HIV Monitoring

# Annual report 2010

## Contributing to the quality of HIV care

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001. Based in Amsterdam, SHM was appointed by the Dutch Minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-infected patients in the Netherlands.

### Our Mission:

To further the knowledge and understanding of the epidemiology and the course of treated and untreated HIV infection.

www.hiv-monitoring.nl

HIV Monitoring


### Colophon

**Annual report 2010, approved by the Board of Governors of the Stichting HIV Monitoring op 28 March, 2011.**

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**Requests for copies:** Stichting HIV Monitoring, Academic Medical Centre of the University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands, T +31 20 5664172, F +31 20 5669189, hiv.monitoring@amc.uva.nl, www.hiv-monitoring.nl

**Visiting address:** Stichting HIV Monitoring, Hogeschool van Amsterdam, Tafelbergweg 51, 1105 BD Amsterdam, The Netherlands

KvK#: 34160453

**Correspondence to:** Frank de Wolf, hiv.monitoring@amc.uva.nl





Editing/Translating: Sally H. Ebeling, Boston, MA, USA; Martin Mevius, Amsterdam
Art Direction and DTP: Kruit communication-design, The Hague

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# Foreword

During 2010, Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, continued to collect, analyse and report data from patients with HIV in the Netherlands. These data are not confined to HIV infection and its treatment; they also concern other infections such as hepatitis B and C and disorders such as cardiovascular disease, renal dysfunction, and certain cancers that do not fall under the definition of AIDS but are commonly seen in people with HIV. Through successful treatment, these people are ageing, and it is therefore expected that such conditions will be found more frequently. Advancing age, however, may not be the only explanation for the prevalence of these conditions. Another explanation currently under investigation in this population is accelerated ageing, which may be linked with the use of antiretroviral medications.

Through its work, SHM continues to contribute significantly to the knowledge of HIV and enables treating physicians to assess and improve patient care. Additionally, SHM provides valuable input into the development of HIV care and prevention policies within the Netherlands and the European Union. The foundation's report, *Monitoring of HIV in the Netherlands*, published on World AIDS Day, 1 December 2010, supplies information on trends over time in the epidemic and the effect of treatment on HIV infection up to 30 June 2010. The 2010 Annual Report presents, in addition to organisational and financial information, updated data on the monitoring of HIV through to the end of 2010. It is important to note that the monitoring figures for 2010 are not yet complete because of ongoing data collection and will undergo updates during the next two years.

Since SHM was founded in 2001, we have focused increasing attention on other infections and diseases that are important in the treatment and course of chronic HIV infection. The infrastructure created by SHM, in collaboration with the network of HIV treatment centres, for the collection, quality control, and analysis of data is easily adaptable for monitoring other infections. As a result, SHM has developed expertise in collecting, analyzing, and reporting data on patients with hepatitis B and hepatitis C virus co-infection. Besides contributing to improved knowledge of HIV, SHM adds to the understanding of other chronic infections and diseases.

SHM is changing. We emphasise this change with this year's Annual Report via a new logo and a new corporate identity of an ambitious organisation. In addition to HIV and AIDS, SHM will be open to monitoring other treatable infections and diseases, which is important for the treatment of people with, and possibly without, HIV. Our first logo, which was conceived during the phase when we developed a monitoring system and built a national HIV observational cohort, symbolised the link between HIV and monitoring. The new logo presents a professional image that is easily identifiable and in line with our current activities and future ambitions. The dots in the logo represent drops of blood, with HIV present in one drop. In all, they represent a population in an ordered pattern, similar to the order in monitoring. Together, they embody our focus on monitoring HIV and other treatable chronic blood-borne viral infections in the Netherlands.

SHM is structurally supported by the Netherlands Ministry of Health, Welfare and Sport. The Dutch government in this way acknowledges the importance of a national monitoring system for HIV and AIDS, and it contributes substantially to the knowledge of the effect of lifelong treatment of HIV on survival and morbidity and on the course of the HIV/AIDS epidemic in the Netherlands and in other Western countries.

The Ministry of Health, Welfare and Sport has specifically appointed the eight academic medical centres and 17 general hospitals as HIV treatment centres. This means that they provide patient data anonymously to SHM as part of patient care. In so doing, the Dutch Government has constructed a unique framework to systematically collect data for the long-term prognostic follow-up of all registered HIV-infected patients in the country.

I would like to thank both professionals and patients for their contribution. Our monitoring approach would not be possible without the ongoing efforts and support of HIV-treating physicians, HIV nurse-consultants, data collection staff, and the staff of various diagnostic laboratories and facilities in the HIV treatment centres. The provision of data by patients living with HIV is of course central to what we do, and we are extremely grateful for their support. Finally, I would like to thank the employees of SHM for their tireless efforts and dedication.

Prof. Frank de Wolf MD

**Director**

**Amsterdam, 28 March 2011**

# Overview

## Quality Data Collection

Stichting HIV Monitoring (SHM) prides itself on its ability to collect and process high-quality data, and during 2010 we continued to refine this process. Continuous collection of data is essential for the work of SHM and is carried out at the 25 HIV treatment centres and subcentres and at the 4 paediatric HIV centres in the Netherlands.

In 2010, extra attention was paid to improving the management of data. Various processes in data management were examined critically, and the obstructions in these processes and in information and communications technology (ICT) infrastructure were defined, as were the steps to correct these problems. During 2010, SHM worked to improve the description of processes and systems and to standardise 'Lab-Link' (the automated link that allows laboratory data from various HIV treatment centres computer systems to be entered directly and anonymously into the SHM database) and other treatment centre databases from which SHM imports data.

## Trends in the Epidemic and Treatment during 2010

The number of people living with HIV infection continues to increase in the Netherlands. As of 31 December 2010, SHM registered a total of 18,380 persons diagnosed with HIV in the Dutch national HIV registration and monitoring database, known as the ATHENA cohort. This includes 1,287 persons who were first registered in 2010, and of these, 66% were diagnosed with HIV infection in 2010. At the end of 2010, the total number of registered HIV-infected children (less than 18 years of age) was 184. Only 1 diagnosis was made in this age group during 2010. Almost one third of the population currently in care was 50 years of age or older.

HIV in the Netherlands is a concentrated epidemic that continues to grow amongst homosexual men more rapidly than it grew at the beginning of the epidemic. In 2010, 79% of the adult patients who were registered and being monitored in the Netherlands were male, and many of these became infected through homosexual contact. The sources that drive the epidemic are men who are probably unaware of having been infected recently and who are involved in high-risk sexual behaviour. It is estimated that approximately 8,000 to 10,000 individuals in the Netherlands do not know they are infected.

Over calendar time, CD4 cell counts found at HIV diagnosis increased, indicating that patients are being diagnosed earlier in their infection. In 2010, the median CD4 cell counts at diagnosis were 390 cells/mm$^3$ for men who have sex with men (MSM), 252 cells/mm$^3$ for male heterosexuals and 250 cells/mm$^3$ for women. More than 50% of MSM with HIV are currently diagnosed when CD4 cell counts are above 350 cells/mm$^3$, which is the threshold above which treatment should be started. However, amongst heterosexual men and women, more than 50% are diagnosed late with CD4 cell counts lower than 350 cells/mm$^3$.

In 2010, 83% of HIV-infected adults were on combination antiretroviral therapy (cART), and 17% were not being treated, mainly because they did not meet the criteria for starting cART or their treatment status was not yet registered. The most frequent combination of drugs at the start of HIV treatment included tenofovir and emtricitabine combined with efavirenz or nevirapine.

Hepatitis B (HBV) and C (HCV) infection are highly prevalent amongst HIV-infected individuals and are associated with major liver diseases. Chronic infection with HBV was found in 6.5% of HIV-infected patients who were tested, and chronic infection with HCV was present in 10%. Co-infection with both HBV and HCV was diagnosed in 1.1%. Of the HBV co-infected patients, liver fibrosis developed in 12.1% and cirrhosis in 6.5%; hepatocellular carcinoma was diagnosed in 1.2%. For the HCV co-infected patients, 17.8% had liver fibrosis, 7.5% cirrhosis, and 0.5% hepatocellular carcinoma. The risk of liver disease in HIV-positive patients with a co-infection was higher than in a comparable group without a co-infection.

Mortality and AIDS incidence rates have dropped since 1996 compared to the period before the introduction of cART, but mortality rates are still higher when compared with the gender- and age-matched general population. AIDS still occurs, with a stable number of 250 to 300 new diagnoses per year.

## Monitoring of HIV Infection in the Netherlands Report 2010

On World AIDS Day, 1 December 2010, SHM published its annual monitoring report that presented major developments in the effects of treatment on the course of HIV infection and the epidemic in the Netherlands, with information extending back to 1996.

The 2010 report confirmed the continuing increase in the number of HIV diagnoses amongst MSM and the late start of cART. In addition, it was reported that cART effectively suppressed virus production in the monitored populations and the incidence of toxicity-driven treatment changes has declined over time. The increase in non-AIDS-related causes of death in the chronically HIV-infected population who receive lifelong treatment has continued. The limit to which CD4 cell counts seem to recover, even when cART is initiated early in the infection, was also reported.

## Quality of Care

In relation to the programme Visible Care (ZiZo), run by the Public Health Inspection Agency as commissioned by the Ministry of Health, SHM has contributed to the development of four quality indicators that will provide insight into HIV care in the 25 HIV treatment centres and subcentres. In addition, SHM cooperated in implementing a feasibility study with these indicators at two HIV treatment centres, with the intention of rolling out these HIV care quality indicators in all HIV treatment centres during 2011. Therefore, SHM's task is to provide the data needed to determine the indicators for each treatment centre. Data will be produced separately for each centre and transferred to the appropriate centre.

In addition to the activities for ZiZo, SHM will continue to implement its Quality of Care programme on the influence of HIV quality of care on the outcome of treatment and disease progression.

A point to consider is the timely start of therapy in patients who present early in the course of their HIV infection at one of the treatment centres. In 2009 and 2010, 6% of the patients who presented with more than 350 CD4 cells/mm$^3$ were started on therapy with less than 200 CD4 cells/mm$^3$. The speed of CD4 cell decline after entry into care is crucial for the timely start of treatment. Consequently, the frequency of monitoring is an important factor in preventing the late start of treatment. Frequency of monitoring is also important after the start of treatment because it plays a major role in early recognition of treatment failure and in avoidance of prolonged exposure to high concentrations of HIV or the development of resistance. It also enables patients to change sooner to a more suitable treatment combination. Through the Quality of Care programme, SHM will help to determine the optimal frequency for monitoring patients.

## Scientific Output

In addition to its yearly scientific report, SHM's contribution to the knowledge and understanding of the HIV/AIDS epidemic and the effect of antiretroviral treatment on the course of HIV infection is visible in its scientific output. In 2010, SHM was involved in 28 publications in peer-reviewed international scientific journals and in 41 presentations at international peer-reviewed conferences, workshops, and meetings.

## NCHIV 2010

SHM's work was also presented at the 2010 National Conference on HIV Pathogenesis, Prevention and Treatment (NCHIV). This yearly conference is organised by SHM in collaboration with the AIDS Fund, the Academic Medical Centre (AMC) in Amsterdam (including the Laboratory of Viral Immune Pathogenesis of the Department of Experimental Immunology, the Amsterdam Institute for Global Health and Development [AIGHD], and the Centre for Poverty-related and Communicable Diseases [CPCD]), the National Institute for Health and the Environment (RIVM), the Sanquin Blood Supply Foundation, and the Netherlands Association of AIDS Treating Physicians (NVAB).

## Collaborations

SHM maintains a strong collaboration with all HIV treatment centres in the Netherlands. The HIV treating physicians, together with data collection staff in HIV treatment centres, are crucial for the work of SHM.

SHM continues to collaborate with other observational cohorts both within and outside Europe. Within the Netherlands, we have an agreement with the Centres for Infectious Disease Control (CIb) of the RIVM for the exchange of data collected through the SHM framework for surveillance purposes that are carried out by the CIb-RIVM. SHM also collaborates with the Academic Medical Centre of the University of Amsterdam and the Public Health

Service (GGD) in Amsterdam on various projects including the national study on HIV and ageing and the Amsterdam Cohort Studies.

Internationally, SHM collaborates with other research groups and observational cohorts in Europe, the United States, and Canada. SHM is involved in international collaborations including A Collaboration on HIV-2 Infection (ACHI$_E$V$_2$E), the Antiretroviral Therapy Cohort Collaboration (ART-CC), the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study, and the Department of Infectious Disease Epidemiology (DIDE) at the Imperial College in London, UK. Other collaborations include the European Centre of Disease Prevention and Control (ECDC), EuroSIDA, HIV Cohorts Analyzed Using Structural Approaches to Longitudinal Data (HIV-CAUSAL), HIV in Europe, and HIV Resistance Response Database Initiative (RDI). The European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCoord) is another collaboration. EuroCoord's governing body, the Council of Partners, is chaired by Frank de Wolf, Director, SHM.

## PhD Programmes

The topics of three ongoing PhD programmes are the clinical implications of immune deficiency and restoration during treatment for HIV infection, the consequences of episodes of HIV viraemia on the clinical outcome of treatment of HIV, and the effect of cART on HIV-infected individuals treated in Curacao compared to that on infected patients from the Netherlands Antilles treated in the Netherlands.

# Organisational report

## HIV Treatment Centres

The monitoring of HIV-infected adults is a collaborative effort involving a total of 25 health institutes that are acknowledged by the Dutch Minister of Health, Welfare and Sport as HIV treatment centres or subcentres and Stichting HIV Monitoring (SHM). In addition, HIV-infected children and adolescents are monitored in four institutes that are recognized as paediatric HIV treatment centres.

In 2010 the following health institutes were involved as (sub)centres for adult HIV care (in alphabetical order of town):

| | | |
|---|---|---|
| 1 | Medisch Centrum Alkmaar | Alkmaar |
| 2 | Flevoziekenhuis | Almere |
| 3 | Academic Medical Centre of the University of Amsterdam | Amsterdam |
| 4 | Onze Lieve Vrouwe Gasthuis (locations Oosterpark and Prinsengracht) | Amsterdam |
| 5 | Sint Lucas Andreas Ziekenhuis | Amsterdam |
| 6 | Slotervaart Ziekenhuis | Amsterdam |
| 7 | Stichting Medisch Centrum Jan van Goyen | Amsterdam |
| 8 | VU Medisch Centrum | Amsterdam |
| 9 | Rijnstate Arnhem | Arnhem |
| 10 | HagaZiekenhuis (location Leyenburg) | Den Haag |
| 11 | Medisch Centrum Haaglanden (location Westeinde) | Den Haag |
| 12 | Catharina Ziekenhuis | Eindhoven |
| 13 | Medisch Spectrum Twente | Enschede |
| 14 | Universitair Medisch Centrum Groningen | Groningen |
| 15 | Kennemer Gasthuis | Haarlem |
| 16 | Medisch Centrum Leeuwarden | Leeuwarden |
| 17 | Leids Universitair Medisch Centrum | Leiden |
| 18 | Academisch Ziekenhuis Maastricht | Maastricht |
| 19 | Universitair Medisch Centrum Sint Radboud | Nijmegen |
| 20 | Erasmus Medisch Centrum | Rotterdam |
| 21 | Maasstad Ziekenhuis | Rotterdam |
| 22 | St. Elisabeth Ziekenhuis | Tilburg |
| 23 | Universitair Medisch Centrum Utrecht | Utrecht |
| 24 | Admiraal De Ruyter Ziekenhuis | Vlissingen |
| 25 | Isala Klinieken (location Sophia) | Zwolle |

Centres for the treatment and monitoring of paediatric HIV and AIDS were:

| | | |
|---|---|---|
| A | Emma Kinderziekenhuis, AMC-UvA | Amsterdam |
| B | Beatrix Kinderkliniek, UMCG | Groningen |
| C | Sophia Kinderziekenhuis, EMC | Rotterdam |
| D | Wilhelmina Kinderziekenhuis, UMCU | Utrecht |


SHM has contracts with each centre or subcentre for the collection of demographic, epidemiologic, clinical, virologic, immunologic, and pharmacologic data for HIV-infected patients who are being followed in one of these hospitals. These contracts are automatically renewed every three years.

In addition to its work in the Netherlands, SHM, in collaboration with the Red Cross Blood Bank in Willemstad, Curacao, also collects the data of HIV-infected persons who are seen by HIV/AIDS doctors at the St. Elisabeth Hospital in Curacao.

## Internal organisation SHM

The Director of Stichting HIV Monitoring, Frank de Wolf, is responsible for the day-to-day management of SHM's activities.

There are two units for SHM's primary activities: one for the collection of patient data and quality control and the other for data processing and analysis, along with one supporting unit.

The data collectors, who are contracted by SHM, work for the patient data and quality control unit. This unit also includes the administration of patient registration for inclusion and exclusion, which involves the assignment of an identification code to each patient. The data monitors, who are responsible for the execution of the data quality control procedures, are also part of this unit.

The patient data and quality control unit coordinates the data management. This function is outsourced to Data Management Support (DMS), which is part of the Department of Clinical Epidemiology and Biostatistics of the Academic Medical Centre of the University of Amsterdam. At least twice a year, in February/March and in June/July, data from the database are merged into a dataset to be used for data processing and analysis.

The patient data and quality control unit is managed by Sima Zaheri. During 2010, an average number of 8.20 fte's was assigned.

Four researchers in the field of epidemiology, statistics, mathematical modelling of HIV, and modelling transmission networks staff the data processing and analysis unit. Together, they execute the HIV registration programme, the results of which are presented in the annual SHM monitoring report, published on 1 December, World AIDS Day, as well as in separate publications in peer-reviewed international scientific journals. This unit supports and collaborates nationally with researchers in HIV treatment centres and internationally with research groups working with comparable observational cohorts in the field of epidemiology and the treatment of HIV. Also, this unit arranges the support of research applications from the Dutch pharmaceutical industry.

In addition to the four researchers, the unit had two assistant researchers in two Ph.D. programmes during 2010. These programmes focus on the study of clinical implications of immune deficiency and restoration during treatment for HIV infection, and on the consequences of episodes of HIV viraemia on the clinical outcome of treatment of HIV. In addition, the unit continues to support a third Ph.D. programme on the effect of cART on HIV-infected individuals treated in Curacao compared to that on infected patients from the Netherlands Antilles treated in the Netherlands.

In 2010, an average number of 5.09 fte's was assigned to the data processing and analysis unit. This unit is led by Frank de Wolf (1.00 fte), Director of SHM.

The primary activities of SHM are supported by the members of the office. The office includes the secretariat, financial and personnel administration and control, and communication. It is supervised by SHM's controller, Daniëlle de Boer, and an average of 3.91 fte's was assigned to it in 2010. This number has remained constant over past years.

As of 31 December 2010, the average total number of personnel was 18.20 fte's. In addition, SHM covers the costs for a total of 8.14 fte's who are appointed in the HIV treatment centres

to handle data collection and entry, but who are not on the staff of SHM. The average sick leave during 2010 was 4.88%.

## Database & data management

In 2010, extra attention was paid to further improving data management of Stichting HIV Monitoring (SHM). Along with the quantitative increase of data over the years, the SHM database has expanded to include subgroups of patients and additional data sets. Data from different sources is merged into a combined dataset for analysis and presentation in tabular and report form to the HIV treatment centres. In 2010, SHM, together with the Clinical Research Unit (CRU) of the AMC, the organisation that has provided data management for SHM since 2002, took a critical look at the various processes in data management. The analysis defined the obstacles in ICT infrastructure and data-management processes, as well as the steps to eliminate them. During 2010, SHM improved the following:

- **Description of processes and systems:**
  The various data-management processes were described in detail by both the CRU and SHM. A data architecture was designed, and the systems were described in terms of characterisation, location, management, data dictionary, data conversion, and validation checks.

