subtypes dan HIV-1 subtype B op de prevalentie van resistentie en op het resultaat van behandeling?

Analyse
Met resistentie geassocieerde posities in RT en protease worden gescoord en vergeleken met resistentie geassocieerde mutaties uit de Stanfordlijst, de ATHENA tabel en het Retrogram. Subtypering wordt geanalyseerd met behulp van neighbour joining analysis. Eindpunten zijn viral load, CD4 aantallen en kliniek (symptomatische HIV). In 16 Europese landen loopt thans een dergelijke prospectieve studie (SPREAD) naar de transmissie van antivirale resistentie. Een subset van de gegevens die in de SHM resistentie prevalentie studie worden verzameld zal tevens ter beschikking worden gespeld aan SPREAD teneinde de Nederlandse situatie te kunnen vergelijken met die in de overige Europese landen.

Tolerance, safety and efficacy of antiretroviral combination therapy in HIV-infected women

TEMS de Vries-Sluijs[1], FJB Nellen[2], MH Godfried[2], K Boer[2], JP Dieleman[1], ME van der Ende[1]
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18-07-2002

Background
Antiretroviral therapy reduces the risk of mother-to-child transmission. In the developed countries, combination antiretroviral regimens of 3 or more compounds have become widely recommended since 1998 although their safety, toxicity and teratogenicity have not been well documented. Furthermore, there are very little data on the influence of pregnancy on pharmacokinetics of the drug and factors influencing tolerability and adherence of combination antiretroviral therapy.

Objective
To evaluate the tolerability, safety and efficacy of antiretroviral triple combination therapy in HIV seropositive women in the Netherlands.

Design
A retrospective study of HIV-1 infected pregnant women who participated in the ATHENA cohort.

Statistics
This study has been set up primarily as a descriptive study. Descriptive statistics will be used to describe tolerability, safety and efficacy. Pearson Chi-squared test will be used to test differences in categorical variables between study groups. Man-Whitney-U-test or student's T-test will be used to test non-parametric and parametric continuous variables respectively. If applicable, we will perform a multivariate logistic regression analysis to explore risk factors for adverse outcome.

Colophon

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Mission
The HIV Monitoring Foundation is appointed by the Dutch Minister of Health, Welfare and Sports (Ministerie van Volksgezondheid, Welzijn en Sport) as the national executive organisation for the registration and monitoring of HIV infected patients in follow-up in one of the Dutch Treatment Centres. Our mission is to further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

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