HIV Monitoring

Annual report 2012

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 2012, approved by the Governing Board of Stichting HIV Monitoring on 15 April 2013.

We would like to thank Rosalind Beard, Daniela Bezemer, Daniëlle de Boer, Irene de Boer, Louise Dolfing, Anouk Kesselring, Luuk Gras, Mireille Koenen, Henk van Noort, Ard van Sighem, Colette Smit and Sima Zaheri for their support.

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Foreword

It is only appropriate that I begin by thanking my predecessor, Professor Frank de Wolf, for establishing Stichting HIV Monitoring (SHM) as such a competent and well run organisation. He has handed over an organisation staffed by highly professional and motivated people who are rightfully proud of what they have accomplished and continue to accomplish.

Over the past year, SHM, the Dutch HIV monitoring foundation, has successfully continued its mission in monitoring the HIV epidemic and systematically collecting, analysing and reporting data concerning people living with HIV. Importantly, this mission can be accomplished only by a fruitful collaboration with health care professionals in the 26 appointed HIV treatment centres throughout the Netherlands. As a result of this collaboration, SHM is uniquely positioned to provide a truly nationwide picture of the outcome of care for those living with HIV and, thereby, to contribute significantly to monitoring the quality of HIV care. Moreover, this allows SHM to provide individual treatment centres with regular updates of their own centre-specific data, which enables the centres to critically review and improve their performance where it is needed.

Apart from monitoring HIV-specific outcomes such as degrees of viral load suppression, immune recovery, emergence of HIV drug resistance and overall survival, SHM continues to invest much time and effort in monitoring non-AIDS comorbidities, which continues to gain in importance as patients with HIV in care continue to age. The efforts to expand and improve the data collection for hepatitis B and C co-infections in those with HIV that were started some time ago have been successfully continued. In turn, these methods have paved the way to explore their application in monitoring patients with hepatitis B and C mono-infection.

We are fortunate that Frank de Wolf will continue to carry out part of his work in the Department of Infectious Disease Epidemiology at Imperial College in London, which hopefully will ensure the continued fruitful collaboration amongst SHM, Imperial College and the RIVM in modelling various aspects of the HIV epidemic. Over the past year, SHM has continued to contribute importantly to various European and other, more global HIV observational cohort collaborations in the volume of both data and science. Such a contribution makes it possible to tackle scientific questions that cannot be answered by any individual cohort on its own and outcomes of this research have led to modifications in HIV treatment guidelines.

Last but not least, I would like to thank all the people living with HIV in care for allowing us to capture their data, store blood samples and learn how we may continue to improve their care.

Prof. Peter Reiss MD, PhD

Director

Amsterdam, 15 April 2013

Message from the Governing Board Chair

The year 2012 was a year of development and notable change for Stichting HIV Monitoring (SHM) with Frank de Wolf stepping down from his role of director on 1 December 2012. Frank was one of the initiators of the establishment of SHM in 2001, following the successful project entitled "AIDS Therapy Evaluation in the Netherlands" (ATHENA). Since 2002, the SHM has been recognized by the Ministry of Health as the organization that monitors the HIV epidemic in the Netherlands, together with HIV treatment centres, and contributes to the promotion of quality HIV care.

Under Frank's leadership, SHM has grown over an 11-year period to an organisation of more than 40 employees. The foundation took over the ATHENA database, which it has continued to develop and expand to include many more data items per patient. Routine procedures that streamline data collection and monitoring have also been developed and SHM now has one of the best data sets in Europe, if not the world.

SHM has formed a comprehensive overview of the HIV epidemic in the Netherlands. It has also developed a system that can be used by doctors for patient care, as well as by officials for policy issues related to HIV care. Additionally, the foundation has made important contributions both nationally and internationally to the knowledge of HIV-related comorbidities, the effect of treatment and the issues related to treatment.

The work carried out by SHM stresses the need for continued monitoring of HIV infection in the Netherlands. Monitoring is crucial not only for assessing the quality of care for people with HIV, including the effect of antiretroviral treatment and the development of resistance, but also for understanding changes in the epidemic.

Frank's knowledge, ability to understand and articulate the state of affairs to various authorities, ability to work collegially with stakeholders and partners, and his support for staff, board and working group members has been greatly appreciated. Thank you, Frank, and all the very best for the future.

I would also like to take this opportunity to welcome Peter Reiss, who has taken over the role of director. Peter's long history in the field of HIV research and his association with SHM make him a logical successor in this role, and I believe his knowledge and capabilities will serve SHM well.

Finally, I would like to thank the board members for their work. Two members, Tony Lamping and Roel Coutinho, left us in 2012 and I would like to thank them for their involvement in the organisation. I would also like to thank all the SHM employees for their dedication and hard work and all the health professionals and patients for their continued support.

The next few years promise to be a time of change within health care. I feel confident that SHM is ready to embrace the challenges ahead.

Dr. Frank Kroon

Chairman of the Governing Board

Amsterdam, 15 April 2013

Progress Report

Stichting HIV Monitoring (SHM) contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. In the Netherlands, SHM follows the treatment of every registered HIV-infected man, woman and child. In this way we are able to comprehensively map the HIV epidemic and HIV treatment outcomes in the Netherlands.

Since its founding in 2001, SHM has worked with HIV treatment centres throughout the Netherlands to develop a framework for systematically collecting HIV data for the long-term follow-up of all registered patients. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

Continuous collection of data is essential for the work of SHM and is carried out at 26 HIV treatment centres and subcentres and at 4 paediatric HIV centres in the Netherlands. This is performed either by staff of the treatment centre or by SHM data collecting staff in cooperation with the responsible HIV physician. Patient data are collected anonymously and then entered into the registration database for storage and analysis.

The progress report includes an overview of the 26 treatment centres, as well as overviews of SHM's organisation, data collection, database and data quality management. It also includes reports on registration and monitoring, and the Amsterdam Cohort Studies, which receives it's funding through SHM. An overview of SHM's national and international collaborations, and ways in which SHM disseminated information during 2012 are also reported.

HIV Treatment Centres

The monitoring of HIV-infected adults is a collaborative effort involving the Stichting HIV Monitoring (SHM) and a total of 26 health institutes that are acknowledged by the Dutch Minister of Health, Welfare and Sport as HIV treatment centres or subcentres. In addition, HIV-infected children and adolescents are monitored in four institutes that are recognized as paediatric HIV treatment centres.