- **Standardisation of 'Lab-Link':**
  'Lab-Link' (the automated link that allows laboratory data from various computer systems in the HIV treatment centres to be entered directly and anonymously into the SHM database) was first introduced in 2005 at AMC Amsterdam and then implemented through until the beginning of 2009 at other treatment centres, including St. Elisabeth Hospital Tilburg, Slotervaart Hospital Amsterdam, MC Twente Enschede, LUMC Leiden, Maasstad Hospital Rotterdam, UMCU Utrecht and Isala Clinics (Sophia) Zwolle. The datasets delivered by the eight centres vary in format and structure, resulting in the need for many manual controls of data structure and content per delivery. For the further implementation of Lab-Link at the remaining HIV treatment centres, a standardisation project was started in 2010 with the aim of fully automating data delivery. To achieve this, arrangements were made with the General Services ICT (ADICT) and CRU departments of the AMC for the launch of a pilot project with the MCA Alkmaar, whereby the laboratory results from the MCA Alkmaar are now sent in HL7 messaging form via a secure connection to a server at the AMC. In addition, other centres identified the possibilities for implementing a similar connection.

- **Standardisation of import databases:**
  Until 2003, data from patients was collected in local Access databases (HIVREG) and merged every six months. In 2003, an Oracle Clinical database for centralized data col-

*Table 1: Data collection results 2004–2010*

| | 2010 | 2009 | 2008 | 2007 | 2006 | 2005 | 2004 |
|---|---|---|---|---|---|---|---|
| **Manual data collection** | | | | | | | |
| HIV infected adults | | | | | | | |
| Anamneses | 186,507 | 78,396 | 69,364 | 53,359 | 56,700 | 64,062 | 126,924 |
| Follow-up | 6,044,689 | 4,941,270 | 4,824,298 | 4,316,778 | 3,615,436 | 3,325,594 | 2,575,088 |
| End of follow-up | 11,680 | 11,123 | 9,778 | 11,561 | 13,043 | 8,691 | 7,799 |
| Laboratory results | 8,166,082 | 7,637,999 | 6,833,090 | 7,124,209 | 7,112,151 | 5,961,439 | 5,760,663 |
| Subtotal (data points) | 14,408,958 | 12,668,788 | 11,736,530 | 11,505,907 | 10,797,330 | 9,359,786 | 8,470,474 |
| HIV infected children | | | | | | | |
| Anamneses | 944 | 1,976 | 688 | 1,051 | 1,750 | 4,148 | 1,425 |
| Follow-up | 80,126 | 113,967 | 118,562 | 168,704 | 314,136 | 311,260 | 75,263 |
| End of follow-up | 195 | 150 | 0 | 63 | 165 | 75 | 0 |
| Laboratory results | 10,4370 | 271,267 | 200,129 | 441,003 | 536,153 | 809,088 | 261,036 |
| Subtotal (data points) | 18,5635 | 387,360 | 319,379 | 610,821 | 852,204 | 1,124,571 | 337,724 |
| HIV exposed children | | | | | | | |
| Anamneses | 2,040 | 80 | 901 | | | | |
| Follow up | 11,243 | 4,787 | 2,870 | | | | |
| End of follow-up | 1069 | 192 | 28,793 | | | | |
| Laboratory results | 11,407 | 2,916 | 15,336 | | | | |
| Subtotal (data points) | 25,759 | 7,975 | 47,900 | | | | |
| Pregnancies | | | | | | | |
| Anamneses | 2,682 | 940 | 1,705 | 1,275 | 3,876 | 3,648 | 0 |
| Follow-up and end of pregnancies | 8,816 | 7,548 | 16,044 | 12,020 | 37,216 | 35,540 | 0 |
| Laboratory results | 7,632 | 5,865 | 14,123 | 10,532 | 42,905 | 31,332 | 0 |
| Subtotal (data points) | 19,130 | 14,353 | 31,872 | 23,827 | 83,997 | 70,520 | 0 |
| Additional data | | | | | | | |
| Causes of death (numbers) | 152 | 113 | 108 | 128 | 164 | 27 | 1 |
| Cardiovascular accidents (numbers) | 219 | 167 | 55 | 81 | 151 | 108 | 45 |
| Other comorbidities | 199 | 529 | | | | | |
| Subtotal additional data (numbers) | 570 | 809 | 163 | 209 | 315 | 135 | 46 |
| **Total manual collection (data points)** | **14,640,052** | **13,079,285** | **12,135,681** | **12,140,555** | **11,733,531** | **10,554,877** | **8,808,198** |
| **Increase (%) manually collected data (data points)** | **12%** | **8%** | **0%** | **3%** | **11%** | **20%** | |

| | 2010 | 2009 | 2008 | 2007 | 2006 | 2005 | 2004 |
|---|---|---|---|---|---|---|---|
| **Automated data collection (Lab-Link)** | | | | | | | |
| Number of lab results per year | 433,254 | 389,015 | 222,668 | 119,668 | 95,685 | | |
| **Total automated collection (estimated data points)** | **1,733,016** | **1,556,060** | **890,672** | **478,672** | **382,740** | | |
| Lab-Link from total lab results (%) | 9% | 9% | 11% | 6% | 5% | | |
| **Increase (%) Lab-Link data** | **11%** | **75%** | **86%** | **25%** | | | |
| **Total data collection (data points)** | **16,373,068** | **14,635,345** | **13,026,353** | **12,619,227** | **12,116,271** | **10,554,877** | **8,808,198** |
| **Increase (%) total data** | **12%** | **16%** | **3%** | **4%** | **15%** | **20%** | |
| Number of patients in follow-up | 14,844 | 14,138 | 13,296 | 11,666 | 10,275 | 9,399 | 8,537 |
| **Increase (%) patients in follow-up** | **5%** | **6%** | **14%** | **14%** | **9%** | **10%** | |

lection via a secure Internet connection was implemented. To date, the differently formatted data from these two types of databases have been synchronised and merged. Data corrections resulting from data quality controls are then entered in both systems. In 2010, a standardization process was begun, with the aim of using the Oracle Clinical database as the principle database for manual data entry and corrections. To achieve this, data from the HIVREG databases still needs to be imported on a single occasion into the Oracle Clinical database. To assist in this process, tables from the HIVREG databases were clustered, synchronized and processed.

In addition to the steps taken to improve data management, a number of data processing steps resulting in data products were automated during 2010. Work was also carried out on developing Centre Specific (CS) reports, with the aim of providing treatment teams in HIV treatment centres with a biannual overview of developments, trends and issues within their own patient population. This data product was presented to a panel of HIV specialists who agreed on the content and presentation format.

## Volume of data collection

The results of the data collection are summarised in *Table 1*. The total volume of data collected manually increased in 2010 by 12% in comparison to 2009. This is due to the data collection of new registrations in 2010 and increased retrospective data collection at some hospitals to reduce their data backlog. The volume of automated data collection with Lab-Link increased by 11% compared to 2009. This increase is proportional to the increase of data as a result of new registrations in 2010 and follow-up data from patients already registered in the database.

*Table 2: Percentage of patients being followed in each treatment centre with average data collection backlog of more than and fewer than 365 days*

| HIV treatment centre | >365 days | | <365 days | |
|---|---|---|---|---|
| | 2010 | 2009 | 2010 | 2009 |
| MC Alkmaar | 1% | 2% | 3% | 10% |
| Flevoziekenhuis Almere | 0% | 0% | 30% | 21% |
| AMC Amsterdam | 2% | 3% | 25% | 20% |
| OLVG Oosterpark Amsterdam | 0% | 0% | 6% | 10% |
| Slotervaart Ziekenhuis Amsterdam | 0% | 1% | 14% | 8% |
| St. Lucas Andreas Ziekenhuis Amsterdam | 0% | 2% | 22% | 7% |
| MC Jan van Goyen Amsterdam | 0% | 0% | 5% | 3% |
| VUMC Amsterdam | 1% | 1% | 25% | 23% |
| Ziekenhuis Rijnstate Arnhem | 0% | 1% | 32% | 33% |
| Haga Ziekenhuis (Leyenburg) Den Haag | 3% | 5% | 4% | 5% |
| MC Haaglanden (Westeinde) Den Haag | 4% | 7% | 30% | 30% |
| Catharina Ziekenhuis Eindhoven | 4% | 4% | 6% | 7% |
| Medisch Spectrum Twente Enschede | 0% | 0% | 4% | 39% |
| UMCG Groningen | 1% | 55% | 45% | 15% |
| Kennemer Gasthuis (EG) Haarlem | 6% | 44% | 31% | 14% |
| MCL Leeuwarden | 0% | 1% | 17% | 55% |
| LUMC Leiden | 0% | 2% | 9% | 10% |
| AZM Maastricht | 40% | 39% | 14% | 24% |
| UMC St. Radboud Nijmegen | 5% | 1% | 41% | 20% |
| Erasmus MC Rotterdam | 5% | 2% | 17% | 19% |
| Maastad Ziekenhuis Rotterdam | 0% | 4% | 10% | 30% |
| St. Elisabeth Ziekenhuis Tilburg | 3% | 5% | 3% | 4% |
| UMCU Utrecht | 0% | 4% | 3% | 24% |
| Admiraal De Ruyter Ziekenhuis Vlissingen | 1% | 0% | 2% | 3% |
| Isala Klinieken (Sophia) Zwolle | 4% | 3% | 9% | 15% |
| **Total** | **3%** | **7%** | **16%** | **18%** |

*Table 2* shows the percentage of patients with delays in data collection (data backlog) at each HIV treatment centre. A distinction is made between an estimated backlog of more than 365 days and one of less than 365 days. The estimated data backlog is based on the difference between the predicted time and the actual time between the most recent patient visit and the following visit. The predicted time is calculated based on the frequency of visits during the previous year and the last visit.

In 2010, the long-term backlog in data collection decreased by 4% in comparison to 2009. This is largely due to the ongoing training of data collectors in efficiently organising the logistics of data collection, so that the follow-up data of patients with the largest data-entry backlog takes priority. The long-term backlog at the UMCG Groningen and Kennemer Gasthuis Haarlem has been dramatically reduced through the placement of SHM data collectors who have supported the local data collectors. The long-term backlog at AZM Maastricht is the largest and relates to the loss and replacement of the relevant data collector. A SHM data collector has since been placed at AZM Maastricht to assist with reducing the backlog.

The short-term data collection backlog decreased 2% in 2010. This is a result of the accurate monitoring of data-entry backlogs by data collectors and monitors.

## Quality control (QC)

In 2010, priority was given to controlling data related to the liver and liver disorders. A recognised scientific formula, based on the number of laboratory values, was used to predict which patients would be more likely to develop liver fibrosis. Accordingly, medical records of 1,147 patients were monitored in a case controlled study. The results of quality controls have been analysed and published in SHM's *Monitoring of HIV Infection in the Netherlands* report.

The controlling of data related to cause of death and co-morbidity, defined as "endpoints", continued to be controlled in 100% of the cases in 2010. These endpoints were also classified for data analysis.

As part of the individual coaching programme of the 39 data collectors, at least three patient files of each data collector were selected for quality control. The results of the checks were discussed with the responsible data collectors, and item-specific training was given.

The number of verified patient files per selection procedure is summarised in *Table 3*. In 2010, a total of 1,850 different patients were checked by SHM data monitors. Within the framework of the DAD study, 418 patient files were checked for cardiovascular accidents and other co-morbidities. The causes of death of 152 patients were verified and classified. On average, each HIV treatment centre was visited nine times during the year by the SHM data monitor(s) responsible for that centre.

The number of patients whose files were quality-controlled increased by 96% in 2010 compared to 2009. This can be explained by the selection of many patient records to monitor liver disease, co-morbidity and cause of death.

*Table 3: Number of patients' files checked by data monitors per data selection criterion*

| Selection criteria for quality checks: | 2010 | 2009 | 2008 | 2007 | 2006 | 2005 | 2004 |
|---|---|---|---|---|---|---|---|
| Random selection | | | | | | | |
| Random selection of adverse events data | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Random selection of antiretroviral medication data | 0 | 2 | 8 | 3 | 13 | 6 | 0 |
| Random selection of baseline data | 0 | 0 | 0 | 52 | 17 | 7 | 1 |
| Random selection of CDC events data | 0 | 0 | 1 | 2 | 11 | 0 | 0 |
| Random selection of co-medication data | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Random selection of all patient data | 1 | 0 | 2 | 1 | 17 | 87 | 118 |
| Random selection of data from last year of follow-up | 0 | 0 | 0 | 0 | 38 | 126 | 203 |
| **Subtotal random selection** | **1** | **2** | **11** | **60** | **99** | **226** | **322** |
| Consistency checks | | | | | | | |
| Inconsistencies adverse events data | 1,147 | 74 | 1,056 | 30 | 69 | 1 | 0 |
| Inconsistencies in antiretroviral medication data | 2 | 23 | 209 | 1 | 18 | 3 | 0 |
| Inconsistencies in baseline data | 0 | 0 | 116 | 362 | 97 | 161 | 0 |
| Priority analyses baseline data | 0 | 10 | 0 | 207 | 0 | 0 | 0 |
| Inconsistencies in CDC events data | 2 | 3 | 257 | 122 | 289 | 0 | 0 |
| Inconsistencies in co-medication data | 0 | 4 | 2 | 7 | 17 | 0 | 0 |
| Inconsistencies in laboratory data | 4 | 16 | 93 | 18 | 5 | 0 | 0 |
| **Subtotal consistency checks** | **1,155** | **130** | **1,733** | **747** | **495** | **165** | **0** |
| Morbidity and causes of death checks | | | | | | | |
| Pregnancies | 0 | 0 | 1 | 0 | 129 | 10 | 0 |
| Total cardiovascular accidents: | 219 | 167 | 55 | 92 | 151 | 108 | 45 |
| *Myocardial infarction* | *46* | *36* | *16* | *17* | *31* | *33* | *14* |
| *Invasive cardiovascular procedures* | *49* | *43* | *14* | *10* | *40* | *16* | *10* |
| *Diabetes mellitus* | *101* | *62* | *19* | *40* | *55* | *37* | *16* |
| *Stroke* | *23* | *26* | *6* | *25* | *25* | *22* | *5* |
| Chronic liver disease | 10 | 22 | | | | | |
| End stage renal disease | 12 | 13 | | | | | |
| Non-aids defining malignancy | 177 | 381 | | | | | |
| Causes of death 100% of cases | 152 | 113 | 108 | 128 | 164 | 27 | 1 |
| **Subtotal morbidity and causes of death checks** | **570** | **696** | **164** | **220** | **444** | **145** | **46** |
| **Subtotal personal coaching of data collectors** | **124** | **114** | **241** | **268** | **216** | **0** | **0** |
| **Total number of patients' files checked** | **1,850** | **942** | **2,149** | **1,295** | **1,254** | **536** | **368** |
| **% change per year** | **96%** | **-56%** | **66%** | **3%** | **179%** | **19%** | |

In addition to the patient files selected for quality control, validation checks were carried out on separate records in the SHM data warehouse. There were 173 validation checks performed on 17 tables in the SHM database. All records relating to HIV-related conditions that showed discrepancies following the validation checks were sent to the responsible data collectors and the results of the quality controls were incorporated in the database.

### Training and education

In September 2010, a review day was organised for the data collectors, during which a lecture was given on malignancies. SHM's data monitors also discussed a number of cases based on patient files. In addition, the data collectors were trained in procedures and work related to the collection of co-morbidity data and the improvement of data quality. In December 2010, a proportion of the data monitors were trained to recognise various infectious diseases. Other data monitors were trained in information security standard ISO 27001/27002.

## Monitoring report

### Development in the number of registered and monitored persons with HIV

By the end of 2010, a cumulative total of 18,380 patients with HIV infection were registered through the HIV treatment centres *(Table 4)* by SHM, an increase of 1,290 (7%) in comparison to 2009. AIDS developed in a cumulative number of 4,892 (26.6%) patients, and 1,729 (9.4%) died; of those, 1,604 died before 2010 and 125 in 2010.

In total, 2,340 (12.7%) patients were recorded as lost-to-follow-up, because no data were obtained from these patients in 2010. This number is reduced compared to 2009. However, given the distribution throughout the participating HIV treatment centres, backlogs in data entry probably had a substantial role in the lack of data. Figures for the treatment centres Academische Ziekenhuis Maastricht, the MCH-Westeinde and the HagaZiekenhuis Leyenburg in The Hague are especially of concern. The number of patients actively monitored to the end of 2010 rose to 14,436, an increase of 10% in comparison to 2009.

Of the 1,287 new patients included in the monitoring of HIV between 1 January 2010 and 1 January 2011, 174 (13.5%) were diagnosed with AIDS, and 18 (1.4%) died in 2010 *(Table 5)*.

As of 31 December 2010, data from a total of 702 HIV-infected persons, including 18 children, monitored at the Sint Elisabeth Hospital in Willemstad, Curacao, were included in the SHM database. This is an increase of 86 persons compared to the number in 2009.