In 2012, the following health institutes were involved as centres or subcentres for adult HIV care (in alphabetical order by town):

1	Medisch Centrum Alkmaar (MCA)	Alkmaar
2	Flevoziekenhuis	Almere
3	Academic Medical Centre of the University of Amsterdam (AMC-UvA)	Amsterdam
4	Onze Lieve Vrouwe Gasthuis (OLVG)	Amsterdam
5	Sint Lucas Andreas Ziekenhuis	Amsterdam
6	Slotervaartziekenhuis	Amsterdam
7	Stichting Medisch Centrum Jan van Goyen (MC Jan van Goyen)	Amsterdam
8	VU Medisch Centrum (VUMC)	Amsterdam
9	Rijnstate	Arnhem
10	HagaZiekenhuis (location Leyenburg)	Den Haag
11	Medisch Centrum Haaglanden (MCH, location Westeinde)	Den Haag
12	Catharina Ziekenhuis	Eindhoven
13	Medisch Spectrum Twente (MST)	Enschede
14	Universitair Medisch Centrum Groningen (UMCG)	Groningen
15	Kennemer Gasthuis	Haarlem
16	Medisch Centrum Leeuwarden (MC Leeuwarden)	Leeuwarden
17	Leids Universitair Medisch Centrum (LUMC)	Leiden
18	MC Zuiderzee*	Lelystad
19	Academisch Ziekenhuis Maastricht (AZM)	Maastricht
20	Universitair Medisch Centrum Sint Radboud (UMC St Radboud)	Nijmegen
21	Erasmus Medisch Centrum (Erasmus MC)	Rotterdam
22	Maasstad Ziekenhuis	Rotterdam
23	St Elisabeth Ziekenhuis	Tilburg
24	Universitair Medisch Centrum Utrecht (UMCU)	Utrecht
25	Admiraal De Ruyter Ziekenhuis	Vlissingen
26	Isala Klinieken (location Sophia)	Zwolle

** MC Zuiderzee was designated an HIV treatment centre in 2012.*

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

A	Emma Kinderziekenhuis, AMC-UvA	Amsterdam
B	Beatrix Kinderziekenhuis, UMCG	Groningen
C	Erasmus MC-Sophia	Rotterdam
D	Wilhelmina Kinderziekenhuis, UMCU	Utrecht

SHM has contracts with each centre or subcentre for the collection of demographic, epidemiologic, clinical, virological, immunologic and pharmacologic data for HIV-infected patients who are 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 and upon the request of the Red Cross Blood Bank in Willemstad, Curaçao, provides assistance to collect the data of HIV-infected persons seen by HIV/AIDS doctors at the St. Elisabeth Hospital in Curaçao.

SHM Organisation

Stichting HIV Monitoring (SHM) is overseen by a Governing Board that includes trustees who represent the National Association of Health Insurers, the Netherlands HIV Association (HVN), HIV/AIDS treatment centres and the Dutch Association of HIV-Treating Physicians (NVHB). The board members determine the budget and the annual report.

Furthermore, SHM has an Advisory Board that reviews SHM's activities from a strategic perspective and advises the Governing Board and Director. The members of the Advisory Board are appointed by the Governing Board for a four-year period.

The SHM Working Group, consisting of members and reviewers, advises the Director on executive matters regarding use of data stored in the national HIV database. The Working Group is also responsible for reviewing research proposals submitted to SHM.

The Director of SHM 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.

SHM's data collectors, which are employed in the patient data and quality control unit, had an average 13.19 full-time equivalents (fte's) in 2012. This includes the administration of patient registration, which involves the inclusion and exclusion of data and assignment of an anonymous identification code to each patient.

The data quality staff, including data monitors and assistent data monitors, are also part of the patient data and quality control unit. During 2012, the average number of data quality staff was 7.34 fte's. Data management activities, a responsibility of this unit, are also partly outsourced to the Clinical Research Unit (CRU), Department of Clinical Epidemiology and Biostatistics of the Academic Medical Center of the University of Amsterdam. At least twice a year, in February/March and in June/July, a data freeze takes place producing a dataset that is used for processing and analysis. The patient data and quality control unit is managed by Sima Zaheri (0.8 fte). During 2012, the average number of fte's in the unit was 21.33.

Researchers in the field of epidemiology, statistics, mathematical modelling of HIV and modelling transmission networks staff the data processing and analysis unit. During 2012, the unit increased to six researchers following the successful completion of a PhD programme. Together, they execute the HIV registration and monitoring programme, the results of which are presented in the annual SHM monitoring report published around the time of 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 for support of approved research applications from the Dutch pharmaceutical industry.

In 2012, the unit also had two assistant researchers in two PhD programmes. One of these PhD programmes was successfully completed in November 2012 and focused on the clinical implications of immune recovery during antiretroviral treatment for HIV infection. The focus of the other PhD programme is on controlling the HIV epidemic in the Netherlands. In addition, the unit continues to support two other researchers in PhD programmes, one in comparing the effect of combination retroviral therapy (cART) on HIV-infected individuals treated in Curaçao with that on patients from the Netherlands Antilles treated in the Netherlands, and the other is focused on the optimalisation of quality of care for HIV-infected patients in HIV treatment centres in the Netherlands.

In 2012, an average of 5.08 fte's was assigned to the data processing and analysis unit, which was led by Frank de Wolf (0.92 fte), Director of SHM, up until his resignation on 30 November 2012.

The primary activities of SHM are supported by the members of the office staff, which includes the secretariat, financial and personnel administration, internal controlling and communications. It is supervised by SHM's controller, Danielle de Boer (0.7 fte), with an average of 3.41 fte's assigned in 2012. This number has remained constant over the past years.

As of 31 December 2012, SHM had an average total of 31.44 fte's. In addition, SHM covers the costs for a total of 12.5 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 2012 was 4.27%, which was 1.2% more than in 2011.

A list of members of SHM's Governing Board, Advisory Board, Working Group and personnel can be found in *Appendix 1: Composition of SHM*.

Data Collection, Database & Data Quality Management

In 2012, the Stichting HIV Monitoring (SHM) continued the steps to improve the data production processes in conformity with its quality management system. Spearheads were:

- To standardise and improve data collection, data quality management and data processing;
- To improve the ICT infrastructure and data management processes;
- To centralize, where possible, the collecting of data from the SHM office by specifically trained staff;
- To establish an automated link that allows laboratory data from various hospital computer systems to be entered directly and anonymously into the SHM database;
- To intensify quality control of the collected data by concentrating on information that is essential for the output and data consistency;
- To teach and train the data collectors and data quality staff.

The following results were achieved in 2012:

Standardisation, automation and steps for improvement

- **Improvement and standardisation of data collection:**
  In 2012 the protocols for the collection of data from HIV-infected children in the four paediatric HIV centres were evaluated and improved in consultation with the treating physicians in these centres. The protocol for the collection of pregnancy data was also revised.
  On the advice of the Hepatitis Working Group, a collaboration between the Dutch Association of HIV-Treating Physicians (NVHB) and the SHM that was founded in March 2010, objectives have been defined for the collection of data on viral hepatitis infections in HIV-infected patients. The protocol for data collection on viral hepatitis infections was drawn up on the basis of these objectives which relate to liver diagnostics, liver morbidity, treatment and response to treatment.
  As part of the harmonisation of data extracted from the sources of information in the HIV treatment centres and the coding and entry of these data in the national database of the SHM, in accordance with the SHM protocols, plans were made for setting up a helpdesk system for the data collectors. This system will be implemented in 2013.

- **Centralised data collection:**
  The efficiency and quality of the data collecting and data entry process in the treatment centres appear to correlate with the availability of data collectors in the participating hospitals. Centralised data collection, utilizing specifically trained staff from the SHM office on a flexible basis, will help this process. In 2012, the data collection in five HIV treatment centres (Universitair Medisch Centrum Groningen; Medisch Centrum Leeuwarden; Universitair Medisch Centrum St Radboud, Nijmegen; Catharina Ziekenhuis, Eindhoven; and MC Zuiderzee, Lelystad) was centralised in consultation with the responsible treating physician on location. As of 1 July 2012, the centralised collection

of data on viral hepatitis in HIV-infected patients was started, both prospectively and retrospectively.

- **Standardisation of data entry:**
  Until 2003, patient data were collected in local Access databases (HIVREG) and merged every six months. In 2003, an Oracle Clinical database for centralised data collection via a secure Internet connection was implemented. Until 2010 the data from these two databases with different formats were synchronised and merged. Data corrections resulting from data quality checks were entered into both systems. In 2010, a standardisation process was started, with the aim of only using the Oracle Clinical database for manual data entry and corrections. In 2011, the implementation of these processes was continued; the importing of data was tested and any problems that arose were identified and remedied. In 2012, the importing of data was executed definitively and successfully.
  In addition, data entry screens were developed in 2012 in the national SHM database for the collection of data on viral hepatitis.

- **Patient reports, graphs and standard data queries:**
  In 2012, the patient reports, custom reports, graphs and standard data queries that were built into Microsoft Report Builder in 2011 were further developed and improved. Additional data overviews were built to enable the data collectors and data monitors to work better and more efficiently. The data collectors, data quality staff and treating physicians in the participating hospitals started using these reports and graphs in the second half of 2012.

- **Standardisation of Lab-Link:**
  Standardising Lab-Link, the automated link that allows laboratory data from various hospital computer systems to be entered directly and anonymously into the SHM database, was continued in 2012. The standard protocol that was developed in collaboration with the Clinical Research Unit (CRU) and General ICT Service (ADICT) of the Academic Medical Center (AMC) of the University of Amsterdam for sending laboratory results as HL7 messages (an international standard for electronic data exchange between healthcare information systems) has been presented to all HIV treatment centres for the implementation of Lab-Link. The Lab-Link standard protocol was tested as a pilot at the Medisch Centrum Alkmaar and then implemented. Subsequently, five treatment centres that already used a Lab-Link to send their data (Medisch Spectrum Twente, Enschede; Leids Universitair Medisch Centrum, Leiden; Maasstad Ziekenhuis, Rotterdam; Universitair Medisch Centrum Utrecht; and Isala Klinieken (Sophia), Zwolle) started sending their data in accordance with the new standard protocol. Two other treatment centres (St Elisabeth Ziekenhuis, Tilburg and Slotervaartziekenhuis, Amsterdam) started the Lab-Link standard method test phase in 2012. The AMC continued sending the results directly from the lab system via an internal connection in 2012. The laboratory results received through Lab-Link from these seven treatment centres represent data from 28%

of all patients in the SHM database. The remaining treatment centres were approached in 2012 and asked to participate in the Lab-Link automation, after which they received the standard protocol and the possibility to implement Lab-Link was surveyed. The necessary preparations have been started in 12 hospitals.

- **Harmonisation of Lab-Link data:**
  A Lab-Link 'mapping tool' has been developed by the CRU in Microsoft Access, which receives and standardises laboratory results from different treatment centres with different terminology. In 2012, 2,023 combinations of laboratory terms and the accompanying samples were harmonised.

- **Centre-Specific (CS) reports:**
  On SHM's website, standard reports have been developed with the aim of providing the treatment groups in the treatment centres with an overview of the developments, trends and issues within their own patient population every six months. This data product was tested in 2012 by a panel of clinicians who had already reached agreement on the content and form of presentation in 2010. After testing, the CS reports were presented to all HIV treatment centres nationally.

- **Standardisation of data processing:**
  In 2012 data from different sources were merged and imported into SHM's data warehouse. The data warehouse is updated daily with data entered manually into the national SHM database on the previous day and with data sent by the treatment centres via Lab-Link. The SHM data warehouse contains 160 tables and 159,079,711 records which are available daily for data analysis and for presentation of data to the treatment centres in table and report form. The raw data in the data warehouse tables are processed twice a year and adapted for data analysis. The data are cleaned, clustered and coded according to the standard protocols of different national and international collaborations and the Anatomical Therapeutic Chemical (ATC) classification.
  In 2012 these data processes resulted in data sets for Centre-Specific reports, the Comorbidity and Aging with HIV (AGEhIV) cohort study, the MSM Observational Study of Acute Infection with hepatitis C (MOSAIC) study and Zichtbare Zorg (ZiZo, Visible Care). Also, data processes have been carried out and data sets were created for two international collaborations, the D:A:D study and COHERE. The latter is part of EuroCoord, an EU-supported network which enhances clinical and epidemiological HIV research in Europe through cohort collaboration.

Volume of data collection

The results of the data collection are summarised in *Table 1*. The total volume of data increased in 2012 by 111% in comparison to 2011. This can be explained by the increased growth of both the automated data collection by Lab-Link and the manual data collection. The volume of the automated data collection by Lab-Link increased in 2012 by 61%; the volume of manual data collection increased by no less than 104%. This large increase can be explained by a

more detailed collection of data on viral hepatitis in HIV- and viral hepatitis-co-infected patients and standardisation of import databases, which means that the manually entered data from the HIVREG database are cleaned and imported in the Oracle Clinical database. The increase in the volume of manual data collection from HIV-infected children, HIV-exposed children and pregnancies has diminished in 2012 as a result of a reduced backlog of retrospective data in 2012.

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 estimation 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 in the year prior to the last visit. A difference of 180 days or less is not considered a delay.

In 2012, the average long-term backlog in data collection decreased by 1% compared to 2011. This is largely due to the ongoing training of data collectors in efficiently organising the logistics of data collection, where individual patient reports and standard data queries are importantly used to establish priorities. Entry of follow-up data of patients with the largest data-entry backlog takes priority. The long- and short-term backlogs at Slotervaart Ziekenhuis, Amsterdam; Kennemer Gasthuis, Haarlem; Medisch Centrum Leeuwarden; and Erasmus Medisch Centrum, Rotterdam has been reduced through the placement of SHM data collectors who have supported the local data collectors.
The average short-term data collection backlog increased 1% in 2012. This may be the result of a decline in the visit frequency of patients in follow-up, compared to 2011, which cannot be accounted for in the backlog calculations.

Quality Control (QC)

In 2012, automated quality checks were introduced to support the manual quality checks by data quality staff as well as efficiency improvement. A number of validation rules that select inconsistencies and missing data to be checked by the data collectors have been defined for each item of data collection. *Table 3* shows the results of the automated quality checks in 2012. Checks on baseline and follow-up data were given priority in 2012. A total of 73 validation rules, selecting 26,204 records that were sent to the data collectors in order to be checked, were defined. The data collectors received instructions and training and the results of their checks were implemented in the SHM national database.