As of 31 December 2010, data from a total of 18,085 persons (14,298 [79.1%] men and 3,787 [20.9%] women) from the total HIV-infected population who did not object to further data collection were included in this annual report. Amongst those newly registered in 2010,

*Table 4: Cumulative numbers and percentages of HIV-infected patients registered and monitored in one of the HIV Treatment Centres in the Netherlands and Curacao on 31 December 2010 by SHM.*

| HIV Treatment Centre | Location | Total N | Total % | Alive N | Alive % | Deaths N | Deaths % | AIDS N | AIDS % | In follow-up N | In follow-up % | Lost to follow-up N | Lost to follow-up % | Deaths before 2010 N | Deaths before 2010 % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adults | | | | | | | | | | | | | | | |
| MCA | Alkmaar | 247 | 1.4 | 228 | 92.3 | 19 | 7.7 | 70 | 28.3 | 201 | 81.4 | 28 | 11.3 | 18 | 7.3 |
| Flevoziekenhuis | Almere | 86 | 0.5 | 85 | 98.8 | 1 | 1.2 | 25 | 29.1 | 84 | 97.7 | 1 | 1.2 | 1 | 1.2 |
| AMC-UvA | Amsterdam | 2,496 | 13.7 | 2,244 | 89.9 | 252 | 10.1 | 727 | 29.1 | 1,995 | 79.9 | 259 | 10.4 | 242 | 9.7 |
| MC Jan van Goyen | Amsterdam | 548 | 3 | 521 | 95.1 | 27 | 4.9 | 97 | 17.7 | 489 | 89.2 | 33 | 6 | 26 | 4.7 |
| OLVG-Oosterpark | Amsterdam | 2,599 | 14.3 | 2,365 | 91 | 234 | 9 | 698 | 26.9 | 2,084 | 80.2 | 299 | 11.5 | 216 | 8.3 |
| OLVG-Prinsengracht | Amsterdam | 41 | 0.2 | 9 | 22 | 32 | 78 | 30 | 73.2 | 0 | 0 | 9 | 22 | 32 | 78 |
| St Lucas Andreas Zkh | Amsterdam | 282 | 1.6 | 251 | 89 | 31 | 11 | 97 | 34.4 | 230 | 81.6 | 24 | 8.5 | 28 | 9.9 |
| Slotervaart Zkh | Amsterdam | 787 | 4.3 | 670 | 85.1 | 117 | 14.9 | 243 | 30.9 | 599 | 76.1 | 76 | 9.7 | 112 | 14.2 |
| VUMC | Amsterdam | 470 | 2.6 | 409 | 87 | 61 | 13 | 150 | 31.9 | 347 | 73.8 | 66 | 14 | 57 | 12.1 |
| Rijnstate Zkh | Arnhem | 567 | 3.1 | 512 | 90.3 | 55 | 9.7 | 137 | 24.2 | 464 | 81.8 | 51 | 9 | 52 | 9.2 |
| HagaZkh-Leyenburg | Den Haag | 612 | 3.4 | 555 | 90.7 | 57 | 9.3 | 196 | 32 | 436 | 71.2 | 122 | 19.9 | 54 | 8.8 |
| MCH-Westeinde | Den Haag | 731 | 4 | 672 | 91.9 | 59 | 8.1 | 171 | 23.4 | 552 | 75.5 | 127 | 17.4 | 52 | 7.1 |
| Catharina Zkh | Eindhoven | 436 | 2.4 | 414 | 95 | 22 | 5 | 79 | 18.1 | 356 | 81.7 | 62 | 14.2 | 18 | 4.1 |
| MST | Enschede | 391 | 2.2 | 331 | 84.7 | 60 | 15.3 | 113 | 28.9 | 298 | 76.2 | 48 | 12.3 | 45 | 11.5 |
| UMCG | Groningen | 714 | 3.9 | 658 | 92.2 | 56 | 7.8 | 196 | 27.5 | 599 | 83.9 | 63 | 8.8 | 52 | 7.3 |
| Kennemer Gasthuis | Haarlem | 355 | 2 | 316 | 89 | 39 | 11 | 95 | 26.8 | 270 | 76.1 | 47 | 13.2 | 38 | 10.7 |
| MC Leeuwarden | Leeuwarden | 218 | 1.2 | 198 | 90.8 | 20 | 9.2 | 51 | 23.4 | 172 | 78.9 | 26 | 11.9 | 20 | 9.2 |
| LUMC | Leiden | 544 | 3 | 504 | 92.6 | 40 | 7.4 | 142 | 26.1 | 442 | 81.3 | 65 | 11.9 | 37 | 6.8 |
| AZM | Maastricht | 641 | 3.5 | 550 | 85.8 | 91 | 14.2 | 157 | 24.5 | 292 | 45.6 | 261 | 40.7 | 88 | 13.7 |
| UMC St Radboud | Nijmegen | 549 | 3 | 493 | 89.8 | 56 | 10.2 | 156 | 28.4 | 432 | 78.7 | 63 | 11.5 | 54 | 9.8 |
| Erasmus MC | Rotterdam | 1,903 | 10.5 | 1,721 | 90.4 | 182 | 9.6 | 502 | 26.4 | 1,495 | 78.6 | 241 | 12.7 | 167 | 8.8 |
| Maasstad Zkh | Rotterdam | 414 | 2.3 | 389 | 94 | 25 | 6 | 90 | 21.7 | 363 | 87.7 | 31 | 7.5 | 20 | 4.8 |
| St Elsabeth Zkh | Tilburg | 796 | 4.4 | 750 | 94.2 | 46 | 5.8 | 177 | 22.2 | 667 | 83.8 | 88 | 11.1 | 41 | 5.2 |
| UMCU | Utrecht | 1,311 | 7.2 | 1,188 | 90.6 | 123 | 9.4 | 364 | 27.8 | 1,079 | 82.3 | 118 | 9 | 114 | 8.7 |
| Admiraal de Ruyter Zkh | Vlissingen | 112 | 0.6 | 101 | 90.2 | 11 | 9.8 | 30 | 26.8 | 86 | 768 | 16 | 14.3 | 10 | 8.9 |
| Isala Klinieken-Sophia | Zwolle | 321 | 1.8 | 309 | 96.3 | 12 | 3.7 | 50 | 15.6 | 283 | 88,2 | 29 | 9 | 9 | 2.8 |
| **Total Adults** | | **18,171** | **98.9** | **16,443** | **90.5** | **1,728** | **9.5** | **4,843** | **26.7** | **14,315** | **78.8** | **2,253** | **12.4** | **1,603** | **8.8** |

| HIV Treatment Centre | Location | Total N | Total % | Alive N | Alive % | Deaths N | Deaths % | AIDS N | AIDS % | In follow-up N | In follow-up % | Lost to follow-up N | Lost to follow-up % | Deaths before 2010 N | Deaths before 2010 % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Children/adolescents | | | | | | | | | | | | | | | |
| Emma Kinderzkh, AMC-UvA | Amsterdam | 61 | 29.2 | 61 | 100 | 0 | 0 | 15 | 24.6 | 57 | 93.4 | 0 | 0 | 0 | 0 |
| Beatrix Kinderkliniek, UMCG | Groningen | 13 | 6.2 | 13 | 100 | 0 | 0 | 3 | 23.1 | 3 | 23.1 | 10 | 76.9 | 0 | 0 |
| Sophia Kinderzkh, EMC | Rotterdam | 74 | 35.4 | 73 | 98.6 | 1 | 1.4 | 20 | 27 | 52 | 70.3 | 15 | 20.3 | 1 | 1.4 |
| Wilhelmina Kinderzkh, UMCU | Utrecht | 61 | 29.2 | 61 | 100 | 0 | 0 | 11 | 18 | 9 | 14.8 | 52 | 85.2 | 0 | 0 |
| **Total children/adolescents** | | **209** | **1.1** | **208** | **99.5** | **1** | **0.5** | **49** | **23.4** | **121** | **57.9** | **77** | **36.8** | **1** | **0.5** |
| **Total Netherlands** | | **18,380** | **100** | **16,651** | **90.6** | **1,729** | **9.4** | **4,892** | **26.6** | **14,436** | **78.5** | **2,330** | **12.7** | **1,604** | **8.7** |
| Curacao | | | | | | | | | | | | | | | |
| SEHOS | Willemstad | 684 | 97.4 | 550 | 80.4 | 134 | 19.6 | 181 | 26.5 | 441 | 64.5 | 125 | 18.3 | 116 | 17 |
| SEHOS kinderkliniek | Willemstad | 18 | 2.6 | 9 | 50 | 9 | 50 | 6 | 33.3 | 0 | 0 | 9 | 50 | 9 | 50 |
| **Total Curacao** | | **702** | **100** | | | | | | | | | | | | |

66% also received the diagnosis of HIV in 2010, whereas 13% had received the diagnosis in 2009.

Of the 14,298 men, 188 (1.3%) were younger than 18 years of age at HIV diagnosis, 5,868 (41%) were 18 to 34 years, 7,196 (50.3%) were 35 to 54 years, and 942 (6.6%) were 55 years or older. Of the 3,787 women, 212 (5.6%) were younger than 18 years of age at HIV diagnosis, 2,346 (61.9%) were 18 to 34 years, 1,034 (27.3%) were 35 to 54 years, and 142 (3.7%) were 55 years or older. The date of HIV diagnosis, and therefore age at diagnosis, is still unknown for 104 men and 53 women.

Of the 1,065 men who were registered in 2010, 1% were younger than 18 years of age, 35% were 18 to 34 years, 49% were 35 to 54 years, and 9% were 55 years or older. Of the 191 women registered in 2010, 5% were younger than 18 years of age, 49% were 18 to 34 years, 29% were 35 to 54 years, and 7% were 55 years or older. The date of HIV diagnosis was unknown for 63 (6%) men and 19 (10%) women.

*Table 5: New HIV diagnosed patients registered and monitored in 2010 in one of the HIV treatment centres in the Netherlands and in Curacao.*

| | | Total | | Alive | | Deaths | | AIDS | | In follow-up | | Lost to follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HIV treatment centre** | **Location** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Adults | | | | | | | | | | | | | |
| MCA | Alkmaar | 17 | 1.3 | 17 | 100 | 0 | 0 | 2 | 11.8 | 17 | 100 | 0 | 0 |
| Flevoziekenhuis | Almere | 23 | 1.8 | 23 | 100 | 0 | 0 | 5 | 21.7 | 23 | 100 | 0 | 0 |
| OLVG - Oosterpark | Amsterdam | 186 | 14.6 | 184 | 98.9 | 2 | 1.1 | 17 | 9.1 | 185 | 99.5 | 0 | 0 |
| AMC-UvA | Amsterdam | 119 | 9.3 | 119 | 100 | 0 | 0 | 13 | 10.9 | 119 | 100 | 0 | 0 |
| MC Jan van Goyen | Amsterdam | 35 | 2.7 | 35 | 100 | 0 | 0 | 1 | 2.9 | 35 | 100 | 0 | 0 |
| St Lucas Andreas Zkh | Amsterdam | 30 | 2.4 | 29 | 96.7 | 1 | 3.3 | 4 | 13.3 | 30 | 100 | 0 | 0 |
| VUMC | Amsterdam | 26 | 2 | 25 | 96.2 | 1 | 3.8 | 5 | 19.2 | 26 | 100 | 0 | 0 |
| Slotervaart Zkh | Amsterdam | 22 | 1.7 | 22 | 100 | 0 | 0 | 3 | 13.6 | 22 | 100 | 0 | 0 |
| Rijnstate Zkh | Arnhem | 54 | 4.2 | 53 | 98.1 | 1 | 1.9 | 3 | 5.6 | 54 | 100 | 0 | 0 |
| HagaZkh - Leyenburg | Den Haag | 19 | 1.5 | 19 | 100 | 0 | 0 | 4 | 21.1 | 19 | 100 | 0 | 0 |
| MCH - Westeinde | Den Haag | 53 | 4.2 | 51 | 96.2 | 2 | 3.8 | 5 | 9.4 | 53 | 100 | 0 | 0 |
| Catharina Zkh | Eindhoven | 40 | 3.1 | 40 | 100 | 0 | 0 | 3 | 7.5 | 40 | 100 | 0 | 0 |
| MST | Enschede | 48 | 3.8 | 34 | 70.8 | 14 | 29.2 | 13 | 27.1 | 35 | 72.9 | 0 | 0 |
| UMCG | Groningen | 65 | 5.1 | 64 | 98.5 | 1 | 1.5 | 9 | 13.8 | 65 | 100 | 0 | 0 |
| Kennemer Gasthuis | Haarlem | 27 | 2.1 | 27 | 100 | 0 | 0 | 6 | 22.2 | 27 | 100 | 0 | 0 |
| MCL | Leeuwarden | 11 | 0.9 | 11 | 100 | 0 | 0 | 2 | 18.2 | 11 | 100 | 0 | 0 |
| LUMC | Leiden | 39 | 3.1 | 38 | 97.4 | 1 | 2.6 | 8 | 20.5 | 39 | 100 | 0 | 0 |
| AZM | Maastricht | 37 | 2.9 | 36 | 97.3 | 1 | 2.7 | 10 | 27 | 37 | 100 | 0 | 0 |
| UMC St Radboud | Nijmegen | 40 | 3.1 | 40 | 100 | 0 | 0 | 6 | 15 | 40 | 100 | 0 | 0 |
| Erasmus MC | Rotterdam | 140 | 11 | 138 | 98.6 | 2 | 1.4 | 21 | 15 | 140 | 100 | 0 | 0 |
| Maasstad Zkh | Rotterdam | 32 | 2.5 | 31 | 96.9 | 1 | 3.1 | 4 | 12.5 | 32 | 100 | 0 | 0 |
| St Elisabeth Zkh | Tilburg | 63 | 4.9 | 63 | 100 | 0 | 0 | 8 | 12.7 | 63 | 100 | 0 | 0 |
| UMCU | Utrecht | 96 | 7.5 | 94 | 97.9 | 2 | 2.1 | 15 | 15.6 | 96 | 100 | 0 | 0 |
| Admiraal de Ruyter Zkh | Vlissingen | 15 | 1.2 | 14 | 93.3 | 1 | 6.7 | 2 | 13.3 | 15 | 100 | 0 | 0 |
| Isala Klinieken - Sophia | Zwolle | 37 | 2.9 | 36 | 97.3 | 1 | 2.7 | 5 | 13.5 | 37 | 100 | 0 | 0 |
| **Total Adults** | | **1274** | **100** | **1243** | **97.6** | **31** | **2.4** | **174** | **13.7** | **1260** | **98.9** | **0** | **0** |
| Children | | | | | | | | | | | | | |
| Emma Kinderzkh, AMC-UvA | Amsterdam | 3 | 23.1 | 3 | 100 | 0 | 0 | 0 | 0 | 3 | 100 | 0 | 0 |
| Beatrix Kinderkliniek, UMCG | Groningen | 2 | 15.4 | 2 | 100 | 0 | 0 | 0 | 0 | 2 | 100 | 0 | 0 |
| Sophia Kinderzkh, EMC | Rotterdam | 7 | 53.8 | 7 | 100 | 0 | 0 | 0 | 0 | 7 | 100 | 0 | 0 |
| Wilhelmina Kinderzkh, UMCU | Utrecht | 1 | 7.7 | 1 | 100 | 0 | 0 | 0 | 0 | 1 | 100 | 0 | 0 |
| **Total Children** | | **13** | **100** | **13** | **100** | **0** | **0** | **0** | **0** | **13** | **100** | **0** | **0** |
| Curacao | | | | | | | | | | | | | |
| SEHOS | Willemstad | 87 | 100 | 75 | 86.2 | 12 | 13.8 | 19 | 21.8 | 77 | 88.5 | 0 | 0 |

## Registration of HIV-infected adults

In 2010, out of a total of 18,085 registered persons, 12,734 (78.7%) were men, currently alive and aged 18 years or older, and 3,443 (21.3%) were women. Amongst men, homosexual contact was by far the greatest risk factor (72%), whereas heterosexual transmission was the greatest risk factor for women (89%). The median age at diagnosis was 36.6 (IQR, 30.1-43.7) for men and 30.6 (25.3-37.2) for women. Five percent of the total population had known their HIV status for less than a year. The infection state had been known in 27% for 1 to 5 years, in 30% for 5 to 10 years, and in 37% for more than 10 years.

Of the 1,210 adults who were registered in 2010 and whose data was processed by the end of 2010, 1,033 (85.4%) were men, and 177 (14.6%) were women. Homosexual contact was still the most frequent risk factor (72%) amongst men, and heterosexual contact was the most frequent amongst women (89%). In 2010, the median age at diagnosis was 38.7 years (IQR, 30.3-46.7) in men and 33.5 (27.0-41.8) in women. Of the registered persons, 67% had known their HIV status for less than a year, 18% for 1 to 5 years, 3% for 5 to 10 years, and 4% for more than 10 years. The diagnosis date was not known for the remaining 8%.

## Registration of HIV-infected children

As of 31 December 2010, 184 children aged 17 years or younger were registered as HIV-positive. Amongst that group, 97 (53%) were boys, and 87 (47%) were girls. The median age at diagnosis was 1.9 years (IQR 0.5-5.2) for boys and 1.9 years for girls (0.4-4.7). In 2010, 10 diagnoses were recorded in this age group. Vertical mother-to-child transmission was the route of infection in almost all (85%); apart from that, a few cases were recorded as sexual transmission. In total, 48% of the infected children were of Dutch origin, and 43% were born in sub-Saharan Africa.

## Registration of HIV-infected pregnant women

In 2010, the total number of registered pregnancies in 1,299 HIV-infected women increased to 2,038. In 55% of the cases, HIV was diagnosed before the start of the pregnancy, and it was diagnosed in 45% during the pregnancy. The transmission route of HIV amongst the pregnant women was mostly through heterosexual contact (93%). The median age at the first pregnancy was 29 years (IQR, 24-33). In 32% cART was started before the onset of the first pregnancy and in 64% during the pregnancy. In 19% of the cases gestation lasted less than 16 weeks; in those who were still pregnant after the initial 16 weeks, the median gestation was 39 weeks (IQR, 36–40).

## Monitoring of HIV-infected adults and children

The median follow-up of the population of infected adults was 6.7 years (IQR, 3.0-12.1); 6.5 years for men and 7.0 years for women. For children, the median follow-up was 6.5 years (IQR, 2.8–9.6). The total follow-up in 2010 in the adult population was 129,755 person years, and for children it was 1,185 person years.

*Table 6: Most frequently used initial cART combination 2008–2010 (cART=combination antiretroviral therapy, TDF=tenofovir, FTC=emtricitabine, EFV=efavirenz, NVP=nevirapine, ATV/r=atazanavir/ritonavir, LOP/r=lopinavir/ritonavir, AZT=zidovudine, 3TC=lamivudine, DRV/r=darunavir/ritonavir, ABC=abacavir, SAQ/r=saquinavir/ritonavir, RAL=raltegravir).*

*More than 90% of the initial cART regimens used in 2010 consisted of tenofovir combined with emtricitabine as the nucleotide/nucleoside HIV-1 reverse transcriptase inhibitor backbone. Efavirenz was the most frequently used supplementation to this backbone. In 2010, efavirenz was used in 610 (60%) and the integrase inhibitor raltegravir was used in 22 (2.2%) initial cART regimens.*

| | 2008 | | 2009 | | 2010 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Total number of patients commencing first cART regimen | 1228 | 100.0 | 1241 | 100.0 | 1009 | 100.0 | 3478 | 100.0 |
| TDF+FTC+EFV | 641 | 52.2 | 719 | 57.9 | 587 | 58.2 | 1947 | 56.0 |
| TDF+FTC+NVP | 162 | 13.2 | 133 | 10.7 | 107 | 10.6 | 402 | 11.6 |
| TDF+FTC+ATV/r | 62 | 5.0 | 93 | 7.5 | 73 | 7.2 | 228 | 6.6 |
| TDF+FTC+LOP/r | 71 | 5.8 | 66 | 5.3 | 20 | 2.0 | 157 | 4.5 |
| AZT+3TC+LOP/r | 60 | 4.9 | 53 | 4.3 | 38 | 3.8 | 151 | 4.3 |
| TDF+FTC+DRV/r | 4 | 0.3 | 17 | 1.4 | 80 | 7.9 | 101 | 2.9 |
| TDF+FTC+LOP/r+EFV | 37 | 3.0 | 42 | 3.4 | 18 | 1.8 | 97 | 2.8 |
| ABC+3TC+EFV | 33 | 2.7 | 12 | 1.0 | 5 | 0.5 | 50 | 1.4 |
| AZT+3TC+NVP | 11 | 0.9 | 18 | 1.5 | 16 | 1.6 | 45 | 1.3 |
| ABC+3TC+NVP | 23 | 1.9 | 5 | 0.4 | 8 | 0.8 | 36 | 1.0 |
| AZT+3TC+SAQ/r | 12 | 1.0 | 9 | 0.7 | 5 | 0.5 | 26 | 0.7 |
| ABC+3TC+LOP/r | 17 | 1.4 | 5 | 0.4 | 2 | 0.2 | 24 | 0.7 |
| AZT+3TC+EFV | 11 | 0.9 | 8 | 0.6 | 4 | 0.4 | 23 | 0.7 |
| TDF+FTC+EFV+RAL | 3 | 0.2 | 4 | 0.3 | 13 | 1.3 | 20 | 0.6 |
| TDF+FTC+LOP+NVP | 8 | 0.7 | 2 | 0.2 | 2 | 0.2 | 12 | 0.3 |
| 3TC+TDF+EFV | 8 | 0.7 | 3 | 0.2 | 1 | 0.1 | 12 | 0.3 |
| ABC+3TC+ATV/r | 6 | 0.5 | 4 | 0.3 | 1 | 0.1 | 11 | 0.3 |
| Other | 84 | 6.8 | 61 | 4.9 | 46 | 4.5 | 191 | 5.5 |

*Table 7: Number of HIV-1 RT and protease gene sequences generated by virological laboratory and registered as per 31 December 2010 with SHM. (* Figures not available at time of print.)*

| | Number of sequences obtained | | |
|---|---|---|---|
| **Laboratory** | **Before 2010** | **In 2010** | **Total** |
| AMC, Amsterdam | 3,569 | 302 | 3,871 |
| UMCU, Utrecht | 3,070 | 0* | 3,070 |
| LUMC, Leiden | 1,035 | 52 | 1,078 |
| EMC, Rotterdam | 559 | 52 | 611 |
| VUMC, Amsterdam | 357 | 43 | 400 |
| Slotervaart, Amsterdam | 86 | 52 | 138 |
| CLB, Amsterdam | 391 | 0 | 391 |
| Total | 9,067 | 501 | 9,568 |

## Monitoring of treatment

The majority of HIV-infected patients in 2010 lived in the western part of the country; 74% of the patients were being monitored in one of the centres in the Randstad, which comprises the large cities of Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht.