Automated procedures for checking the Lab-Link data were also considered. A distinction is made between one-time and structural checks on Lab-Link data in a testing, acceptance and production environment. The one-time checks for acceptance of the new Lab-Links are performed on data in a testing and acceptance environment. The structural checks on Lab-Link data will be performed in 2013 on Lab-Link data in the production environment.

Table 4 shows the results of the manual quality checks that were performed by the SHM

Table 1: Data collection results 2004–2012.

	2012	2011	2010
Manual data collection			
HIV-infected adults			
Baseline	197,452	258,734	186,507
Follow-up	13,827,787	5,779,482	6,044,689
End of follow-up	11,827	11,996	11,680
Laboratory results	16,186,750	8,690,310	8,166,082
Subtotal (data points)	30,223,816	14,740,522	14,408,958
HIV- and viral hepatitis-co-infected adults			
Baseline	90		
Follow-up	7,971		
Laboratory results	837,688		
Liver diagnostics	15,475		
Subtotal (data points)	861,224		
HIV-infected children			
Baseline	2,291	4,271	944
Follow-up	135,126	174,232	80,126
End of follow-up	430	783	195
Laboratory results	242,022	478,313	104,370
Subtotal (data points)	379,869	657,599	185,635
HIV-exposed children			
Baseline	271	2,893	2,040
Follow-up	1,607	14,401	11,243
End of follow-up	252	1,549	1,069
Laboratory results	1,738	19,331	11,407
Subtotal (data points)	3,868	38,174	25,759
Pregnancies			
Baseline	5,299	5,020	2,682
Follow-up and end of pregnancies	17,890	16,684	8,816
Laboratory results	7,028	12,138	7,632
Subtotal (data points)	30,217	33,842	19,130
Additional data			
Causes of death (numbers)	227	185	152
Cardiovascular disease (numbers)	186	223	219
Other co-morbidities (numbers)	322	194	199
Subtotal additional data (numbers)	735	602	570
Total manual collection (data points)	**31,499,729**	**15,470,739**	**14,640,052**
Increase (%) manually collected data (data points)	**104%**	**6%**	**12%**
Automated data collection			
Number of lab results per year	5,802,388	3,612,404	433,254
Total automated collection (estimated data points)	**23,209,552**	**14,449,616**	**1,733,016**
(%) Lab-Link from total lab results	57	61	9
Increase (%) Lab-Link data	**61%**	**734%**	**11%**
Total data collection (data points)	**62,998,723**	**29,920,355**	**16,373,068**
Increase (%) total data	**111%**	**83%**	**12%**
Cumulative number of patients with data	17,118	16,223	14,877
Increase (%) patients in follow-up	**6%**	**9%**	**5%**

2009	2008	2007	2006	2005	2004
78,396	69,364	53,359	56,700	64,062	126,924
4,941,270	4,824,298	4,316,778	3,615,436	3,325,594	2,575,088
11,123	9,778	11,561	13,043	8,691	7,799
7,637,999	6,833,090	7,124,209	7,112,151	5,961,439	5,760,663
12,668,788	11,736,530	11,505,907	10,797,330	9,359,786	8,470,474
1,976	688	1,051	1,750	4,148	1,425
113,967	118,562	168,704	314,136	311,260	75,263
150		63	165	75	
271,267	200,129	441,003	536,153	809,088	261,036
387,360	319,379	610,821	852,204	1,124,571	337,724
80	901				
4,787	2,870				
192	28,793				
2,916	15,336				
7,975	47,900				
940	1,705	1,275	3,876	3,648	
7,548	16,044	12,020	37,216	35,540	
5,865	14,123	10,532	42,905	31,332	
14,353	31,872	23,827	83,997	70,520	
113	108	128	164	27	1
167	55	81	151	108	45
529					
809	163	209	315	135	46
13,079,285	**12,135,681**	**12,140,555**	**11,733,531**	**10,554,877**	**8,808,198**
8%	**0%**	**3%**	**11%**	**20%**	
389,015	222,668	119,668	95,685		
1,556,060	**890,672**	**478,672**	**382,740**		
9	11	6	5		
75%	**86%**	**25%**			
14,635,345	**13,026,353**	**12,619,227**	**12,116,271**	**10,554,877**	**8,808,198**
16%	**3%**	**4%**	**15%**	**20%**	
14,138	13,296	11,666	10,275	9,399	8,537
6%	**14%**	**14%**	**9%**	**10%**	

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

		>365 days		<365 days	
HIV treatment centre	**Location**	**2012**	**2011**	**2012**	**2011**
MCA	Alkmaar	0%	0%	4%	0%
Flevo Zkh	Almere	0%	0%	20%	2%
AMC-UvA	Amsterdam	0%	0%	8%	7%
OLVG	Amsterdam	0%	0%	5%	1%
St Lucas Andreas Zkh	Amsterdam	0%	0%	5%	23%
Slotervaart Zkh	Amsterdam	0%	0%	13%	2%
MC Jan van Goyen	Amsterdam	0%	0%	3%	1%
VUMC	Amsterdam	0%	0%	18%	3%
Rijnstate Zkh	Arnhem	0%	0%	15%	1%
Haga Zkh – Leyweg	Den Haag	1%	0%	3%	2%
MCH – Westeinde	Den Haag	0%	0%	23%	16%
Catharina Zkh	Eindhoven	0%	0%	22%	6%
MST	Enschede	0%	5%	8%	1%
UMCG	Groningen	0%	0%	31%	45%
Kennemer Gasthuis	Haarlem	1%	0%	10%	8%
MC Leeuwarden	Leeuwarden	0%	0%	10%	8%
LUMC	Leiden	0%	1%	12%	1%
MC Zuiderzee	Lelystad	2%	NA*	5%	NA*
AZM	Maastricht	0%	0%	10%	19%
UMC St Radboud	Nijmegen	0%	0%	1%	15%
Erasmus MC	Rotterdam	0%	0%	10%	17%
Maasstad Zkh	Rotterdam	0%	0%	4%	18%
St Elisabeth Zkh	Tilburg	2%	0%	1%	1%
UMCU	Utrecht	0%	1%	3%	6%
Admiraal de Ruyter Zkh	Vlissingen	1%	0%	7%	9%
Isala Klinieken – Sophia	Zwolle	2%	9%	7%	4%
Mean		**0%**	**1%**	**10%**	**9%**

* *MC Zuiderzee was designated an HIV treatment centre in 2012 and data collection commenced at that time.*

Table 3: Number of automated validation rules per criterion and records sent to data collectors for verification in 2012.

Selection criteria for quality checks	Number of validation rules	Number of records
Consistency checks		
Inconsistencies and/or missing adverse event data	6	522
Inconsistencies and/or missing antiretroviral medication data	15	20,697
Inconsistencies and/or missing baseline data	32	3,190
Inconsistencies and/or missing CDC event data	6	161
Inconsistencies and/or missing co-medication data	4	337
Inconsistencies and/or missing end of follow-up data	10	1,297
Total number of quality checks	**73**	**26,204**

Table 4: Number of patient files checked by data monitors per data selection criterion.