In 2010, 83% percent of the registered infected adults were being treated with cART, 15.4% were not being treated, and in 1.6% this information was unknown (in most cases, this was because treatment data were not yet registered).

The median CD4-cell count at the time of HIV diagnosis was 330 cells/mm$^3$ (IQR, 140-530) for the adult population. This number decreased to 220 cells/mm$^3$ (IQR, 100-320) at the start of cART. Since 2005, an increase in CD4-cell counts has been seen at the start of cART.

After 24 weeks of treatment, 88% of the patients had an HIV-RNA plasma concentration below 500 copies/ml; after 48 weeks this percentage was 86%. In 93% of the treated population, the most recently measured HIV-RNA plasma concentration was lower than 500 copies/ml.

More than 85% of the initial cART regimens used in 2010 consisted of tenofovir combined with emtricitabine as the nucleotide/nucleoside HIV-1 reverse transcriptase inhibitor (NRTI) backbone, supplemented with either a non-nucleoside reverse transcriptase inhibitor (nNRTI) or a booster protease inhibitor (PI). The most popular initial cART regimen in 2010 was tenofovir+emtricitabine+efavirenz *(Table 6)*, followed by tenofovir+emtricitabine +nevirapine and tenofovir+emtricitabine+atazanavir/ritonavir, respectively.

The AIDS incidence in the cART-treated population has decreased since the introduction of cART in 1996 from 14.1 (95% CI, 11.3-17.3) per 100 person-years of follow-up to 1.02 (0.83-1.24) in 2009. The overall mortality rate in the treated group also decreased from 4.5 (95% CI, 3.0-6.5) in 1996 to 1.28 (1.07-1.51) in 2009.

## Monitoring of resistance

Data were obtained regarding the results of genotyping of the HIV reverse transcriptase and protease gene from five out of seven virology laboratories involved in the monitoring of resistance. A total of 9,568 sequences were collected *(Table 7)*; 501 of those were collected in 2010.

In 102 (9.4%) of the 1,088 patients with a recent infection in or after 2002, one or more resistance-associated mutations was found. Similarly, 258 (10.2%) of the 2,519 patients with a recent diagnosis had at least one mutation. In 2010, of the 137 newly diagnosed patients, 15 (11%) were resistant, whereas 7 (12%) of the 60 recently infected patients were resistant.

In total, 501 sequences obtained in 2010 were available for analysis. Of these sequences, 134 (27%) harboured at least one resistance-associated mutation. Of these 134 sequences with resistance, 92 (69%) harboured mutations associated with resistance to NRTIs, 37 (28%) had mutations against PIs, and 66 (49%) had mutations against nNRTIs.

## Monitoring of HBV and HCV co-infections

Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can cause hepatic cirrhosis, hepatic fibrosis, and hepatocellular carcinoma. In combination with HIV, the course of such diseases is probably accelerated. Therefore, HBV and HCV are monitored in the HIV-infected population over time. In 2010, a chronic co-infection with HCV was found in 10% of patients with HIV. The HCV prevalence is lower compared to previous years. This decrease is the result of changing from screening patients only after the appearance of symptoms caused by increased hepatic enzyme values to a general screening. A co-infection with HBV was found in 6.5% of patients, and 1.1% had a co-infection with both HCV and HBV. Of the patients with HBV co-infection, hepatic fibrosis developed in 12.1%, and hepatic cirrhosis developed in 6.5%; hepatocellular carcinoma was found in 1.2%. For patients co-infected with HCV, the totals were 17.8% (hepatic fibrosis), 7.5% (hepatic cirrhosis), and 0.5% (hepatocellular carcinoma).

## Registration and monitoring in Curacao

The registration and monitoring of HIV-infected persons being followed in the St. Elisabeth Hospital in Willemstad, Curacao, was continued during the past year. Results from the monitoring in the Netherlands Antilles in 2010 will be presented in 2011. In total, 702 patients (684 adults and 18 children) were registered; 87 of those were added in 2010.

## Sample collection

Since the start of the ATHENA project in 1996, a total of 407,742 plasma samples from patients in follow-up have been stored in the microbiological laboratories at or associated with the HIV treatment centres. This sample collection is exceptionally valuable for clinical epidemiologic research, especially that involving resistance development over the course of time and that involving the response of subtypes of HIV-1, other than the most common subtype B, to antiviral therapy. Results of such research is meaningful both for the quality of care of individual patients and for public health.

## Quality of Care

In relation to the Visible Care (ZiZo) programme, SHM developed four quality indicators in 2010 to provide insight into HIV care in the different HIV treatment centres throughout the Netherlands. The ZiZo programme was commissioned by the Ministry of Health in 2007 and was set up by the Public Health Inspection Agency. In 2010, quality indicators were developed for 24 diseases, including HIV. SHM is involved in developing the indicators for HIV and a pilot study in which the feasibility of these indicators will be established. The first assessment of these quality indicators will take place in 2011. SHM serves to deliver the quality care indicators to every HIV treatment centre.

In 2011, SHM continued to develop a Quality of Care programme, which shall determine what influence the quality of HIV care has on the outcomes of HIV treatment and HIV disease progression. One area of attention is the timely start of therapy in patients presenting early in the course of their infection. In 2009 and 2010, 6% of patients who presented with more than 350 CD4 cells/mm$^3$ were started on therapy with less than 200 CD4 cells/mm$^3$. The frequency of monitoring HIV patients between entry into care and start of treatment is closely related to the rate of CD4 decline and is important in preventing a late start of treatment. Even after the start of treatment, monitoring of patients plays an important role in the early recognition of treatment failure; with such recognition, the therapy combination can be changed well before the patient is exposed to high HIV viral levels. SHM, through the Quality of Care programme, shall help to determine the optimal frequency for monitoring patients.

# Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV and AIDS were started amongst homosexual men in 1984 and amongst drug users in 1985. The ACS were started with the purpose of making epidemiologic, pathogenic, and clinical research on HIV and AIDS possible, thereby contributing to the worldwide fight against HIV/AIDS. The realisation of these studies has been a collaboration involving the Sanquin Blood Supply Foundation, the Municipal Health Service of Amsterdam, the Academic Medical Hospital of the University of Amsterdam, and the University Medical Center Utrecht. The financing of the ACS is accomplished through a combination of contributions of the participating institutes and the National Institute for Public Health and the Environment (RIVM).

The ACS is unique because it allows for the follow-up of two populations at risk for HIV infection, that is, the HIV-negative populations of homosexual men and drug users. Those populations are followed by the Municipal Health Service, and HIV-infected persons in the ACS are still followed mostly through HIV care and through the monitoring of HIV by SHM. In addition to the provision of care, research material has been provided by patients and stored for specific immunologic and virologic studies. This includes material from persons who were initially HIV-negative and were infected during follow-up, as well as those who began participating in the ACS after being infected subsequent to the study design in 1984-5.

# Registration programme

## Trends in treatment

As of June 2010, amongst adults with a known year of HIV-1 diagnosis, 79% started cART. Of these patients, 16% had been treated with mono- or dual antiretroviral therapy before starting cART, whilst 83% started cART as therapy-naïve patients.

The median CD4 cell count in 2009, although higher than in previous years, is well below the currently recommended threshold of 350 cells/mm$^3$. Of all patients diagnosed between 1996 and 2009 with CD4 cell counts of 350 cells/mm$^3$ or more, 13% started cART too late for successful treatment (<200 CD4 cells/mm$^3$).

After starting cART, 50% of the patients achieved HIV RNA plasma concentrations of less than 50 copies/ml in less than 5 months. After the initial suppression, with less than 50 copies/ml, the probability of maintaining that level increased with a longer time on cART and with later calendar years. Virological suppression was increased in female patients, patients who were of older age, and patients with lower CD4 cell counts. This finding may be explained by a lesser perceived necessity and, consequently, a lesser level of adherence to cART in younger, male patients with high CD4 cell counts.

Seven years of cART-induced viral suppression resulted in an increase of CD4 cell counts to a median of 750 cells/mm$^3$, provided that therapy was started when the counts were between 350 and 500 cells/mm$^3$. This result is only slightly lower than normal values in uninfected individuals. Interestingly, in patients with a longer time on cART, an older age, and higher CD4 cell counts during follow-up, the counts decreased in an increasing proportion of patients on virologically successful cART. Decreased thymic output with older age, chronic inflammation, and persistent immune activation have been shown to be associated with reduced restoration of CD4 cell counts, but persistent low-level viral replication may also have an effect.

On the basis of the declining incidence of toxicity-driven therapy changes since 2000, it appears that less toxic drugs, together with better insights into prevention of toxicity, have improved the clinical management of HIV-infected patients on cART. Regimens that are easy to tolerate are especially important when cART is initiated at higher CD4 cell counts and the perceived necessity of treatment by the patient is lower.

HIV testing rates will need to improve to achieve a timely start of cART (≥ 350 cells/mm$^3$) in most patients. Monitoring changes in viral load and CD4 cell count remains important in patients on cART to identify those at risk for disease. The measurement of markers for immune activation and low-level plasma viral load below the detection limit of 50 copies/ml and the introduction of a clear definition of decreasing CD4 cell counts, taking the natural variability into account, may also help in this respect.

The most frequently used first-line cART combination in 2010 was tenofovir+emtricitabine +efavirenz, which was prescribed in 58.2% of cases. Overall, the prescription of tenofovir increased from 89% of cases in 2009 to 91% in 2010. Emtricitabine was part of 88% of initial regimens in 2009 and 91% in 2010, whereas the use of lamivudine decreased from 11% of cases in 2009 to 9% in 2010. The most frequent additions in 2010 were efavirenz (63%), nevirapine (14%), lopinavir (9%), and atazanavir (8%) *(Table 6)*.

### Virologic response

The proportion of patients with viral suppression to below 50 copies/ml varied between 82% and 84% after 36 weeks of starting cART. Patients starting cART in 2009 had a significantly longer time to viral suppression than patients starting in 2005. This appears to be largely related to the use of a new HIV-RNA test at various hospital laboratories. In concordance with other studies, time to suppression was significantly longer in patients younger than 30 years compared to those who were 30 to 40 years. Time to suppression was also longer in patients starting with CD4 counts ≥500 cells/mm$^3$ and in patients starting on a PI-based regimen.

### Immunologic response

Since 2008, treatment guidelines have recommended that therapy should start when CD4 cell counts are 350 cells/mm$^3$ or higher. This is reflected in a higher CD4 cell count at the

start of cART. The median CD4 count at the start of cART in 2009 was 280 cells/mm$^3$, in 2008 it was 240 cells/mm$^3$, and 200 cells/mm$^3$ between 2004 and 2007. The percentage of patients with a CDC-C diagnosis prior to starting cART was lower in patients starting in 2008 compared to patients starting between 2004 and 2007.

### cART toxicity-driven regimen change

During the first 3 years of cART, the overall incidence of toxicity-driven regimen changes was 21.7 per 100 person-years on cART. Patients could change the regimen more than once during the first 3 years. During follow-up, 66.8% of patients did not change the regimen because of toxicity. The maximum number of changes because of toxicity in a single patient was 14. The incidence was higher amongst women and highest in the first 3 months of cART.

## Trends in resistance

Sub-optimal adherence to antiretroviral treatment may result in incomplete suppression of HIV replication and subsequently in selection of HIV virus strains that are resistant to one or more of the drugs used in the therapy regimen. Resistance limits future therapy options and may lead to a worsened prognosis. Resistant strains can be transmitted to uninfected patients, restricting therapy options from the start.

### Resistance following treatment failure

In recent years, virologic failure has been observed annually in 8% to 10% of patients. In patients who had been pre-treated with mono- or dual therapy before switching to a cART regimen, virologic failure after start of cART was more common, but it has decreased from 51% in 1998 to levels now comparable to those in previously therapy-naïve patients.

In the total HIV-infected population, 3,682 sequences were obtained after the patients started cART. Of these sequences, 41% were obtained from pre-treated patients and 59% from previously therapy-naïve patients; 70% contained at least one resistance-associated mutation, and the rest (30%) contained none.

High-level resistance to at least one antiretroviral drug was found in 12% of those tested. This percentage probably underestimates the true prevalence of resistance in the total population, since a resistance test was performed in less than 30% of the patients with treatment failure.

In the patients tested for resistance, the number of patients with high-level resistance to drugs from one class was 36%. Resistance to drugs from two classes was found in 34% patients, whereas 11% were found to be resistant to drugs from all three classes. High-level resistance to emtricitabine and lamivudine was found in 60% of the patients and 29% had HIV resistant to at least one other NRTI. High-level resistance to at least one PI was found in 21% of patients and to at least one nNRTI in 49%.

### Transmission of resistance

Since 2003, treatment guidelines have recommended obtaining a genotypic sequence at HIV diagnosis to assess whether patients are infected with a drug-resistant virus strain, because the presence of resistant virus limits future therapy options. Between 2003 and 2009, 7,713 new HIV diagnoses were registered, and a pol sequence was available within one year after diagnosis and before the start of antiretroviral treatment from only 3,113 (40%). The prevalence of resistance-associated mutations found in the total population diagnosed in or after 2003 was estimated to be 9%.

The proportion of patients with evidence of transmitted drug resistance in the Netherlands was similar to proportions found in other European countries. In the EuroSIDA study, the prevalence of transmitted drug resistance between 1996 and 2004 was 11.4%. In Switzerland, the prevalence was 7.7% during the same period, and no changes over time were observed.

## Trends in causes of death, AIDS, and serious non-AIDS events

The life expectancy of patients infected with HIV-1 has increased significantly since the introduction of cART, although still not to the level of the age- and gender-matched general population. AIDS is still diagnosed, but to a lesser extent and often as a result of delayed HIV testing. As the HIV-1 infected population ages, non-AIDS diseases are increasingly more common.

### Mortality and incidence of AIDS

The average mortality rate of HIV-infected persons was 1.31 deaths per 100 person-years. Since 1997, the mortality has decreased and in 2009 was 1.04 per 100 person-years, while the rate of AIDS diagnoses has decreased to 1 to 2 per 100 person-years.

In the population of patients starting cART in 1995 or later, the overall mortality rate declined from 4.5 per 100 person-years in 1996 to 0.75 in 2010. In the total group who ever started cART, the incidence of new AIDS diagnoses decreased dramatically from 14.8 per 100 person-years in 1996 to 0.93 in 2009.

### Cause of death

The proportion of deaths due to AIDS after the start of cART between July 1996 and December 2010 showed a decreasing trend over time; it was 45% between 1996 and 2000, 34% between 2001 and 2005, and 25% between 2006 and 2010. The proportion of deaths due to non-AIDS cancers increased from 8% between 1996 and 2000 to 18% between 2006 and 2010. The proportion of deaths due to cardiovascular disease between 2001 and 2005 was similar to that seen between 2006 and 2010 and was higher than it was between 1996 and 2000 (10% vs. 5%).

The mortality rate due to non-AIDS-defining cancer was 3.19 (95% CI, 2.37-4.19) for pre-treated male patients and 1.43 (0.46-3.63) per 1000 person-years for female patients. This compares to 1.25 and 0.60 per 1000 person-years for the male and female age-standardized

general population. In men, the incidence of death after starting cART was due to cardiovascular disease, myocardial infarction, and suicide, and it was higher compared to the age-standardized population, both in pre-treated and therapy-naive patients. Other studies have also reported this result for myocardial infarction and certain non-AIDS-defining cancers, even after adjustment for other risk factors.

### AIDS and serious non-AIDS morbidity

Serious non-AIDS events in the ageing HIV-infected population are the same as the events associated with older age in uninfected subjects, such as non-AIDS-defining malignancies and cardiovascular, renal and hepatic disease, but they are seen more often in infected individuals than in uninfected controls. Apart from the well known risk factors of older age and antiretroviral therapy, there is increasing evidence that HIV infection itself is associated with a higher incidence of these events. In ATHENA, data are collected routinely for 7 serious non-AIDS events: renal insufficiency (chronic and acute disease), hepatic steatosis, diabetes mellitus, myocardial infarction, cerebrovascular accident, osteoporosis and non-AIDS-defining malignancies.

The incidence of AIDS in the first year after the start of cART was 77 per 1000 person-years and the incidence of non-AIDS events was 32. Beginning 3 years after the initiation of cART onwards, the incidence of serious non-AIDS events was higher than that of AIDS events. All serious non-AIDS events clearly showed an increasing incidence with older age.

The increasing number of older patients living with HIV-1 partly explains the increasing trend of serious non-AIDS morbidity over time. Cardiovascular disease, osteoporosis, malignancies, and renal disease are associated with older age in the general population. However, the higher number of patients of older age living with HIV alone does not completely explain the increasing trend of certain events with more recent calendar years. The incidence of non-AIDS malignancies is higher in HIV-infected patients than in the general population across all age groups, except for women between 60 and 65 years of age. The incidence among men is higher than amongst women, and risk factors such as smoking and lifestyle may play a role. Although the number of smokers may be higher in the HIV-infected population than in the general population, other studies that adjusted for age and other risk factors still found a higher incidence of non-AIDS malignancies, renal disease and myocardial infarction in patients infected with HIV-1 compared to uninfected controls. This has led to the hypothesis that HIV is associated with an accelerated ageing process, further supported by a study showing an increased frailty amongst HIV-infected patients compared to uninfected individuals.

Finally, serious non-AIDS mortality and morbidity is higher when CD4 cell counts are lower. Likewise, prevention of AIDS, early identification of infected patients at risk for co-morbidities, and a timely start of cART may help stop progression to non-AIDS diseases.

## Recommendations

The HIV epidemic in the Netherlands is a concentrated one and is still growing amongst homosexual men. The increase in the number of new HIV diagnoses registered by SHM fits an estimated number of new infections, which is higher than at the beginning of the epidemic in the early 1980's. People who do not know that they are infected with HIV most likely contribute to the spread of HIV. More testing for HIV, changing risk behaviour, and suppressing HIV through HIV antiviral therapy will help to control the ongoing HIV epidemic.

Based on the course of infection, it is assumed that individuals who are recently infected with HIV and have a high viral load contribute significantly to the spread of HIV. Additionally, a high viral load is detected in people who are infected for a longer time but present only when symptoms develop as a result of their weakened immune response.

HIV testing policies have improved, and the effect is obvious; with the increasing proportion of recently HIV-infected patients, the time from infection to diagnosis has been shortened. It is important that the testing policy, in conjunction with measures to reduce transmission risk behaviour, is sustained.

At diagnosis, more than 40% of people registered by SHM presented with symptoms or a CD4 count below 200 cells/mm$^3$. It is important to reduce this percentage for both individual patients and to control the epidemic. Providing information about diseases associated with HIV to people at risk of contracting HIV and to health professionals could contribute to earlier testing and earlier detection and diagnosis of the infection. A timely start of antiretroviral treatment is clinically significant for improving the chances of survival as well as the general public health.

The number of people starting therapy on time, that is, before the CD4 cell count falls to below 350 cells/mm$^3$, has risen in recent years, but for more than 50% of people it is still too late. Of all patients diagnosed with CD4 cell counts of 350 cells/mm$^3$ or more, 13% started cART too late. To reduce the late start of treatment, in addition to an active testing policy, it is worth considering offering cART directly after a positive test result. A drastic reduction in the toxicity of currently available antiviral drugs, combined with increased knowledge of treatment side effects, makes this approach possible. Monitoring of the long-term impact and cost effectiveness of the test and treatment approach is part of SHM's monitoring and registration programme.

Although the response to cART has improved over time, CD4 cell counts seem to decline in an increasing proportion of successfully treated patients with a longer time on cART, together with older age and higher CD4 cell counts during follow-up. This observation might reflect a decrease in thymic output with older age or might be the result of continuous low-level immune activation due to persistent low-level viral production. SHM will continue to carefully monitor these developments.

In association with the monitoring of HIV, SHM invested in monitoring infection with hepatitis B or hepatitis C virus. Consideration is also being given to extending SHM's monitoring system to include viral hepatitis in people without HIV.

During recent years, virological failure amongst patients on therapy has remained constant at 10% per year. However, the frequency of measuring HIV RNA plasma levels has been in decline, and we reported earlier on the relationship between frequency of measurement and observation of episodes of viraemia. SHM will make an effort to further analyse this relationship and the occurrence of resistance.

Observed resistance-associated mutations amongst patients in whom therapy has failed is about 15%, with 9% having high-level resistance to at least one drug. The low level of measurement of drug resistance in patients with treatment failure has resulted in a substantial underestimation of the true prevalence of resistance. SHM continues to recommend the need to follow treatment guidelines in cases of resistance. This is partly because in those patients who were tested, a third had resistance to 2 of the 3 drug classes for antiviral treatment, and 1 patient out of 10 was resistant to all 3 of the classes.

The population of HIV-infected individuals who are being monitored through HIV care and who have access to cART is growing. By monitoring this population carefully and by predicting the outcomes, SHM is in a position to contribute substantially to the further development of both HIV health care and public health policies. Important parameters include predicting time to entry into health care, to the start and failure of therapy, to AIDS-related and non-AIDS defining events, and to death, as well as predicting the distribution of CD4 cell counts over time, viral load peaks, and risk groups including migrants. These factors need to be analysed and used in modelling the progression of HIV, the effect of cART, and subsequently, the estimates of people living with HIV. SHM will conduct further data analyses and model development, and it will continue to contribute to the understanding and prediction of changes in the HIV-infected population in the Netherlands. Together with our modelling partners at Imperial College in London and in collaboration with groups such as the AntiRetroviral Therapy Cohort Collaboration (ART-CC), the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) and the European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCOORD), SHM can help reliably answer questions on diagnosis, treatment, and prevention of HIV in Europe.

# Collaborations

## National collaborations

### National Institute for Public Health and the Environment (RIVM)

The Centre of Disease Control (CIb, headed by Professor Roel A. Coutinho) of the National Institute for Public Health and the Environment (RIVM) receives and coordinates data on the registration of new HIV infections within the framework of the national HIV registration and surveillance programme.

The registration activities of SHM are associated with the CIb in regard to HIV as well as to other sexually transmitted diseases, such as hepatitis B (HBV) and hepatitis C (HCV), and infectious diseases such as tuberculosis. The CIb-RIVM and SHM entered into an agreement at the beginning of 2009 for the exchange of data collected through the SHM framework for surveillance purposes carried out by the CIb-RIVM.

### GGD Amsterdam

SHM collaborates with the Public Health Service of Amsterdam (GGD Amsterdam) on research into the changes in transmission of HIV since the introduction of HAART; the introduction of other suptypes than HIV-1 subtype B in the Netherlands; and the transmission of HIV strains that are resistant to antiviral agents. SHM and GGD Amsterdam also work together on the Amsterdam Cohort Studies (ACS, reviewed earlier in the report), in collaboration with the Academic Medical Center of the University of Amsterdam.

## International collaborations

### $ACHI_EV_{2E}$

$ACHI_EV_{2E}$ (A Collaboration on HIV-2 Infection) was established in 2005 as a collaboration of 15 observational cohort studies in 10 European countries, Gambia, and North America that record demographic and clinical data on HIV-2-infected patients. Since HIV-2 is mainly found in Western Africa and only occasionally in western countries, there is only a limited number of studies specifically focussing on HIV-2. In particular, the effect of antiretroviral treatment on outcome has not been studied in great detail. The $ACHI_EV_{2E}$ collaboration aims to fill in this gap in knowledge by studying different aspects of the treated HIV-2 infection.

### ART-CC

The Antiretroviral Therapy Cohort Collaboration (ART-CC) (coordinated by Prof. Jonathan Sterne, University of Bristol, Bristol, UK) is a long-standing international collaboration, including 19 cohort studies in Europe and North America. ART-CC was initiated to carry out prognostic studies to assess the effect of cART in therapy-naïve patients. Peter Reiss and Frank de Wolf are the principal investigators for this collaboration on behalf of SHM. Frank de Wolf is also in ART-CC's Executive Committee and Steering Committee. ART-CC has financial support from the Medical Research Council of the United Kingdom.

In 2010, the following article was published for ART-CC:
*Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: Collaborative analysis of 13 HIV cohort studies*. The Antiretroviral Therapy Cohort Collaboration Study Group (ART-CC). Clin Infect Dis. 2010 May 15;50(10):1387-96

## COHERE

The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) is a unique collaboration of cohorts in Europe that helps to answer scientific questions requiring a large sample size of patients which the contributing cohorts cannot answer individually and which do not overlap with existing collaborations between participating COHERE cohorts. COHERE'S mission is conduct epidemiological research on the prognosis and outcome of HIV-infected people from across Europe including pregnant mothers, children, and adults. Two Regional Co-ordinating Centres have been established; one is located in Bordeaux and one in Copenhagen.

Six papers have been published to date. In 2010, publications included:

- *Is it safe to discontinue primary Pneumocystis jiroveci pneumonia prophylaxis in patients with virologically suppressed HV infection and a CD4 cell count <200 cells/mL?* The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). Clin Infect Dis. 2010 Sep 1;51(5):611-9.
- *Triple-Class Virologic Failure in HIV-Infected Patients Undergoing Antiretroviral Therapy for Up to 10 Years.* The Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Arch Intern Med. 2010 Mar 8;170:410-419.

## DAD Study

This collaboration with several different observational clinical cohorts focuses on the early recognition of adverse events, amongst which cardiovascular problems, liver and renal diseases that could result from HIV treatment with antiretroviral agents. Jens Lundgren (Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Denmark) coordinates the study, and Peter Reiss (Department of Internal Medicine, AMC, Amsterdam) is the principal investigator for ATHENA/SHM.

Publications related to the DAD study in 2010 include:

- *High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome.* Worm SW, Friis-Møller N, Bruyand M, D'Arminio Monforte A, Rickenbach M, Reiss P, El-Sadr W, Phillips A, Lundgren J, Sabin C; D:A:D study group. AIDS. 2010 Jan 28;24(3):427-35.
- *Predicting the risk of cardiovascular disease in HIV-infected patients: the Data collection on Adverse Effects of Anti-HIV Drugs Study.* Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG; for the DAD study group. Eur J Cardiovasc Prev Rehabil. 2010 Oct;17(5):491-501. Epub 2010 Jun 10.

## DIDE

The Department of Infectious Disease Epidemiology (DIDE) is part of the Faculty of Medicine, Imperial College, London, UK. Prof. Sir Roy Anderson, Prof. Geoffrey Garnett and Dr. Christophe Fraser coordinate the collaboration with SHM. DIDE and SHM have been in collaboration since 2002. The focus of this collaboration is DIDE's statistical and mathematical support of SHM for analysis of observational cohort data and execution of the HIV registration programme. An important goal of the DIDE research programme is to gain more insight into the interplay of variables that determine the typical progress of infection in a host, as well as into those variables that determine the progress of infection in a particular population. To provide answers to such questions, necessary techniques include the study of the qualities of nonlinear differential equations, organisation and management of large-scale field studies into transmission and control of an infection in populations, and analysis of large data sets.

The long-standing collaboration with DIDE has resulted in a model analysing the impact of large-scale administration of cART on the epidemic in the Netherlands and in a model comparing quality of care in the Netherlands. Another study focuses on the variation in HIV-1 plasma RNA set-points, the clustering around those set-points that maximise the transmission potential, and the changes in viral set-point over time.

Frank de Wolf, Director of SHM, is Professor of Clinical Retrovirology at Imperial College, London.

## ECDC

The European Centre of Disease Prevention and Control (ECDC) was established in 2005. It is an EU agency with aim to strengthen Europe's defences against infectious diseases. ECDC works in partnership with national health protection bodies across Europe to strengthen and develop continent-wide disease surveillance and early warning systems. By working with experts throughout Europe, ECDC pools Europe's health knowledge, so as to develop authoritative scientific opinions about the risks posed by current and emerging infectious diseases.

In 2010, another project was launched to better estimate the prevalence of HIV in Europe and within individual European countries. This project was commissioned by the European Centre for Disease Control and Prevention (ECDC) in Stockholm, Sweden. SHM has a leading role in this project together with the Department of Infectious Disease Epidemiology at Imperial College in London, UK.

## EuroCoord

The European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCoord) was set up on 6 February 2006 for the purpose of integrating the projects across the partners and to coordinate the submission of funding applications for the seventh EU Framework Program. EuroCoord

comprises a cooperation initiative taken by leaders representing the following four Coordinating Actions (CAs): CASCADE, COHERE, EuroSIDA, PENTA.

It is EuroCoord's goal to:
- Facilitate the conduct of collaborative research.
- Work towards integration/harmonisation of the four CAs with the aim of having a robust organisation with a common platform.
- Establish collaboration with existing EU-funded networks.

Frank de Wolf is currently chair of EuroCoord's governing body, the Council of Partners.

SHM also participates in the EuroCoord CHAIN project. The joint project on transmitted drug resistance and their impact on treatment response was identified as a pilot project because a large number of patients is required to address the scientific question raised. The objective is to compare virological, immunological and clinical outcome up to 12-16 months following initiation of cART, according to markers of virus variability (specific mutations, subtypes), and relevant to the drugs in the regimen. A project team with epidemiologists, statisticians, virologists and clinicians was established (project lead: Geneviève Chêne).

### EuroSIDA

The EuroSIDA study is a prospective observational cohort study of more than 16,500 patients followed in 103 hospitals in 33 European countries plus Israel and Argentina. The main objective of the study is to assess the impact of antiretroviral drugs on the outcome of the general population of HIV-infected patients living in Europe. The primary hospital in the Netherlands that provides information for this study is the AMC in Amsterdam. At the request of the principal investigator of EuroSIDA, Prof. Dr Peter Reiss, SHM collects data from the AMC in Amsterdam for EuroSIDA.

Publications in 2010 related to EuroSIDA include:
- *A comparison of the long-term durability of nevirapine, efavirenz and lopinavir in routine clinical practice in Europe: a EuroSIDA study.* Reekie J, Reiss P, Ledergerber B, Sedlacek D, Parczewski M, Gatell J, Katlama C, Fätkenheuer G, Lundgren JD, Mocroft A; for the EuroSIDA study group. HIV Med. 2010 Aug 31. [Epub ahead of print]
- *Dialysis and Renal Transplantation in HIV-Infected Patients: a European Survey.* Trullas JC, Mocroft A, Cofan F, Tourret J, Moreno A, Bagnis CI, Fux CA, Katlama C, Reiss P, Lundgren J, Gatell JM, Kirk O, Miró JM; the EuroSIDA Investigators. J Acquir Immune Defic Syndr. 2010 Aug 31. [Epub ahead of print]
- *Serious fatal and nonfatal non-AIDS-defining illnesses in Europe.* Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, Gatell J, Rakhmanova A, Johnson M, Kirk O, Lundgren J; EuroSIDA Study Group. J Acquir Immune Defic Syndr. 2010 Oct 1;55(2):262-70.
- *Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.* Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M,

Gatell J, Phillips AN, Ledergerber B, Lundgren JD; EuroSIDA Study Group. AIDS. 2010 Jul 17;24(11):1667-78.

### HIV-CAUSAL

The HIV-CAUSAL Collaboration is a multinational collaboration of prospective studies of HIV-infected individuals from six European countries and the United States. HIV-CAUSAL stands for HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data. The collaboration aims at answering three main questions: when to start antiretroviral therapy, what antiretroviral regime to use initially, and when to switch to another regime. These questions are unlikely to be answered by a single study and thus the need for a collaborative project. The HIV-CAUSAL Collaboration pools data collected for clinical purposes within health care systems with few barriers to access in the populations they serve. The HIV-CAUSAL Collaboration is designed to inform evidence-based guidelines and the planning of clinical trials. In addition, the collaboration will facilitate understanding and training in causal modelling across leading HIV observational research groups in the United States and Europe.

The HIV-CAUSAL Collaboration published the following paper in 2010:

- *The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals.* HIV-CAUSAL Collaboration. AIDS. 2010 Jan 2;24(1):123-37. Epub 2009 September 18.

### HIV in Europe

HIV in Europe is a pan-European initiative initiated in Brussels in 2007. The initiative provides a European platform for exchange and activities to improve early diagnosis and earlier care of HIV across Europe. The initiative is directed by an independent group of experts with representation from civil society, policy makers, health professionals and European public health institutions. The initiative has proven to be able to put the issue of earlier diagnosis of HIV on the political agenda and to involve the different constituencies. Also, the initiative has been able to initiate specific projects to enhance optimal testing and care. The overall objective of HIV in Europe is to ensure that HIV positive patients enter care earlier in the course of their infection than is currently the case, as well as to study the decrease in the proportion of HIV positive persons presenting late for care.

### RDI

The HIV Resistance Response Database Initiative (RDI) is made up of a small research team based in the UK, an International Scientific Advisory Group and a network of collaborators and supporters. The main activities of the RDI are exploring the relationship between changes in the genetic code of HIV (genotype), other clinical and laboratory factors and response to HIV drug therapy, and developing computational models for helping physicians and their patients to select the best combination of drugs for the individual.

# Financial report

## Income

### Income for regular HIV monitoring activities in the Netherlands

Stichting HIV Monitoring (SHM) is recognized by the Dutch Ministry of Health as an official health care institute with a structural subsidy (Health Subsidy Regulation, Chapter II Institute Grants).

The Governing Board established the 2010 budget on 21 October 2009 at € 2,739,033. On 18 January 2010, the Dutch Ministry of Health approved the budget. The indexation for the wage-sensitive part of the budget was set by the Ministry of Health on 6 September 2010 at 1.75% (€ 36,715). The material costs were not indexed. The total budget for 2010 allocated by the Ministry of Health for the monitoring of HIV in the Netherlands and available to SHM was fixed at € 2,775,748.

As of 1 June 2010, 13,844 of the registered patients (13,674 adults and 170 children) were in active follow-up, which represents an increase of 7.14% compared to the number of patients in 2009. The increase in the number of patients in active follow-up is actually higher than that recorded, which is largely due to backlogs in the processing of data by some HIV treatment centres.

In 2010, the budget for the costs of HIV monitoring in the Netherlands included the processing of the increased number of new patients. Before 2009, this was excluded from the budget at the request of the Ministry of Health.

### Income through projects related to HIV monitoring

During 2010, income of € 1,032,381 was obtained from the following four HIV monitoring-related projects:

1. Amsterdam Cohort Studies
   SHM has been responsible for governing and administering the Amsterdam Cohort Studies (ACS) since 2005. Since 1984, research has been carried out on the natural course of HIV infection and on the development of the epidemic with data and materials provided by HIV-infected persons and persons at high risk of contracting HIV. The Ministry of Health subsidises the ACS via the National Institute for Public Health and the Environment (RIVM). The Academic Medical Centre (AMC) of the University of Amsterdam and the Municipal Health Service (GGD) of Amsterdam remain available to carry out projects within the ACS. The Academic Medical Centre Utrecht (UMCU) also carries out projects in which data and material from ACS participants is used. For such use, the UMCU pays a fee to the ACS. The GGD Amsterdam and the AMC each contribute to these studies by storing patient data and material.

The contribution from the Ministry of Health and the UMCU are, in accordance with the budget, transferred by SHM to the GGD Amsterdam and the AMC. Sanquin Blood Supply Foundation receives a contribution via the AMC for the processing and storage of patient material (specifically, white blood cells). SHM does not invoice costs for the maintenance of the ACS.

2. Data Collection on Adverse Events of Anti-HIV Drugs (DAD)
   DAD is a large international collaboration between observational cohorts with an aim of identifying early severe side effects of treatment with antiretrovirals. SHM is a major partner in DAD. SHM collects data on side effects in registered patients for the benefit of the DAD study. The validity of this data is subject to 100% quality-control (in contrast to the usual 10%) through source-data verification. In 2010, SHM contributed for the eleventh time to the data merge and received compensation for this from the Hvidovre University in Copenhagen, Denmark, the organisation that leads the DAD study.

   In 2010, SHM was granted € 95,620 from the Hvidovre University Hospital for the registration of specific DAD-related events. This grant was paid in full by SHM to the HIV treatment centres that report DAD-related events.

3. EuroSIDA
   SHM participates in the EuroSIDA study within a European-based context. The Academic Medical Center (AMC) of the University of Amsterdam participates on behalf of the Netherlands in EuroSIDA, a European clinical cohort, with SHM delivering the AMC's patient data to the cohort. EuroSIDA carries out comparative studies among the participating European countries, including a focus on new EU member states, on the effect of the treatment of HIV. For its participation in the EuroSIDA study group in 2010, SHM received compensation of € 2,662.

4. Other projects
   In 2010, SHM received a contribution of € 47,099 for its active participation in the following international projects: Antiretroviral Cohort Collaboration (ART-CC), Collaboration of Observational HIV Epidemiological Research Europe (COHERE), and Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN).

## Expenditure

Three different types of expenses for 2010 are outlined below:

1. Compensation to the HIV treatment centres for data collection and data entry
   In 2010, in accordance with the approved budget, SHM compensated the HIV treatment centres in the amount of € 67.82 per patient. The compensation to the HIV treatment centres is based on the number of patients who were in active follow-up on 31 December 2009. HIV treatment centres with a backlog in data collection received less of the budg-

eted amount than centres without a backlog. In 2010, by request from a number of hospitals, SHM offered assistance in data collection. The personnel costs incurred by SHM for this service were then charged to the hospital in question.

The compensation of € 67.82 per patient in 2010 increased by 1.07%, compared to € 67.10 per patient in 2009. A number of treatment centres have transferred the role of data collection to SHM. The costs incurred by SHM for this service are subtracted from the compensation to these centres.

In total, SHM paid the HIV treatment centres € 167,462.34 to cover the costs for sampling and storing patients' plasma during 2010.

2. Personnel costs
   Personnel costs were once again the largest expenditure for SHM during 2010. SHM has a total of 33 employees (26 fte). This number does not include the employees of HIV treatment centres responsible for carrying out data collection for which the HIV treatment centres receive compensation from SHM.

3. Material costs
   In addition to staff expenses, in 2010 there were structural costs made in relation to database licenses, maintenance of the national HIV monitoring database, data management and operations.

## Reservations

In 2005, money was set aside for the Host Genetics project. The project was developed in collaboration with the Academic Medical Centre of the University of Amsterdam. No expenses were incurred in 2010.

In 2007, € 2,000 was put aside for the first Netherlands Conference on HIV Pathogenesis, Prevention and Treatment (NCHIV). The conference has since been organised annually by SHM in collaboration with the Dutch AIDS Fund, the Laboratory for Viral Immune Pathogenesis (LVIP) at the Academic Medical Center of the University of Amsterdam, the Amsterdam Institute for Global Health and Development (AIGHD), the Center for Poverty-related Communicable Diseases (CPCD), the National Institute for Public Health and the Environment (RIVM), Sanquin Blood Supply foundation and the Dutch Association of Physicians in AIDS (NVAB). The earmarked sum of € 2,000 was maintained in 2010.