Selection criteria for quality checks	2012	2011
Random selection		
Random selection of adverse event data	0	0
Random selection of antiretroviral medication data	0	1
Random selection of baseline data	56	81
Random selection of CDC event data	0	0
Random selection of co-medication data	0	0
Random selection of all patient data	0	0
Random selection of data from last year of follow-up	0	0
Subtotal random selection	**56**	**82**
Consistency checks		
Inconsistencies in adverse event data	32	237
Inconsistencies in antiretroviral medication data	2	2
Inconsistencies in baseline data	0	11
Priority analysis baseline data	0	0
Inconsistencies in CDC event data	0	1
Inconsistencies in co-medication data	0	0
Inconsistencies in laboratory data	0	1
Subtotal consistency checks	**32**	**252**
Co-morbidity and cause of death checks		
Pregnancies	0	0
Total cardiovascular disease:	186	223
Myocardial infarction	*51*	*38*
Invasive cardiovascular procedures	*49*	*49*
Diabetes mellitus	*54*	*76*
Stroke	*32*	*60*
Chronic liver disease	12	23
End-stage renal disease	16	34
Non-AIDS-defining malignancy	294	137
Cause of death in 100% of cases	227	185
Subtotal co-morbidity and cause of death checks	**735**	**602**
Subtotal personal coaching of data collectors	168	154
Total number of quality checks	**991**	**1,090**
% change per year	**-9%**	**-41%**

Number of patient files						
2010	**2009**	**2008**	**2007**	**2006**	**2005**	**2004**
0	0	0	2	1	0	0
0	2	8	3	13	6	0
0	0	0	52	17	7	1
0	0	1	2	11	0	0
0	0	0	0	2	0	0
1	0	2	1	17	87	118
0	0	0	0	38	126	203
1	**2**	**11**	**60**	**99**	**226**	**322**
1,147	74	1,056	30	69	1	0
2	23	209	1	18	3	0
0	0	116	362	97	161	0
0	10	0	207	0	0	0
2	3	257	122	289	0	0
0	4	2	7	17	0	0
4	16	93	18	5	0	0
1,155	**130**	**1,733**	**747**	**495**	**165**	**0**
0	0	1	0	129	10	0
219	167	55	92	151	108	45
46	*36*	*16*	*17*	*31*	*33*	*14*
49	*43*	*14*	*10*	*40*	*16*	*10*
101	*62*	*19*	*40*	*55*	*37*	*16*
23	*26*	*6*	*25*	*25*	*22*	*5*
10	22					
12	13					
177	381					
152	113	108	128	164	27	1
570	**696**	**164**	**220**	**444**	**145**	**46**
124	114	241	268	216	0	0
1,850	**942**	**2,149**	**1,295**	**1,254**	**536**	**368**
96%	**-56%**	**66%**	**3%**	**179%**	**19%**	

data quality staff in 2012. These manual checks focus on collected data that are essential for output, complex data that can be used for training data collectors, and data consistency.

Data from 56 patients were randomly selected and the baseline data from this selection were checked. Data related to cause of death and co-morbidity, defined as "endpoints", continued to be controlled in 100% of the cases in 2012 and were also classified for data analysis.

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

During 2012, data of a total of 991 patients were checked manually by SHM data quality staff. Five hundred and eight patient files were selected and the data collected from these files were checked for cardiovascular diseases or other co-morbidities. The causes of death for 227 patients were verified and classified. On average, each HIV treatment centre was visited 11 times by the SHM data quality staff responsible for that centre.

The number of patients whose file was quality-controlled decreased in 2012 by 9% compared to 2011. This can be explained by two factors: an increase in the number of selected co-morbidities and causes of death that were checked in a more comprehensive and detailed manner; and by the introduction of automated and more efficient controlling of data in the SHM data warehouse at table and record level, such that no patient files needed to be consulted.

Training and education

In September 2012, an intensive internal training was organised for new employees in the Quality Control (QC) group. A number of data quality staff received custom training in the use of SAS® software during a two-day training session.

In addition to their personal coaching, a review day was organised for the SHM data collectors in November 2012. During the day a lecture on viral hepatitis infections in HIV-infected patients was given. SHM's data quality staff gave information about data processing, new online reports and changes in the data structure at the SHM and discussed the collection of hepatitis B and C data and other types of data that will be collected in 2013. The data collectors were trained in procedures and activities related to collecting new types of data and maintaining data quality.

In December 2012 a proportion of the data quality staff were trained to recognise various infectious diseases.

Registration & Monitoring of HIV-Infected Individuals

General

As of 31 December 2012, a cumulative total of 21,012 persons with HIV infection were registered through the Dutch HIV treatment centres by Stichting HIV Monitoring (SHM) *(Table 5)*. Compared to 2011, this represents an increase of 1,260 (6%) newly registered individuals in the SHM database *(Table 6)*. Among the 21,012 persons, 16,656 (79%) were men and 4,355 (21%) were women, whereas the sex of one person was not registered. A total of 235 persons were registered with an HIV treatment centre specialising in HIV-care for children and adolescents. An AIDS-defining event was recorded in 5,445 (26%) persons and 2,073 (10%) died.

Further clinical data has been collected for 20,676 of the registered persons. The remaining 336 (1.6%) persons indicated that they were opposed to the collection of such data. In 2012, data was collected from 16,653 (79%) persons in total. Of the 4,359 (21%) persons with no data collected in 2012, 1,937 persons were deceased prior to 2012, 831 had moved abroad and 1,591 had disappeared from care for an unknown reason. Taking into account the persons that in 2012 had objections to data collection and those who died during the year, as of 31 December 2012, there were 16,446 HIV-infected persons in care whose data was collected in 2012.

Adults

Out of the total of 20,676 persons registered in 2012, 20,315 (98%) were adults at the time of registration, including 16,261 (80%) men and 4,054 (20%) women. The most common route of HIV transmission in men was homosexual contact (72%) and in women heterosexual contact (88%). The median age at diagnosis was 37.1 years (interquartile range [IQR], 30.4-44.6) for men and 31.2 (25.9-38.3) for women. At the end of 2012, 4% of the total group had been aware of their positive HIV status for less than a year, 22% had known for 1 to 5 years, 26% for 5 to 10 years and 37% for more than 10 years, whereas for 1% the HIV diagnosis date is not yet registered. Ten percent of the 20,351 adults are deceased. The median follow-up duration was 7.3 years (IQR, 3.3-12.9), 7.1 years for men and 8.0 for women. The total follow-up in the adult group is 175,380 person-years.

Of the 1,241 adults newly registered in 2012, 1,035 (83%) were men and 206 (17%) were women. Homosexual contact was still the main transmission route amongst men (73%) and heterosexual contact amongst women (85%). The median age at diagnosis was 38.7 years (IQR 29.2-47.4) in men and 33.2 (27.0-42.4) in women. In total, 32 people objected to further registration of clinical data.

Table 5: Cumulative numbers and percentages of HIV-infected patients registered and monitored by SHM in one of the HIV Treatment Centres in the Netherlands and Curaçao on 31 December 2012. Patients are recorded by the last known HIV treatment centre where they were registered.

		Total		Alive or not registered as deceased		Deceased		Data in 2012[a]		No data in 2012				Objection[d]	
										Deceased before 2012[b]		Other[c]			
HIV Treatment Centre	**Location**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Adults															
MCA	Alkmaar	282	1.4	259	91.8	23	8.2	230	81.6	22	7.8	30	10.6	1	0.4
Flevo Zkh	Almere	142	0.7	138	97.2	4	2.8	134	94.4	2	1.4	6	4.2	2	1.4
AMC-UvA	Amsterdam	2,659	12.8	2,380	89.5	279	10.5	2,100	79.0	266	10.0	293	11.0	6	0.2
MC Jan van Goyen	Amsterdam	662	3.2	630	95.2	32	4.8	595	89.9	30	4.5	37	5.6	3	0.5
OLVG	Amsterdam	2,982	14.4	2,670	89.5	312	10.5	2,328	78.1	288	9.7	366	12.3	118	4.0
Slotervaart Zkh	Amsterdam	820	3.9	684	83.4	136	16.6	592	72.2	132	16.1	96	11.7	8	1.0
St Lucas Andreas Zkh	Amsterdam	336	1.6	298	88.7	38	11.3	275	81.8	35	10.4	26	7.7	0	0
VUMC	Amsterdam	530	2.6	463	87.4	67	12.6	395	74.5	64	12.1	71	13.4	11	2.1
Rijnstate	Arnhem	658	3.2	598	90.9	60	9.1	545	82.8	56	8.5	57	8.7	2	0.3
Haga Zkh - Leyweg	Den Haag	654	3.1	586	89.6	68	10.4	451	69.0	66	10.1	137	20.9	29	4.4
MCH - Westeinde	Den Haag	878	4.2	805	91.7	73	8.3	677	77.1	68	7.7	133	15.1	21	2.4
Catharina Zkh	Eindhoven	516	2.5	488	94.6	28	5.4	435	84.3	28	5.4	53	10.3	3	0.6
MST	Enschede	509	2.4	410	80.6	99	19.4	312	61.3	95	18.7	102	20.0	1	0.2
UMCG	Groningen	771	3.7	707	91.7	64	8.3	642	83.3	59	7.7	70	9.1	11	1.4
Kennemer Gasthuis	Haarlem	411	2.0	367	89.3	44	10.7	327	79.6	41	10.0	43	10.5	2	0.5
MC Leeuwarden	Leeuwarden	251	1.2	230	91.6	21	8.4	206	82.1	21	8.4	24	9.6	0	0
LUMC	Leiden	622	3.0	571	91.8	51	8.2	491	78.9	47	7.6	84	13.5	27	4.3
MC Zuiderzee	Lelystad	48	0.2	48	100	0	0	48	100	0	0	0	0	0	0
AZM	Maastricht	747	3.6	637	85.3	110	14.7	554	74.2	103	13.8	90	12.0	3	0.4
UMC St Radboud	Nijmegen	630	3.0	569	90.3	61	9.7	528	83.8	57	9.0	45	7.1	13	2.1
Erasmus MC	Rotterdam	2,184	10.5	1,952	89.4	232	10.6	1,712	78.4	214	9.8	258	11.8	8	0.4
Maasstad Zkh	Rotterdam	574	2.8	537	93.6	37	6.4	510	88.9	28	4.9	36	6.3	1	0.2
St Elisabeth Zkh	Tilburg	936	4.5	880	94.0	56	6.0	791	84.5	53	5.7	92	9.8	3	0.3
UMCU	Utrecht	1,451	7.0	1,309	90.2	142	9.8	1,165	80.3	130	9.0	156	10.8	44	3.0
Admiraal De Ruyter Zkh	Vlissingen	137	0.7	125	91.2	12	8.8	100	73.0	11	8.0	26	19.0	4	2.9
Isala Klinieken-Sophia	Zwolle	387	1.9	366	94.6	21	5.4	323	83.5	18	4.7	46	11.9	14	3.6
Total adults		**20,777**		**18,707**	**90.0**	**2,070**	**10.0**	**16,466**	**79.3**	**1,934**	**9.3**	**2,377**	**11.4**	**335**	**1.6**

Table 5 continued

HIV Treatment Centre	Location	Total N	Total %	Alive or not registered as deceased N	Alive or not registered as deceased %	Deceased N	Deceased %	Data in 2012[a] N	Data in 2012[a] %	No data in 2012: Deceased before 2012[b] N	No data in 2012: Deceased before 2012[b] %	No data in 2012: Other[c] N	No data in 2012: Other[c] %	Objection[d] N	Objection[d] %
Children/adolescents															
Emma KZ, AMC-UvA	Amsterdam	69	29.4	69	100	0	0	63	91.3	0	0	6	8.7	0	0
Beatrix KK, UMCG	Groningen	23	9.8	23	100	0	0	9	39.1	0	0	14	60.9	0	0
Erasmus MC – Sophia	Rotterdam	72	30.6	70	97.2	2	2.8	54	75.0	2	2.8	16	22.2	1	1.4
Wilhelmina KZ, UMCU	Utrecht	71	30.2	70	98.6	1	1.4	61	85.9	1	1.4	9	12.7	0	0.0
Total children/adolescents		**235**		**232**	**98.7**	**3**	**1.3**	**187**	**79.6**	**3**	**1.3**	**45**	**19.1**	**1**	**0.4**
Curaçao															
SEHOS	Willemstad	812	98.1	660	81.3	152	18.7	465	57.3	148	18.2	199	24.5	0	0
SEHOS kinderkliniek	Willemstad	16	1.9	6	37.5	10	62.5	0	0	10	62.5	6	37.5	0	0
Total Curaçao		**828**		**666**	**80.4**	**162**	**19.6**	**465**	**56.2**	**158**	**19.1**	**205**	**24.8**	**0**	**0**

[a] *Data in 2012: Registered by SHM in 2012, or deceased during or after 2012, or last contact with a HIV treatment centre during or after 2012.*

[b] *No data in 2012 – Deceased before 2012: Patients who are not included in 'Data in 2012' and were deceased before 2012.*

[c] *No data in 2012 – Other: Patients who are not included in 'Data in 2012', because they moved abroad before 2012 or for an unknown reason did not have contact with a HIV treatment centre in 2012.*

[d] *Objection: Consent not given for collection of clinical data.*

Table 6: HIV-infected patients newly registered in 2012 by SHM in HIV Treatment Centres in the Netherlands and Curaçao.