The DAD financial reserve has been created so that the European commitments to the study can be maintained.

## Operating result

The operating result shows that the total expenditure for 2010 remains within SHM's income.

The operating result of the HIV monitoring activities shows a marginal positive result of € 7,109. This is due to:

1. Limiting salary increases in 2010. Increased employer costs could in this manner be absorbed through the salary-related indexation of the subsidy received through the Ministry of Health;

2. The approval from the Ministry of Health to include the processing of the increased number of new patients in the budget from 2009 onwards; and

3. Interest income for 2010.

The bulk of the addition to SHM's general reserves is from projects related to HIV monitoring.

## Reserves

The total financial reserves of SHM (including continuity reserve, general reserve and earmarked reserves for investment) amounted to € 1,705,605 on 31 December 2010.

1. Continuity reserve
   The continuity reserves amounted to a deficit of € 25,668 on 31 December 2010. This amount includes the 2010 result of HIV monitoring in the Netherlands.

2. General reserve
   From 2002 through 2007, SHM built a general reserve of € 382,205 via the budget from the Health Tariffs Authority (CTG), later merged into the Dutch Healthcare Authority (NZa). In relation to the negative continuity reserve, this fund is held in reserve to guarantee six months of salary payments.

3. Earmarked reserves for investment, HIV-related projects
   A total of € 1,349,067 has been reserved for HIV-related projects. SHM has committed to participating in these projects for three years. SHM's Governing Board will make further decisions on the amount of this reserve in the spring of 2011. Any decisions will be based partly on the advice of SHM's Advisory Board on new registration and monitoring proposals.

## Continuity risks

SHM applies the rule that 25% of the annual turnover is to be kept in reserve to cover continuity risks for the registration and monitoring of HIV in the Netherlands. The reserve for the regular HIV registration and monitoring activities in 2010 equals approximately 13% of the budget.

# Balance sheet as of 31 December

| | 31-Dec-10 (€) | 31-Dec-09 (€) |
|---|---|---|
| **Assets** | | |
| **Fixed assets** | | |
| Tangible fixed assets | 12,704 | 27,080 |
| **Total fixed assets** | **12,704** | **27,080** |
| | | |
| **Current assets** | | |
| Debtors and accrued assets | 171,997 | 528,900 |
| Cash | 2,566,433 | 1,797,973 |
| **Total current assets** | **2,738,430** | **2,326,873** |
| | | |
| **Total Assets** | **2,751,134** | **2,353,953** |
| **Liabilities** | | |
| **Capital and reserves** | | |
| • Continuity reserve - HIV monitoring activities | -25,667 | -32,777 |
| • General reserve - HIV monitoring activities | 382,205 | 382,205 |
| • Earmarked reserves for investment - HIV-related projects | 1,349,067 | 978,100 |
| **Total reserves** | **1,705,605** | **1.327,528** |
| | | |
| **Short-term liabilities** | | |
| Sort-term liabilities and accrued expenses | 1,045,529 | 1,026,425 |
| **Total short-term liabilities** | **1,045,529** | **1,026,425** |
| | | |
| **Total Liabilities** | **2,751,134** | **2,353,953** |

# Profit and Loss Account

| | 2010 (€) | 2009 (€) |
|---|---|---|
| **Profits** | | |
| Total subsidies | 3,808,129 | 3,590,919 |
| Other profits | 9,900 | 14,085 |
| **Total net revenue** | **3,818,029** | **3,605,004** |
| | | |
| **Operation costs** | | |
| Personnel expenses | 1,805,316 | 1,717,741 |
| Depreciation on tangible fixed assets | 15,196 | 25,803 |
| Other operation charges | 360,266 | 383,385 |
| Compensation HIV-treatment centres | 630,328 | 616,479 |
| Compensation DAD-events | 95,620 | 58,400 |
| Compensation Amsterdam Cohort Studies | 553,088 | 571,733 |
| Compensation NCHIV | 11,500 | 6,727 |
| **Total operation costs** | **3,471,314** | **3,380,268** |
| | | |
| **Operating result** | 346,715 | 224,736 |
| Financial income and expenses | 31,361 | 31,358 |
| **Total operating result** | **378,076** | **256,094** |
| | | |
| **Year Result** | **378,076** | **256,094** |

# Composition SHM

## Governing Board SHM

| Name | Position | Affiliation |
|---|---|---|
| Dr. F.P. Kroon | Chairman | NVAB |
| Drs. P. van der Velpen | Secretary | GGD Nederland (until April 16, 2010) |
| Dr. J.S.A. Fennema | Secretary | GGD Nederland (from April 16, 2010) |
| Drs. A.J. Lamping | Treasurer | Zorgverzekeraars Nederland |
| Prof. R.A. Coutinho | Observer | RIVM |
| Drs. J.C.H.G. Arts | Member | NVZ |
| Dr. R.J.M. Hopstaken | Member | NFU |
| Dhr. H.G.P.M. van Rooij MD | Member | HIV Vereniging Nederland |
| Prof. K. Stronks | Member | AMC-UvA |
| Drs. M.I. Verstappen | Member | AGIS |

## Advisory Board

| Name | Affiliation |
|---|---|
| Prof. J.M.A. Lange (chairman) | AMC, Dept. of Internal Medicine, Amsterdam |
| Prof. Sir R.M. Anderson | Imperial College, Faculty of Medicine, Dept. of Infectious Disease Epidemiology, London, United Kingdom |
| Prof. M. Egger | University of Bern, Switzerland / Bristol, United Kingdom |
| Dr. S.E. Geerlings | AMC, Dept. of Internal Medicine, Amsterdam |
| Prof. D.R. Kuritzkes | Brigham and Women's Hospital Infectious Disease, Boston, MA, USA |
| Prof. J. Lundgren | Copenhagen HIV Programme, Denmark |
| Dhr. C. Rümke | Dutch HIV Association, Amsterdam |
| Prof. J. Schuitemaker | AMC, Dept. of Internal Medicine, Amsterdam |

## Working group SHM

### Members

| Name | Affiliation |
|---|---|
| Dr. M.E. van der Ende (chairman) | Erasmus Medical Centre, Dept. of Internal Medicine, Rotterdam |
| Dr. K. Boer | AMC, Dept. of Obstetrics/Gynaecology, Amsterdam |
| Prof. C.A.B. Boucher | Erasmus Medical Centre, Dept. of Internal Medicine, Rotterdam |
| Dr. F.C. Leth | KNCV Tuberculosis Foundation, The Hague |
| Dr. W.M.C. Mulder | Dutch HIV Association, Amsterdam |
| Prof. P. Reiss | AMC, Dept. of Internal Medicine, Amsterdam |
| Dr. R. Schuurman | UMCU, Dept. of Virology, Utrecht |

### Reviewers

| Name | Affiliation |
|---|---|
| Dr. N.K.T. Back | AMC, Dept. of Human Retrovirology, Amsterdam |

| | |
|---|---|
| Prof. K. Brinkman | Onze Lieve Vrouwe Gasthuis, location Oosterpark, Dept. of Internal Medicine, Amsterdam |
| Dr. D.M. Burger | UMCN – St. Radboud, Dept. of Clinical Pharmacy, Nijmegen |
| Dr. H.C.J. Claas | LUMC, Clinical Virological Laboratory, Leiden |
| Prof. G.J.J. Doornum | Erasmus Medical Centre, Dept. of Virology, Rotterdam (Emeritaat) |
| Prof. J.M.D. Galama | UMCN - St. Radboud, Dept. of Medical Microbiology, Nijmegen |
| Dr. S.P.M. Geelen | UMCU-WKZ, Dept. of Paediatrics, Utrecht |
| Prof. A.I.M. Hoepelman | UMCU, Dept. of Virology, Utrecht |
| Dr. S. Jurriaans | AMC, Dept. of Human Retrovirology, Amsterdam |
| Dr. J.R. Juttmann | St. Elisabeth Hospital, Dept. of Internal Medicine, Tilburg |
| Dr. R. Kauffmann | HAGA Ziekenhuis, location Leyenburg, The Hague |
| Dr. P.P. Koopmans | UMCN – St. Radboud, Dept. of Internal Medicine, Nijmegen |
| Prof. A.C.M. Kroes | LUMC, Clinical Virological Laboratory, Leiden |
| Prof. T.W. Kuijpers | AMC, Dept. of Paediatrics, Amsterdam |
| Dr. W.J.G. Melchers | UMCN - St. Radboud, Dept. of Medical Microbiology, Nijmegen |
| Dr. C.H.H. ten Napel | Medisch Spectrum Twente, Dept. of Internal Medicine, Enschede |
| Prof. J.M. Prins | AMC, Dept. of Internal Medicine, Amsterdam |
| Prof. P.H.M. Savelkoul | VU Medical Centre, Dept. of Medical Microbiology, Amsterdam |
| Dr. G. Schreij | Academic Hospital, Dept. of Internal Medicine, Maastricht |
| Dr. H.G. Sprenger | Academic Hospital, Dept. of Internal Medicine, Groningen |
| Dr. A. Wensing | UMCU, Dept. of Virology, Utrecht |

## Personnel SHM

| Position | Name |
|---|---|
| Director | Prof. F. de Wolf MD |
| Research – Senior | Dr. D.O. Bezemer |
| | Drs. L.A.J. Gras |
| | Dr. A.I. van Sighem |
| | Dr. Ir. C. Smit |
| Research – PhD students | Drs. A.M. Kesselring (from April 1, 2010) |
| | Drs. S. Zhang |
| Patient Data & Quality Control – Manager | Drs. S. Zaheri |
| Patient Data & Quality Control – Registration | R.F. Beard |
| Patient Data & Quality Control – Data collectors | M. van den Akker |
| | Y.M. Bakker |
| | M. Broekhoven-van Kruijne |
| | C.W.A.J. Deurloo-van Wanrooij |
| | L.G.M. de Groot-Berndsen |

| | |
|---|---|
| | C.R.E. Lodewijk |
| | B.M. Peeck |
| | Y.M.C. Ruijs-Tiggelman |
| | E.M. Tuijn-de Bruin |
| | D.P. Veenenberg-Benschop |
| | T.J. Woudstra |
| Patient Data & Quality Control – Data monitors | Drs. E. van der Beele (from May 17, 2010) |
| | Drs. M. Berkhof (from January 15 until April 30, 2010) |
| | Drs. S. Grivell |
| | Drs. J.M.T. van der Heijden (until March 31, 2010) |
| | Drs. M.M.J. Hillebregt |
| | Drs. A.M. Jansen (from April 1, 2010) |
| | V. Kimmel MSc |
| | Drs. B. Lascaris (from June 1, 2010) |
| | Drs. B. Slieker |
| | Drs. C.A.H. Welling (until June 23, 2010) |
| Office, Administration, Communication - Manager | D. de Boer |
| Office | M.M.T. Koenen Bsc |
| | Drs. G.E. Scholte |
| Administration– Personnel & Administration | I.H.M. de Boer |
| | Drs. H.J.M. van Noort |
| Communication | L.J. Dolfing-Tompson BVSc (from January 4, 2010) |

# Scientific output 2010

In 2010, 8 requests were made for access to the national HIV monitoring data. During the year, 28 papers for which Stichting HIV Monitoring (SHM) data were used were published in peer-reviewed journals. 39 abstracts of SHM were accepted for presentation at 11 meetings and conferences (29 posters and 10 oral presentations).

All of these research projects and publications from SHM are listed on our website www.hiv-monitoring.nl.

## Ongoing research projects

### I06208 Long-term quality of life and self-reported symptoms among HIV-infected patients treated with highly active antiretroviral therapy

M.A.G. Sprangers, P.T. Nieuwkerk
Date of Approval: December 2006
No progress report received. Project ongoing.

### I0000 Role of host genetics in the clinical course of HIV infection

H. Schuitemaker, A. van 't Wout, F de Wolf
Date of Approval: 14 February, 2006

2010 Progress Summary: New studies have shown an association between genetic markers (SNPs) in HIV-1 infected patients and the viral load (VL) 18 months after seroconversion (the "set point"). For example, an SNP in the HCP5 gene (rs2395029) and SNP 35 kilobases upstream of the HLA-C gene region (-35HLA-C; rs9264942) have both been associated with a lower VL set point [1]. In addition, it has been found that individuals heterozygous for a 32-base-pair deletion in the CCR5 gene (CCR5Δ32) have a lower VL set point. We have recently confirmed these associations in the homosexual participants of the Amsterdam Cohort Studies on HIV infection and AIDS (ACS) with seroconversion prior to 1996 [2]. Interestingly, a recent study in which the VL set point in patients who seroconverted before 2003 was compared with those who seroconverted after 2003 showed that VL set points have risen over the last decade of the HIV epidemic in the Netherlands [3]. This could imply that HIV has adapted to its host at the population level.

To test this hypothesis, we used host genetic data in relation to the viral load set point in the ACS, and in addition, we selected more than 600 patients in follow-up at 1 of the 25 HIV treatment centres in the Netherlands with a known date of seroconversion (SC) and VL set point. The SC date was defined as the date of occurrence of symptoms of acute HIV infection and/or a first positive HIV test with a last negative HIV test less than 6 months prior to the first positive test. To date, 21 of the 25 HIV treatment centres have approached patients for study participation. As of December 1, 2010, 432 of the SHM-selected patients have given informed consent and donated blood for DNA isolation. The DNA of 355 patients with available VL data from 18 to 24 months after SC has subsequently been typed for the SNPs in HCP5 and -35HLA-C. In addition, the CCR5 genotype has been determined.

Finally, we compared the association between viral load set point and HCP5 rs2395029, -35HLA-C rs9264942, and the CCR5wt/Δ32 genotype in HIV-1-infected individuals in the Netherlands who had seroconverted between 1982 and 2002 (pre-2003 seroconverters, n=459) or between 2003 and 2009 (post-2003 seroconverters, n=231).

Viral load set point in post-2003 seroconverters was significantly higher than in pre-2003 seroconverters (P= 4.5x10-5). The minor alleles for HCP5 rs2395029, -35HLA-C rs9264942 and CCR5wt/Δ32 had a similar prevalence in both groups and were all individually associated with a significantly lower viral load set point in pre-2003 seroconverters. In post-2003 seroconverters, this association was no longer observed for HCP5 rs2395029 and CCR5wt/ 32. The association between viral load set point and HCP5 rs2395029 had significantly changed over time, whereas the change in impact of the CCR5wt/Δ32 genotype over calendar time was not independent of the other markers being studied [4].

Our results suggest that the increase in VL set point in the Netherlands correlates with a decreased protective effect of certain genetic factors on the set point. This suggests that HIV variants less sensitive to genetic factors that protect against disease progression are being selected at the population level. This adaptation of HIV to the host over time is important to take into account in the development of novel therapeutic strategies and vaccines.

In addition to the patients with known SC date and VL set point, we have recruited patients with relatively low VL (viremic and elite controllers) as part of the International HIV Controller Study. In this study, strong associations with elite control of HIV-1 viraemia were again restricted to SNPs on chromosome 6, more specifically in the region encoding HLA-B57 [5].

References:
1. Fellay J et al, Science 2007, 317:944-947.
2. van Manen D et al, AIDS 2009, 23:19-28.
3. Gras L et al, PloS ONE 2009, 4:e7365.
4. van Manen D et al, submitted for publication
5. Int. HIV Controllers Study, Science 2010,330:1551-1557.

## I07252 Study of sexual behaviour among HIV-infected homosexual men

Stolte, A. Krol, M. Prins, A. van Eeden, M. Groot
Date of approval: December 2007

Background: The incidence of sexual risk behaviour and sexually transmitted diseases among homosexual men has increased since the introduction of HAART. Thus, HIV-infected men have become an important target group for prevention. In order to study the changes in sexual risk behaviour, our objective was to ask all HIV-infected homosexual men attending the Jan van Goyen medisch centrum in Amsterdam to participate in a behavioural cohort study, with the aim of beginning in March 2008.

Methods: After giving informed consent, participants were initially asked to fill in a questionnaire on primarily sexual risk behaviour. We plan to repeat the questionnaire once a year to obtain insight into changes in behaviour over time.

Results: The inclusion of MSM at the JvG started in March 2009. By the end of 2009, 19 MSM were willing to participate in the ACS and answered and returned the questionnaire. By the end of 2010 this number remained the same, and all these men are now included in our HOP protocol. This allows us to combine all data from all HIV-positive participants followed at the JvG, resulting in a total population of 49 at the JvG and 79 elsewhere.

In 2010, data on sexual risk behaviour were used for a study investigating change in sexual risk behaviour before and after seroconversion in a period before and after cART. Results indicate that sexual risk behaviour decreases after seroconversion, but this decrease is only temporary during treatment with cART (see attachment; abstract Croi); after 4 years, the level of risk behaviour is almost the same as before seroconversion.

Conclusion: Although the number of HIV-positive participants did not strongly increase as a result of our attempts, study results like these stress the importance of longitudinal collection of behavioural data, including after seroconversion. Thus, we will continue our efforts to maintain these men in the HOP protocol.

Abstract: Changes in Sexual Behaviour Among MSM who Recently Seroconverted Before and After the Introduction of cART
Author: Titia Heijman[1]
Co-authors: R.B Geskus[1,2], U Davidovich[1], R.A. Coutinho[2,3], M Prins[1,2], and I.G. Stolte[1,]
[1] Public Health Service, Amsterdam, The Netherlands; [2] Academic Medical Centre, Amsterdam, The Netherlands; and [3] National Institute for Public Health and the Environment, Centre for Infectious Disease Control, Bilthoven, The Netherlands

### I07267 Novel HIV Protease Inhibitor resistance mechanisms explaining failure of ritonavir-boosted PI-containing HAART

W.F.W. Bierman, M.A. van Agtmael, C. A. B. Boucher, M. Nijhuis.
Date of approval: December 2007
No progress report received. Project ended.

### I05513 HIV Resistance Response Database Initiative (RDI)

A.Revell
Date of approval: October 2005

During 2010 the RDI made the following progress:

1. The development, testing, and launch of an online HIV treatment response prediction system – HIV-TRePS. From its inception in 2002, the primary goal and commitment of the RDI has been to make its computational models freely available over the Internet as an experimental tool to aid treatment decision-making. This was achieved in 2010 and involved the following activities:
   - 1.1 Development of a detailed specification document for the design of the user interface, registration system, and report.
   - 1.2 Development of the HIV-TRePs visual identity (logo and colourways).
   - 1.3 Development of new multiple versions of the reports as required by different user-defined functional options
   - 1.4 Programming of the user interface, linkage with the computational models, and report production
   - 1.5 Design of the user interface
   - 1.6 Testing the system
   - 1.7 Launch of the system
   - 1.8 Maintenance of the system

   To date, the system has attracted more than 300 users in 54 countries.

2. Refinement of RDI modelling methodology - knowledge extraction
   With the evolution of clinical practice and our understanding of HIV-drug resistance and other factors that affect treatment response, there is a need for RDI to re-

examine and optimise the input variables it uses for its computational modelling of treatment response. In particular, it is important to include only those input variables that make a significant contribution to the accuracy of the models, because additional extraneous variables can impair the performance of the models. In this methodological study, the RDI used the results of its last computational modelling to investigate the relative impact of each of the input variables and then developed new computational models without the use of the variables that had little, if any, impact on the output (follow-up viral load). The performance of this model was then compared with that of models developed using the full set of input variables.

3. The development of new computational models to predict virological response to treatment without the genotype for use in HIV-TRePS.
   Most of the RDI's experience has been with models that use HIV genotype as part of the dataset from which predictions of treatment response are made. Genotyping is currently not routinely available in most developing countries. However, previous RDI studies have demonstrated that information about previous drug exposure contributes significantly to the accuracy of our models. It is possible that such information can act as a partial surrogate for genotype, since exposure to certain drugs in a failing regimen usually involves the development of certain signature mutations.
   A previous proof-of-principle study established that models developed with large data sets, including treatment history information but not genotype data, can predict virological response with a high degree of accuracy. In this study, we developed new models using the latest, expanded dataset, and we tested these models with independent test sets with a view to integrating the models into the RDI's online, experimental treatment decision tool, HIV-TRePS.

   Method: Treatment change episodes (TCEs) from >15 countries from the RDI database were partitioned at random into a training set of 14,964 and a test set of 800. A committee of 10 random forest models was developed to predict the probability of follow-up viral load ffi400 copies using 10x leave-n out cross-validation (CV). The input variables were baseline viral load, CD4 count, treatment history, drugs in the new regimen, and time to follow-up. Receiver-operator characteristic (ROC) curves were plotted during cross validation, with the test set of 800 and with test sets from Romania (n=39) and South Africa (n=56). A subset of 57 TCEs from the test set with available genotypes was also tested with the RDI's models that included a genotype.

   Results: The mean area under the curve (AUC) and overall accuracy (OA) were 0.77 and 72% during CV and 0.77 and 71% with the test dataset. With the Romanian test set, the AUC and OA were 0.68 and 67%, and with the South African test set 0.69 and 68%. The RDI genotype models achieved an AUC and OA of 0.77 and 74% with the subset of 57, compared to 0.76 and 68% for the models with no genotype.

   Conclusions: The RF models' predictions were only slightly less accurate than models that included the genotype. They performed well with data from resource-limited clinics not represented in the

training dataset, suggesting they are generalisable. The models are now available via the RDI's online treatment selection tool HIV-TRePS.

4. Publications and presentations
   During 2010, the RDI presented the results at the International HIV & Hepatitis Drug Resistance Workshop, Dubrovnik and the XVIII International AIDS Conference, Vienna, Austria.
   In addition, a description by the RDI of the modelling of virological response to HIV therapy without the use of a genotype was published in the Journal of Antimicrobial Chemotherapy, 65(4):605-607. These publications included Frank de Wolf from the Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands as an author.
   Computational models developed without a genotype for resource-poor countries predict response to HIV treatment with 82% accuracy
   AD Revell, D Wang, R Harrigan, J Gatell, L Ruiz, S Emery, MJ Pérez-Elías, C Torti, J Baxter, F DeWolf, Brian Gazzard AM Geretti, S Staszewski, R Hamers, AMJ Wensing, J Lange, JM Montaner, BA Larder
   Oral slide and poster presentations at:
   XVIII International HIV Drug Resistance Workshop, Fort Myers, Florida, USA, 9-13 June 2009
   Computational models can accurately predict response to antiretroviral therapy without a genotype
   B Larder, D Wang, A Revell, R Harrigan, J Gatell, L Ruiz, S Emery; C Torti, F de Wolf, A Pozniak, JM Montaner

## I05006 Epidemiology and pathology of HIV coinfection with Hepatitis B and C

J.E. Arends, I.M. Hoepelman, C.A.B. Boucher, C. Smit

Date of approval: January 2005

Background: In 2006 we analyzed the registration of Hepatitis B (HBV) and C (HCV) in the Dutch SHM system. It was shown that insufficient numbers were registered, resulting in underreporting of the actual prevalence of HBV and HCV. Furthermore, inaccurate data were available for thorough research in this field. Following our report, SHM started a program to correct this problem. Currently, a more solid registration of HBV and HCV coinfection is entered into the SHM database.

Methods: Data were collected for all patients known to to be treated with HAART and known to have been tested for HBV and HCV, according to the SHM database. The Kaplan-Meier method and Cox proportional hazard model were used to compare the time from HAART initiation until death amongst HIV-infected, HBV/HIV-, HCV/HIV-co-infected, and the triple-infected patients.

Results: 112 of the 11181 patients were triple-infected with HIV/HBV/HCV. During a median follow-up of 5.8 years, triple-infected patients and HCV/HIV-co-infected patients died significantly more rapidly compared to HIV-infected patients (p logrank test<0.001). The adjusted risk of dying was significantly higher in triple-infected patients compared with HIV-mono-infected patients (hazard ratio [HR]: 1.86 [1.08-3.21]) and in HCV/HIV-co-infected patients (HR; 1.50 [CI: 1.11-2.04]).

Conclusion: Although HAART increased the life expectancy in HIV infected patients, those with a chronic triple infection of hepatitis B, C, and HIV, as well as patients co-infected with HCV/HIV, still have an increased mortality risk. Therefore, HCV treatment should receive priority in the treatment of HCV/HIV-infected patients.

2010 Publications in peer reviewed journals : J.E. Arends, M.A.A. Claassen, C.H.S.B. van den Berg, N.M. Nanlohy, K.J. van Erpecum, L.C. Baak, A.I.M. Hoepelman, A. Boonstra and D. van Baarle. T-cell responses at baseline and during therapy with peginterferon- and ribavirin are not associated with outcome in chronic Hepatitis C infected patients. Antiviral Research 2010; 87 (3): 353-360. 2010
Abstracts of presentations:
- poster at the 61th AASLD meeting, Oct 29–Nov 2 2010 in Boston.
- poster at the 50th ICAAC meeting, September 12–15 2010 in Boston.
- poster at the 20th ECCMID meeting, April 10–13 2010 in Vienna.

### Io5511 Influence of HIV-1 co-receptor usage on the clinical course of infection under HAART and the outcome of antiretroviral therapy

H. Schuitemaker, K. Brinkman
Date of approval: October 2005

We previously reported interim results for this study. Below we report the results updated for the complete data sets.

Introduction: HIV-1 coreceptor use is known to influence the natural course of the disease. To investigate whether HIV-1 coreceptor use also influences the immunological and/or virological response to HAART, we determined the baseline coreceptor use of treatment-naïve (n=499) and -experienced (n=233) patients starting a new HAART regimen with the MT-2 assay.

Methods: HIV-1 coreceptor use was determined in duplicate co-cultures of MT-2 cells with patient PBMC samples obtained at HAART baseline (negative = no CXCR4-using HIV-1 present, positive = CXCR4-using HIV-1 present). Differences in baseline CD4 counts and log HIV RNA loads were tested using Student's t-test. Differences in time to undetectable HIV RNA load were tested with Kaplan-Meier survival analysis.

Results: At HAART baseline, 508 patients had MT-2–negative samples and 224 had MT-2–positive samples. Both treatment-naïve and treatment-experienced patients with MT-2–positive samples at HAART baseline had significantly lower CD4 counts and higher HIV RNA loads. Treatment-experienced patients with MT-2–positive samples had a delayed time to undetectable VL, and both experienced and naïve patients reached lower CD4 counts at undetectable VL. However, there was no difference in absolute changes in CD4 counts from HAART initiation to reaching undetectable VL.
To determine why patients with positive MT-2 cultures were started on HAART at worse baseline values, we examined CD4 decline in untreated patients with MT-2–positive or MT-2–negative samples. Patients with positive MT-2 cultures had accelerated CD4 decline and increased VL. Moreover, whereas the majority of first X4 emerge at CD4 counts between 200-400, a significant number of X4 first emerge at CD4>400. There was a stable rate of emergence of CXCR4-using HIV-1 over time, indicating that given enough time, CXCR4-using HIV-1 may emerge in any untreated patient.

Conclusions: Patients with positive MT-2 cultures have more CD4 loss between 2 visits, thus resulting in worse baseline values prior to HAART initiation. We conclude that patients with positive MT-2 cultures may have to be monitored more frequently and/or started on HAART at higher CD4 counts to receive the same benefits as patients with

negative MT-2 cultures. Therefore, monitoring of HIV-1 coreceptor use may have a clinical benefit prior to HAART initiation even when not considering CCR5 antagonists.

Abstracts of presentations:
AB van 't Wout, AI van Sighem, MRA Welkers, I Maurer, MM Mangas-Ruiz, AM Harskamp-Holwerda, JM Prins, K Brinkman, F de Wolf, NA Kootstra, Hanneke Schuitemaker. 2010. HIV-Infected Patients with Positive MT-2 Cultures May Need More Frequent Monitoring and/or HAART Initiation at Higher CD4 Counts. 17th Conference on Retroviruses and Opportunistic Infections, February 27 - March 2, 2010, San Francisco, CA, USA.
AB van 't Wout, AI van Sighem, MRA Welkers, I Maurer, MM Mangas-Ruiz, AM Harskamp-Holwerda, JM Prins, K Brinkman, F de Wolf, NA Kootstra, Hanneke Schuitemaker. 2010. HIV-Infected Patients with Positive MT-2 Cultures May Need More Frequent Monitoring and/or HAART Initiation at Higher CD4 Counts. 8th European HIV Drug Resistance Workshop 17-19 March 2010, Sorrento, Italy.

### I05548 Incidence of HPV-related anogenital cancers in HIV-infected patients

M.E. van der Ende, E. Snoek

No progress report was received. Project ended.

### I04034 The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D)

P. Reiss

The D:A:D Study in 2010 celebrated its 10th anniversary as a highly successful international HIV cohort collaboration. Ten cohorts worldwide were participating, representing close to 200 clinics in over 20 countries in Europe, USA, and Australia. Currently, more than 33.000 HIV-infected persons, with a total of 200.000 person-years of follow-up, are being followed, a sizeable proportion of which has been enrolled within the last year to make sure the patients in the cohort continue to represent the current HIV population at large. The ATHENA cohort ranks amongst the top contributors to D:A:D. Funding for D:A:D has been extended and secured through 2012, largely as a result of its success in meeting its original aim, i.e., to progressively delineate the relationship between the use of antiretroviral drug classes and individual drugs and the risk of myocardial infarction and cardio/cerebrovascular disease in general. The results from the study on several occasions have also informed and influenced changes in international HIV treatment guidelines.

The study continues to follow patients prospectively and focuses on monitoring the risk of cardiovascular disease and its association with extended exposure to cART. However, as a result of this success, the D:A:D study group has been requested more recently by the EMEA to also focus on collecting additional comorbidity endpoints that include end-stage renal disease, chronic severe liver disease, and non-AIDS malignancies. Again, as was the case for cardiovascular disease, the aim is to further delineate the possible contribution of the use of antiretroviral therapy to the risk of development of these endpoints. Finally, the study continues to collect detailed information on causes of death by a standardized coding system of causes of death (CoDe), which has been developed jointly by all participating cohorts as well as by a number of clinical trial networks. The CoDe system has been adopted by various other research groups.

Participation in D:A:D and CoDe has always provided the opportunity and incentive for SHM to implement and improve its data collection on cardiovascular risk factors and morbidity/mortality and on causes of death in general within the entire Athena cohort. The same is now true for the collection of these additional endpoints. Furthermore, by coordinating the way such data are collected with other HIV cohorts, Athena can continue to importantly contribute to other international cross-cohort collaborations.

For additional information, please see www.cphiv.dk.

2010 Publications:

Risk of Myocardial Infarction in Patients with HIV Infection Exposed to Specific Individual Antiretroviral Drugs from the 3 Major Drug classes: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. Worm SW, Sabin S, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, Monforte AD, Friis-Møller N, Fontas E, Weller I, Phillips a, Lundgren J. J Infect Dis. 2010 Feb 1;201(3):318-30. PubMed PMID: 20039804

Predicting the risk of cardiovascular disease in HIV-infected patients: the Data Collecton on Adverse Effects of Anti-HIV Drugs Study. N Friis-Møller, R Thiébaut, P Reiss, R Weber, AD Monforte, S De Wit, W El-Sadr, E Fontas, S Worm, O Kirk, A Phillips, C Sabin, JD Lundgren, M Law; for the DAD study group. Eur J Cardiovasc Prev Rehabil. 2010 Oct;17(5):491-501.

Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group. C Smith, SW Worm, N Friis-Møller, CA Sabin, A Sjøl, JD Lundrgen, R Salbøl-Brandt, M Rickenbach, P Pezzotti, E Krum, L Gras, E Balestre, A Sundström, M Delforge, E Fontas, F Torres, K Petoumenos, J Kjær, S Collins, S Storpher, G Pearce, R Rode, I Weller. AIDS. 2010 Jun 19;24(10):1537-48.

HBV or HCV coinfections and risk of myocardial infarction in HIV-infected individuals: the D:A:D Cohort Study. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. R Weber, C Sabin, P Reiss, S de Wit, SW Worm, M Law, F Dabis, A d'Arminio Monforte, E Fontas, W El-Sadr, O Kirk, M Rickenbach, A Phillips, B Ledergerber, J Lundgren. Antivir Ther. 2010;15(8):1077-86.

Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(‘). K Petoumenos, S Worm, P Reiss, S de Wit, A d'Arminio Monforte, C Sabin, N Friis-Møller, R Weber, P Mercie, C Pradier, W El-Sadr, O Kirk, JD Lundgren, M Law; for the D:A:D study group. HIV Med. 2011 Jan 20. doi: 10.1111/j.1468-1293.2010.00901.x. [Epub ahead of print]

2010 Abstracts of presentations:

12th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV

Oral Presentation:

1. Evaluation of sudden death and non-haemorrhagic stroke and their association with HIV protease inhibitor (PI) usage. S Worm, A Kamara, P Reiss, E Fontas, S De Wit, W El Sadr, A d'Arminio Monforte, M Law, A Phillips, L Ryom, F Dabis, R Weber, C Sabin, JD Lundgren, on behalf of the DAD study group.

17th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 2010

Oral Presentations:

1. Rates of Cardiovascular Disease Following Smoking Cessation in Patients with HIV Infection: Results from the DAD Study.

K Petoumenos, S Worm, P Reiss, S De Wit, A d'Arminio Monforte, N Friis-Moller, R Weber, P Mercie, C Pradier, J Lundgren on behalf of the DAD study group.

2. Triglycerides and the risk of myocardial infarction in the DAD study. S Worm, A Kamara, W El-Sadr, O Kirk, E Fontas, P Reiss, A Phillips, M Bruyand, A d'Arminio Monforte, M Law, R Weber, J Lundgren, C Sabin on behalf of the DAD study group.

### I08115 Proposal for collaboration and data exchange between HMF and RIVM for nation HIV/Aids surveillance and data transfere tot ECDC in the context of EU obligations for reporting on HIV/Aids

E. op den Coul, F. de Wolf, M. van der Sande, A. van Sighem, J. Vlug

European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2008. Stockholm: European Centre for Disease Prevention and Control; 2009. - F Koedijk, HJ Vriend, MG van Veen, ELM Op de Coul, IVF van den Broek, AI van Sighem, RA Verheij. Sexually transmitted infections including HIV, in the Netherlands in 2009.
HJ Vriend, FDH Koedijk, IVF van den Broek, ELM Op de Coul, AI van Sighem, RA Verheij. RIVM report 210261007/2010, Bilthoven 2010.
ELM Op de Coul, JWM van Weert, PJ Oomen, C Smit, CPB van der Ploeg, SJM Hahné, DW Notermans, MAB van der Sande. Prenatale screening op hiv, hepatitis B en syfilis in Nederland effectief. Ned Tijdsch Geneeskd 2010 4 december; 154 (48): 2219-2225
ELM Op de Coul, S Hahne, Y van Weert, P Oomen, C Smit, K van der Ploeg, MAB van der Sande. Effectiveness of antenatal screening for hiv, hepatitis B and syphilis (submitted)
M Kramer, M Cormelissen, D Paraskevis, M Prins, R Coutinho, A van Sighem, L Sabajo, A. Duits, C Winkel, J Prins, M van der Ende, R Kauffmann & ELM Op de Coul. HIV transmission patterns The Netherlands, Suriname, and the Netherlands Antilles: a molecular epidemiological study. Aids research and human retroviruses 2010; Oct 7

### I08196 The effect of Radio Therapy on CD4 cell count in HIV infected patients

S.U.C. Sankatsing, J.M. Prins, A. Verbon, L.A. Gras
No progress report received. Project ongoing.

### I09050 Contribution of multiple genetic variants, previously validated in genome-wide analyses, to acute coronary artery events in HIV-infected individuals-an international collaborative study

H. Schuitemaker, P. Reiss
Date of approval: April 2009

We selected 193 cases (first acute coronary artery disease event between April 2000 and April 2009) and 592 controls (1:3 matching) from the patients in the ATHENA data base who were included in the D:A:D study. Materials were available for 53 cases and 117 controls, whereas 86 cases and 300 controls were alive, but without stored material. From February 2010 on, the living cases and controls were approached to participate in the study through the HIV treatment centres. For each patient willing to participate, written informed consent was obtained prior to the blood draw. Blood was shipped to the AMC (EXIM-LVIP), where DNA was isolated from the white blood cell fraction, and DNA quantity and quality was determined for each sample. As a result, on January 10, 2011, sufficient aliquots of DNA from a final total of 81 cases and 243 controls (3 controls per case) were shipped to Lausanne. The first genotyping pilot results in Lausanne indi-

cated that the DNA specimens are acceptable. Genotyping will be completed in March 2011, and the data analysis will be completed in May 2011.

### I08044 Primo SHM R5x4 HAART

M. Grijsen, M. Welkers

Background: The optimal clinical management of primary HIV infection (PHI) is controversial. Treatment during PHI may result in a more effective immune response to the virus, resulting in lowering of the viral setpoint and delaying the loss of CD4 T-cells. Several ongoing randomized controlled trials in the cART era have addressed the question whether such temporary treatment also has clinical benefits for the patient, but none have been published so far. The aim of the Primo-SHM study was to assess the clinical benefit of temporary cART during PHI.

Methods: The study was a multicenter, open-label, randomized controlled trial in which patients with laboratory evidence of PHI were randomly assigned to receive no treatment or 24 or 60 weeks of cART. If therapy was clinically indicated, subjects were randomized over the 2 treatment arms. Patients were recruited in 13 Dutch HIV treatment centers. Recruitment started in May 2003 and continued until March 2010. Primary endpoints were the viral setpoint, defined as the plasma viral load (pVL) 36 weeks after randomization in the no-treatment arm and 36 weeks after treatment interruption in the treatment arms, and the total time that patients were off therapy, defined as the time between randomization and start of cART in the no-treatment arm and the time between treatment interruption and restart of cART in the treatment arms. cART was (re)started with a confirmed CD4 count <350 cells/mm3 or symptomatic HIV disease. Time off therapy was compared across study arms using KM plots and multivariate Cox survival analyses adjusted for confounding factors.

Results: The modified intention-to-treat-analysis comprised 168 patients: 115 were randomized over the 3 study arms, and 53 were randomized over the 2 treatment arms only. The vast majority of patients randomized over the three study arms were MSM, had a negative or indeterminate Western blot, and were symptomatic during PHI. Therapy in the treatment arms was well tolerated. The mean viral set point was significantly lower in the 24- and 60-week treatment arms compared to the no-treatment arm. The median total time off therapy was significantly longer in the 24- and 60-week treatment arms compared to the no-treatment arm: restart of cART during chronic HIV infection was deferred approximately 2 years. When all treated patients, including the patients randomized over the 2 treatment arms, were combined, the median total time off therapy was no different between the 24- and 60-week treatment arms. In the adjusted Cox analyses, temporary cART was independently associated with time to (re)start of cART.

Discussion: This randomized trial provides the first evidence of a clinical benefit of temporary cART during PHI. Temporary cART lowered the viral setpoint and deferred the need for initiation of cART during chronic HIV infection.

These results have been accepted for an oral presentation at the 18th Conference on Retroviruses and Opportunistic Infections, February 2011 in Boston.