		Total		Alive		Deceased		Objection[a]	
HIV Treatment Centre	**Location**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Adults									
MCA	Alkmaar	21	1.7	21	100	0	0	0	0
Flevo Zkh	Almere	20	1.6	20	100	0	0	0	0
AMC-UvA	Amsterdam	106	8.5	103	97.2	3	2.8	0	0
MC Jan van Goyen	Amsterdam	42	3.4	42	100	0	0	1	2.4
OLVG	Amsterdam	158	12.7	157	99.4	1	0.6	12	7.6
Slotervaart Zkh	Amsterdam	21	1.7	21	100	0	0	1	4.8
St Lucas Andreas Zkh	Amsterdam	23	1.9	23	100	0	0	0	0
VUMC	Amsterdam	27	2.2	27	100	0	0	3	11.1
Rijnstate	Arnhem	52	4.2	51	98.1	1	1.9	0	0
Haga Zkh - Leyweg	Den Haag	27	2.2	27	100	0	0	0	0
MCH - Westeinde	Den Haag	65	5.2	65	100	0	0	1	1.5
Catharina Zkh	Eindhoven	45	3.6	45	100	0	0	0	0
MST	Enschede	25	2.0	23	92	2	8	0	0
UMCG	Groningen	38	3.1	38	100	0	0	0	0
Kennemer Gasthuis	Haarlem	32	2.6	32	100	0	0	1	3.1
MC Leeuwarden	Leeuwarden	18	1.5	18	100	0	0	0	0
LUMC	Leiden	26	2.1	26	100	0	0	1	3.8
MC Zuiderzee	Lelystad	29	2.3	29	100	0	0	0	0
AZM	Maastricht	55	4.4	55	100	0	0	0	0
UMC St Radboud	Nijmegen	36	2.9	36	100	0	0	4	11.1
Erasmus MC	Rotterdam	135	10.9	134	99.3	1	0.7	0	0
Maasstad Zkh	Rotterdam	55	4.4	51	92.7	4	7.3	0	0
St Elisabeth Zkh	Tilburg	63	5.1	63	100	0	0	0	0
UMCU	Utrecht	84	6.8	84	100	0	0	6	7.1
Admiraal De Ruyter Zkh	Vlissingen	8	0.6	8	100	0	0	0	0
Isala Klinieken - Sophia	Zwolle	30	2.4	28	93.3	2	6.7	2	6.7
Total adults		**1,241**		**1,227**	**98.9**	**14**	**1.1**	**32**	**2.6**
Children/adolescents									
Emma KZ, AMC-UvA	Amsterdam	4	21.1	4	100	0	0	0	0
Beatrix KK, UMCG	Groningen	5	26.3	5	100	0	0	0	0
Erasmus MC - Sophia	Rotterdam	3	15.8	3	100	0	0	0	0
Wilhelmina KZ, UMCU	Utrecht	7	36.8	7	100	0	0	0	0
Total children/adolescents		**19**		**19**	**100**	**0**	**0**	**0**	**0**
Curaçao									
SEHOS	Willemstad	66	100	66	100	0	0	0	0

[a] *Objection: Consent not given for collection of clinical data.*

Children

Of the 20,676 persons registered as of 31 December 2012, 361 (2%) were children or adolescents. Amongst that group, 171 (47%) were boys and 190 (53%) were girls. The median age at diagnosis was 2.9 years (IQR, 0.7-9.9) for boys and 4.1 (0.8-15.6) for girls. Vertical mother-to-child transmission was the route of infection in the majority of cases (68%), whereas in 20% of cases the route of infection was recorded as sexual transmission. In total, 35% of the infected children were born in the Netherlands and 54% in sub-Saharan Africa. The median duration of follow-up was 8.3 years for boys and 8.4 for girls (IQR, 3.7-11.7). The total follow-up for the group of children and adolescents is 3,024 person-years.

In 2012, 19 children and adolescents, including 7 boys and 12 girls, were newly registered. Five boys and 8 girls were infected by mother-to-child transmission; none of them were born in the Netherlands. For the other two boys and four girls, the route of HIV transmission is unknown.

Pregnant women

In 2012, the total number of registered pregnancies increased from 2,251 in 2011 to 2,458. These pregnancies occurred in a total of 1,487 HIV-infected women. In 54% of the cases, HIV was diagnosed before the start of the pregnancy and it was diagnosed in 46% during the pregnancy. The transmission route of HIV amongst the pregnant women was mostly through heterosexual contact (94%); in 1% transmission was through injecting drug use. The median age during the first pregnancy was 29 years (IQR, 25-34). In 35% of the women, combination antiretroviral therapy (cART) was started before the onset of the first pregnancy and in 51% during the pregnancy. In 27%, gestation lasted less than 16 weeks; in those who were still pregnant after the initial 16 weeks, the median gestation was 39 weeks (IQR, 37-40).

Antiretroviral treatment

In 2012, 85% of the total 20,676 HIV-patients were treated with cART, whereas 13% of the patients had not yet started treatment. No data was yet registered for 0.8% of patients and 0.9% were treated with non-cART regimens.

In total, more than 92% of the first-line cART regimens in 2012 consisted of tenofovir in combination with emtricitabine as the nucleotide/nucleoside HIV-1 reverse transcriptase inhibitor (NRTI) backbone. Efavirenz was the most widely used supplement to this backbone, followed by ritonavir-boosted darunavir and nevirapine. In 2012, efavirenz was used in 40%, darunavir/ritonavir in 20% and nevirapine in 18% of the first-line cART regimens. The most common initial cART regimens in 2012 were tenofovir + emtricitabine + efavirenz, followed by tenofovir + emtricitabine + darunavir/ritonavir and then tenofovir + emtricitabine + nevirapine *(Table 7)*.

Table 7: Most frequently used initial cART combination 2010–2012 (cART=combination antiretroviral therapy, TDF=tenofovir, FTC=emtricitabine, EFV=efavirenz, DRV/r=darunavir/ritonavir, NVP=nevirapine, ATV/r=atazanavir/ritonavir, AZT=zidovudine, 3TC=lamivudine, LOP/r=lopinavir/ritonavir, RAL=raltegravir, RPV=rilpivirine, ABC=abacavir)

	2010		2011		2012		Total	
	N	%	N	%	N	%	N	%
Total number of patients commencing first-line cART regimen	1,363	100	1,198	100	748	100	3,309	100
TDF+FTC+EFV	733	53.8	565	47.2	276	36.9	1,574	47.6
TDF+FTC+DRV/r	119	8.7	173	14.4	118	15.8	410	12.4
TDF+FTC+NVP	137	10.1	119	9.9	112	15.0	368	11.1
TDF+FTC+ATV/r	112	8.2	133	11.1	63	8.4	308	9.3
AZT+3TC+LOP/r	48	3.5	41	3.4	24	3.2	113	3.4
TDF+FTC+RAL	15	1.1	29	2.4	16	2.1	60	1.8
TDF+FTC+LOP/r	30	2.2	20	1.7	10	1.3	60	1.8
TDF+FTC+RPV	0	0	0	0	57	7.6	57	1.7
TDF+FTC+LOP/r+EFV	24	1.8	19	1.6	2	0.3	45	1.4
AZT+3TC+NVP	22	1.6	9	0.8	9	1.2	40	1.2
TDF+FTC+EFV+RAL	15	1.1	9	0.8	3	0.4	27	0.8
ABC+3TC+EFV	9	0.7	7	0.6	5	0.7	21	0.6
ABC+3TC+NVP	9	0.7	8	0.7	2	0.3	19	0.6
ABC+3TC+LOP/r	9	0.7	7	0.6	1	0.1	17	0.5
ABC+3TC+DRV/r	3	0.2	9	0.8	3	0.4	15	0.5
TDF+FTC+DRV/r+EFV	1	0.1	4	0.3	10	1.3	15	0.5
TDF+FTC+DRV/r+RAL	4	0.3	3	0.3	6	0.8	13	0.4
AZT+3TC+EFV	8	0.6	3	0.3	0	0	11	0.3
Other	65	4.7	40	3.3	31	4.1	136	4.1