2010 Publications:
Grijsen ML, Vrouenraets SME, Steingrover R, Lips P, Reiss P, Wit FWNM, Prins JM. High prevalence of reduced bone mineral density in primary HIV-1 infected men. Aids 2010;24(14):2233-8.

### I09071 The Impact of the presence of TAM's including revertants on the composition and the efficacy of a first line HAART regimen

M.E. van der Ende, A.el. Barzouhi, M. Schutten, B.J.A. Rijnders e.a.
Date of approval: March 2009
No progress report received. Project ongoing.

### I10042 The use of nevirapine dose escalation in patients who switch from efavirenz to nevirapine.

David Burger, Maren Blonk, Ferdinand Wit, Colette Smit, Matthijs van Luin, Luc Gelinck, Herman Sprenger, Peter Koopmans.
Date of approval: 11 May 2010

The proposal was discussed at the NVAB/SHM meeting on March 7, 2010. After approval from the SHM Advisory Board was obtained, support for funding was requested at Boehringer Ingelheim and was eventually approved. A PhD candidate (Maren Blonk) was appointed as of November 1, 2010, and preparations for data analyses were made.

### I010021 Uncovering Determinants of eco-evo Pathogen Dynamica with ABCmu

O. Ratman
Date of approval: 28 May 2010

Oliver Ratman submitted this study to the Wellcome Trust for a fellowship grant, and his application was acknowledged in 2010. This study will start in 2012.

### I10053 Schatting van de onderrapportage van HIV geinfecteerde TBC patienten in Nederland

Frank van Leth, Ferdinand Wit e.a.
Date of approval: 13 January 2011
Ongoing

### I10234 Effectieve en veilige combinaties van cART en chemotherapie in HIV-geinfecteerde patienten met maligne lymfoom

David Burger e.a.
Date of approval: 14 December 2010
Ongoing

### I10043 Evaluatie van het gebruik van therapeutic drug monitoring bij HIV positieve kinderen in Nederland

Diana Bastiaans, David Burger, Mathijs van Luin, Nico Hartwig
Date of approval: 1 November 2010
Ongoing

## Publications 2010

*The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals.*
HIV-CAUSAL Collaboration.
AIDS. 2010 Jan 2;24(1):123-37. Epub 2009 September 18.

*Health-related quality of life and survival among HIV-infected patients receiving highly active antiretroviral therapy: a study of patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort.*
de Boer-van der Kolk IM, Sprangers MA, Prins JM, Smit C, de Wolf F, Nieuwkerk PT.
Clin Infect Dis. 2010 Jan 15;50(2):255-63.

*Transmission networks of HIV-1 among men having sex with men in the Netherlands.*
Bezemer D, van Sighem A, Lukashov VV, van der Hoek L, Back N, Schuurman R, Boucher CA, Claas EC, Boerlijst MC, Coutinho RA, de Wolf F; ATHENA observational cohort.
AIDS. 2010 Jan 16;24(2):271-82.

*High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome.*
Worm SW, Friis-Møller N, Bruyand M, D'Arminio Monforte A, Rickenbach M, Reiss P, El-Sadr W, Phillips A, Lundgren J, Sabin C; D:A:D study group.
AIDS. 2010 Jan 28;24(3):427-35.

*Superinfection with a heterologous HIV strain per se does not lead to faster progression.*
Fung IC, Gambhir M, van Sighem A, de Wolf F, Garnett GP.
Math Biosci. 2010 Mar;224(1):1-9. Epub 2009 Nov 20.

*Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years.*
Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), Lodwick R, Costagliola D, Reiss P, Torti C, Teira R, Dorrucci M, Lederger-ber B, Mocroft A, Podzamczer D, Cozzi
Arch Intern Med. 2010 Mar 8;170(5):410-9.

*Transient lowering of the viral set point after temporary antiretroviral therapy of primary HIV type 1 infection.*
Steingrover R, Garcia EF, van Valkengoed IG, Bekker V, Bezemer D, Kroon FP, Dekker L, Prins M, de Wolf F, Lange JM, Prins JM.
AIDS Res Hum Retroviruses. 2010 Apr;26(4):379-87.

*Modelling response to HIV therapy without a genotype: an argument for viral load monitoring in resource-limited settings.*
Revell AD, Wang D, Harrigan R, Hamers RL, Wensing AM, Dewolf F, Nelson M, Geretti AM, Larder BA.
J Antimicrob Chemother. 2010 Apr;65(4): 605-7.

*Measuring the Quality of Data Collection in a Large Observational Cohort of HIV and AIDS*
Hillebregt M, De Lange-de Klerk E, Knol D, De Wolf F, Smit C
Open AIDS J. May 2010;4:96-102.

*Clinical significance of transient HIV type-1 viraemia and treatment interruptions during suppressive antiretroviral treatment.*
Zhang S, van Sighem A, Gras L, Reiss P, Smit C, Kroon F, Jurriaans S, Prins J, Lange J, de Wolf F.
Antivir Ther. 2010;15(4):555-62.

*Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies.*
Antiretroviral Therapy Cohort Collaboration.
Clin Infect Dis. 2010 May 15;50(10):1387-96.

*27 years of the HIV epidemic amongst men having sex with men in the Netherlands: An in depth mathematical model-based analysis.*
Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Fraser C
Epidemics. 2010 June; 2(2):66-70.

*Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals.*
van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F; ATHENA national observational cohort study.
AIDS. 2010 Jun 19;24(10):1527-35.

*Immune restoration and onset of new AIDS-defining events with combination antiretroviral therapy in HIV type-1 infected immigrants in the Netherlands*
Kesselring AM, Gras L, Wit FW, Smit C, Geerlings SE, Mulder JW, Schreij G, Sprenger HG, Reiss P, de Wolf F
Antivir Ther. 2010;15(6):871-9.

*Death rates in HIV-positive antiretroviral-naive patients with CD4 count greater than 350 cells per microL in Europe and North America: a pooled cohort observational study.*
Study Group on Death Rates at High CD4 Count in Antiretroviral Naive Patients, Lodwick RK, Sabin CA, Porter K, Ledergerber B, van Sighem A, Cozzi-Lepri A, Khaykin P, Mocroft A, Jacobson L, De Wit S, Obel N, Castagna A, Wasmuth JC, Gill J, Klein MB, Gange S, Riera M, Mussini C, Gutiérrez F, Touloumi G, Carrieri P, Guest JL, Brockmeyer NH, Phillips AN.
Lancet. 2010 Jul 31;376(9738):340-5. Epub 2010 Jul 15.

*Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.* Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, Gatell J, Phillips AN, Ledergerber B, Lundgren JD; EuroSIDA Study Group.
AIDS. 2010 Jul 17;24(11):1667-78.

*Dialysis and Renal Transplantation in HIV-Infected Patients*: a European Survey. Trullas JC, Mocroft A, Cofan F, Tourret J, Moreno A, Bagnis CI, Fux CA, Katlama C, Reiss P, Lundgren J, Gatell JM, Kirk O, Miró JM; the EuroSIDA Investigators.
J Acquir Immune Defic Syndr. 2010 Aug 31. [Epub ahead of print]

*A comparison of the long-term durability of nevirapine, efavirenz and lopinavir in routine clinical practice in Europe: a EuroSIDA study.*
Reekie J, Reiss P, Ledergerber B, Sedlacek D, Parczewski M, Gatell J, Katlama C, Fätkenheuer G, Lundgren JD, Mocroft A; for the EuroSIDA study group.
HIV Med. 2010 Aug 31. [Epub ahead of print]

*Adaptation of HIV-1 envelope gp120 to humoral immunity at a population level.*
Bunnik EM, Euler Z, Welkers MR, Boeser-Nunnink BD, Grijsen ML, Prins JM, Schuitemaker H.
Nat Med. 2010 Sep;16(9):995-7. Epub 2010 Aug 29.

*Is it safe to discontinue primary Pneumocystis jiroveci pneumonia prophylaxis in patients with virologically suppressed HV infection and a CD4 cell count <200 cells/mL?*
The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). Mocroft A, Reiss P, Kirk O, Mussini C, Girardi E, Morlat P, Stephan C, De Wit S, Doerholt K, Ghosn J, Bucher HC, Lundgren JD, Chene G, Miro JM, Furrer H.
Clin Infect Dis. 2010 Sep 1;51(5):611-9.

*High prevalence of reduced bone mineral density in primary HIV-1-infected men.*
Grijsen ML, Vrouenraets SM, Steingrover R, Lips P, Reiss P, Wit FW, Prins JM.
AIDS. 2010 Sep 10;24(14):2233-8.

*Predicting the risk of cardiovascular disease in HIV-infected patients: the Data collection on Adverse Effects of Anti-HIV Drugs Study.*
Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG; for the DAD study group.
Eur J Cardiovasc Prev Rehabil. 2010 Oct;17(5):491-501. Epub 2010 Jun 10.

*Serious fatal and nonfatal non-AIDS-defining illnesses in Europe.*
Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, Gatell J, Rakhmanova A, Johnson M, Kirk O, Lundgren J; EuroSIDA Study Group.
J Acquir Immune Defic Syndr. 2010 Oct 1;55(2):262-70.

*The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy.*
Boer K, Smit C, van der Flier M, de Wolf F; on behalf of the ATHENA cohort study group.
Eur J Public Health. 2010 Nov 4. [Epub ahead of print]

*Prenatale screening op hiv, hepatitis B en syphilis in Nederland effectief*
Op de Coul ELM, van Weert YWM, Oomen PJ, Smit C, van der Ploeg CPB, Hahné, Notermans DW, van der Sande MAB.
Ned Tijdschr Geneeskd. 2010;154:A2175

*The Efficacy of Combination Antiretroviral Therapy in HIV Type 1-Infected Patients Treated in Curaçao Compared with Antillean, Surinam, and Dutch HIV Type 1-Infected Patients Treated in The Netherlands.*
Hermanides HS, Gras L, Winkel CN, Gerstenbluth I, van Sighem A, de Wolf F, Duits AJ.
AIDS Res Hum Retroviruses. 2010 Dec 14. [Epub ahead of print]

*Late presentation of HIV infection: a consensus definition.*
Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, Girardi E, Johnson M, Kirk O, Lundgren J, Mocroft A, d'Arminio Monforte A, Phillips A, Raben D, Rockstroh JK, Sabin C, Sönnerborg A, de Wolf F; for the European Late Presenter Consensus working group.
HIV Med. 2011 Jan;12(1):61-4. Epub 2010 Jun 17.

*Estimating the risk of HIV transmission from homosexual men receiving treatment to their HIV-uninfected partners*
Hallett TB, Smit C, Garnett GP, de Wolf F
Sex Transm Infect. 2011 Feb;87(1):17-21. Epub 2010 Jul 18.

## Other printed material

*Handboek Hiv en psychische klachten*
Schadé A, Boenink AD, Danner SA
Uitgeverij De Tijdstroom, Utrecht, June 2010, ISBN 9789058981738.

## Oral presentations

*HIV-monitoring op de Nederlandse Antillen*
van Sighem A
HIV Intervention Monitoring, Curaçao, 26-27 April 2010

*Controlling the HIV epidemic in the Netherlands*
van Sighem A, de Wolf F, Bezemer D, Hollingsworth D, Garnett G, Fraser C
Werkgroep Epidemiologisch Onderzoek Nederland, Nijmegen, The Netherlands, 11-12 June 2010

*Life Expectancy of Recently Diagnosed Asymptomatic HIV-infected Patients Approaches That of Uninfected Individuals*
van Sighem A, Gras L, de Wolf F, Brinkman K, Reiss P
Werkgroep Epidemiologisch Onderzoek Nederland, Nijmegen, The Netherlands, 11-12 June 2010

*Estimating the rate of HIV transmission from men on treatment*
Smit C, Hallett T, Garnett G, de Wolf F
Werkgroep Epidemiologisch Onderzoek Nederland, Nijmegen, The Netherlands, 11-12 June 2010

*Aging with HIV in The Netherlands - Can the health care system cope?*
Cees Smit e.a.
18th International AIDS Conference, Vienna, Austria, 18-23 July 2010

*Overview of HIV estimates models*
van Sighem A
STI and HIV surveillance in EU/EEA, Berlin, Germany, 28-30 September 2010

*Genomic subpopulations and experience of HIV monitoring*
Bezemer D
Genomics subpopulations and health systems responses Workshop, University of Exeter, Exeter, United Kingdom, 11 November 2010

*Developments in the HIV Epidemic in the Netherlands*
de Wolf F
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*The role of cART, immunodeficiency and viraemia in liver-related events in HIV-1 infected patients*
Kesselring A, Wit F, Smit C, Reiss P, de Wolf F
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*Antiretroviral treatment as a strategy for controlling the HIV epidemic amongst men who have sex with men*
van Sighem A, Bezemer D, Garnett G, de Wolf F, Fraser C
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

## Poster presentations

*Episodes of HIV Viraemia and the Risk of Non-AIDS Events amongst Successfully Treated Patients*
Zhang S, van Sighem A, Gras L, Smit C, Prins J, Kauffmann R, Richter C, Reiss P, de Wolf F, and the national observational Athena Cohort
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*Estimating the rate of HIV transmission from men on treatment.*
Smit C, Hallett T, Garnett G and de Wolf F
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*Life Expectancy of Recently Diagnosed Asymptomatic HIV-infected Patients Approaches That of Uninfected Individuals*
van Sighem A, Gras L, Reiss P, Brinkman K, de Wolf F, on behalf of the ATHENA national observational cohort study
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*HIV-Infected Patients with Positive MT-2 Cultures May Need More Frequent Monitoring and/or HAART Initiation at Higher CD4 Counts*
van 't Wout A, van Sighem A, Welkers M, Maurer I, Harskamp A, Prins J, Brinkman K, de Wolf F, Kootstra N, Schuitemaker H
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010
8th European HIV Drug Resistance Workshop, Sorrento, Italy, 17-19 March 2010

*Time with CD4 Cell Count above 500 cells/mm³ allows HIV-Infected Men, but not Women, to Reach Similar Mortality Rates to those of the General Population: A Seven-year Analysis*
Lewden C on behalf of the Mortality Working Group of COHERE
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*Incomplete Immune Recovery on HAART Is Associated with Significant More Cardiovascular Events (CVE) and a Trend for More Non-AIDS Related Malignancies (NAM) in Dutch ATHENA Cohort*
van Lelyveld S, Gras L, Kesselring A, Zhang S, de Wolf F, Wensing A, Hoepelman A
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*Cause or Consequence? Peripheral CD4 Cell Counts and Hodgkin Lymphoma in Patients on cART.*
Bohlius J and Egger M for the Lymphoma working group of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE)
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*May Pneumocystis prophylaxis be safely discontinued in virologically suppressed patients with CD4 counts below 200 cells/μL? - The Collaboration of Observational HIV Epidemiological Research Europe (COHERE).*
Furrer H, on behalf of the Opportunistic Infections Working Group of Collaboration of Observational HIV Epidemiological Research Europe (COHERE)
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*Triple class virologic failure in HIV-infected children*
Green H on behalf of the PLATO II Project Team of COHERE
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*High Prevalence of Reduced Bone Mineral Density (BMD) in Primary HIV-1 infected Men*
Grijsen M, Vrouenraets S, Steingrover R, Lips P, Lange J, Reiss P, Wit F, Prins J
17th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 16-19 February 2010

*Modeling trends in CD4 cell decline before the start of antiretroviral therapy*
Gras L, Geskus R, van Sighem A, de Wolf F
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010

*Occasional transmission of multidrug resistant strains*
Bezemer D, van Sighem A, Back N, Schuurman R, Claas E, Boucher C and de Wolf F for the ATHENA observational cohort
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010

*Immunodeficiency and viral load and the risk of non-AIDS events among untreated HIV-1 infected patients*
Zhang S, van Sighem A, Gras L, Smit C, Prins J, Kauffmann R, Richter C, de Wolf F
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010

*High rate of virological success in etravirine treated patients*
de Wolf F, Smit C, Gras L, van Sighem A, Lange J
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010

*Impact of transmitted drug resistance (TDR) on virological response to initial combination Antiretroviral Therapy (cART)-regimen*
Wittkop L on behalf of the EuroCoord-CHAIN joint project team
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010
International HIV & Hepatitis Virus Drug Resistance Workshop & Curative Strategies, Dubrovnik, Croatia, 8-12 June 2010

*Triple class virologic failure in HIV-infected children*
Castro H on behalf of the PLATO II Project Team of COHERE
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010

*Controlling the transmission of resistant HIV in the Netherlands*
van Sighem A, Bezemer D, Garnett G, de Wolf F, Fraser C
14th International Workshop on HIV Observational Databases, Barcelona, Spain, 25-27 March 2010

*Adherence to TDM guidelines in The Netherlands: combined use of lopinavir/ritonavir plus an NNRTI as an example*
Van Luin M, Wit F, Smit C, Rigter I, Franssen E, Richter C, Kroon F, de Wolf F, Burger D
11th International Workshop on Clinical Pharmacology in HIV Therapy, Sorrento, Italy, 7-9 April 2010

*The development of computational models that accurately predict virological response to HIV therapy to power an online treatment selection tool*
Larder B, Wang D, Revell A, Emery S, de Wolf F, Nelson M, Perez Elias M, Harrigan P, Montaner J
International HIV & Hepatitis Virus Drug Resistance Workshop & Curative Strategies, Dubrovnik, Croatia, 8-12 June 2010

*Assessing quality of HIV care: Using observational data for improving HIV care*
Smit C, Gras L, van Sighem A, Kroon F, Binkman K, van Kasteren M, Geerlings S,
18th International AIDS Conference, Vienna, Austria, 18-23 July 2010

*Expert physicians rate RDI system for predicting response to HIV therapy as easy and useful treatment tool*
Revell A, Mican J, Agan B, Coe D, Wang D, Rivera-Goba M, Metcalf J, Pozniak A, Perez-Elias M, Montaner J, Lane H, Larder B
18th International AIDS Conference, Vienna, Austria, 18-23 July 2010

*Immediate antiretroviral treatment as a strategy for controlling the HIV epidemic amongst men having sex with men*
van Sighem A, Bezemer D, Garnett G, de Wolf F, Fraser C
18th International AIDS Conference, Vienna, Austria, 18-23 July 2010

*National Estimate of HIV Prevalence in The Netherlands: Comparison and Applicabillity of Different Estimation Tools*
van Veen M, Presanis A, Conti S, Xiridou M, Rinder Stengaard A, Donoghoe M, van Sighem A, van der Sande M, de Angelis D
18th International AIDS Conference, Vienna, Austria, 18-23 July 2010

*Lower mortality and more timely start of cART in patients tested repeatedly for HIV compared to those with a positive first test*
Gras L, van Sighem A, Smit C, Bezemer D, Wit F, de Wolf F
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*Modeling trends in CD4 cell decline before the start of antiretroviral therapy*
Gras L, Geskus R, van Sighem A, de Wolf F
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*Dyslipidemia in HIV-infected children and adolescents treated with cART between 1997 and 2009: a longitudinal analysis.*
Smit C, Hartwig N, Geelen S, Schölvinck E, van de Flier M, Scherpbier H
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*AIDS is still there: Decreasing incidence but stable absolute number of new AIDS diagnoses among cART treated HIV infected patients.*
Gras L, Smit C, van Sighem A, de Wolf F
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*Initiation of antiretroviral therapy for HIV infection and the risk of non-AIDS diseases*
Zhang S, van Sighem A, Gras L, de Wolf F
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010

*Delay of entry into care in HIV positive individuals*
van Veen M, de Wolf F, Heijman R, Zaheri S, Fennema J, Gotz H, van der Sande M
NCHIV 2010, Amsterdam, The Netherlands, 23 November 2010