AIDS and all-cause mortality

In 2012, 69 new cases of AIDS were recorded in patients treated with cART, corresponding to an incidence of 0.67 (95% confidence interval [CI] 0.52-0.85) per 100 person-years. This number is likely to somewhat increase due to the processing of short-term data backlogs. In 2010, there were 122 AIDS cases and the incidence was 1.07 (95% CI, 0.89-1.28) per 100 person-years.

In 2012, there were 119 deaths in patients treated with cART. The incidence was 1.07 (95% CI 0.88-1.28) per 100 person-years which is comparable with previous years.

HIV drug resistance

In 2012, data on the results of genotyping of the HIV reverse transcriptase and protease gene was obtained from four virological laboratories involved in monitoring resistance. A cumulative total of 11,505 sequences have been collected thus far; 459 of those were collected in 2012 *(Table 8)*.

Table 8: Number of HIV-1 reverse transcriptase and protease gene sequences generated per virological laboratory and registered with SHM as of 31 December 2012.

	Number of sequences obtained		
Laboratory	**Before 2012**	**In 2012**	**Total**
AMC-UvA, Amsterdam	4,369	225	4,594
UMCU, Utrecht	[a]3,585	[a]0	3,585
LUMC, Leiden	1,376	133	1,509
Erasmus MC, Rotterdam	701	68	769
VUMC, Amsterdam	445	33	478
Slotervaart Zkh, Amsterdam	179	0	179
CLB, Amsterdam	391	0	391
Total	**11,046**	**459**	**11,505**

[a] *Numbers not available at time of printing.*

Since 2003, complete resistance to at least one antiretroviral agent has been found in a gene sequence in 143 (3%) of 4,754 patients within a year of their diagnosis. Among them were 22 patients with resistance to protease inhibitors, 29 patients with resistance to lamivudine and emtricitabine, 36 patients with resistance to other nucleoside reverse transcriptase inhibitors and 104 patients with resistance to non-nucleoside reverse transcriptase inhibitors. In 2012, sequences were available for 253 patients within one year of diagnosis, and four of them were completely resistant to at least one agent.

HBV and HCV co-infections

Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can cause liver cirrhosis, liver fibrosis and hepatocellular carcinoma. In combination with HIV, the course of such diseases is probably accelerated. Therefore, HBV and HCV are also monitored in the HIV-infected population over time. In 2012, a chronic co-infection with HCV was found in 1,503 patients (8.0%) of patients with HIV, 1,463 (7.3%) were co-infected with HBV and 117 (1.1%) were co-infected with both HBV and HCV. Of the patients with HBV co-infection, hepatic cirrhosis developed in 109 patients (7.0%) and hepatocellular carcinoma was found in 14 patients (1.0%). In patients with chronic HCV co-infection, these totals were 157 patients (10.4%, hepatic cirrhosis) and 11 patients (0.7%, hepatocellular carcinoma).

Quality of care

In relation to the Visible Care programme (Zichtbare Zorg, ZiZo), run by the Health Care Inspectorate as commissioned by the Ministry of Health, Welfare and Sport, SHM continues to support HIV treatment centres by delivering quality indicators.

In addition to the activities for ZiZo, in 2012 SHM continued to develop its Quality of Care programme in collaboration with the Academic Medical Centre (AMC) of the University of Amsterdam, the Onze Lieve Vrouw Gasthuis in Amsterdam and the Leids Universitair Medisch Centrum in Leiden. In 2012, the program received a grant from the Aids Fonds and in April 2012 research was started under the direction of Suzanne Geerlings (AMC). The aim of this study is to investigate the determinants (patient, medical professional and hospital-related) that lead to a higher quality of care.

Furthermore, in 2012 the Harmonization of Quality in Healthcare (HKZ, Harmonisatie Kwaliteitsbeoordeling in de Zorgsector) launched the certification process for HIV treatment centres. During this process, standards for HIV treatment and regulations for testing will be developed. Draft regulations are being developed by the HKZ in collaboration with a group of field experts including members of the Dutch Association of HIV-Treating Physicians (NVHB), the Dutch Nurses and Carers Association HIV Nursing Consultants (V&VN verpleegkundig consulenten HIV/AIDS) and SHM. Existing documents that were developed in the field, such as the NVHB guidelines for the treatment of HIV, were used to guide the process.

Sample collection and storage

Since the start of the AIDS Therapy Evaluation in the Netherlands (ATHENA) project in 1996, an estimated total of 392,345 plasma samples from patients in follow-up have been stored in microbiological laboratories at the HIV treatment centres or in laboratories associated with the 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.

Registration of HIV-infected individuals in Curaçao

The registration and monitoring of HIV-infected persons being followed in the St. Elisabeth Hospital in Willemstad, Curaçao, continued during the past year. In total, 828 patients (812 adults and 16 children) were registered; 66 of those were added in 2012. Results from the monitoring in Curaçao were presented in the Monitoring Report 2012.

Entry into care and treatment outcomes[1]

Entry into care

Of all patients in clinical care more than one third were 50 years of age or older. In recent years, approximately 1100 new HIV infections have been diagnosed annually, and 700 to 750 of those have been in men who have sex with men (MSM). The increasing trend in the number of diagnoses amongst MSM, which has been observed since the turn of the millennium, appears to have come to an end. Indeed, amongst MSM between the ages of 35 and 44 years, the number of diagnoses is in a steady decline. On the other hand, the number of diagnoses is still increasing amongst young adult MSM and amongst MSM 55 years of age or older. There is a decreasing trend in diagnoses in the group of patients infected via heterosexual contact, which is mainly due to a reduction in immigration from HIV-endemic regions.

Over a period of years, testing for HIV has become more common, as exemplified by an increase in CD4 cell counts in patients at the time of diagnosis and by a greater proportion of patients diagnosed with a recent infection. Nonetheless, in recent years, 38% of MSM and approximately 60% of heterosexual men and women at the time of entry into care have had CD4 counts below 350 cells/mm^3, i.e. below the threshold for starting treatment according to any guideline. In addition, as a result of the increased age of women currently in follow-up, pregnancy rates have been lower compared to earlier calendar years. This is apparent in HIV-infected women from different geographic areas.

Despite all these positive developments (including more testing, earlier diagnosis and earlier start of treatment), the number of HIV diagnoses amongst MSM and heterosexuals is still not in a convincingly sufficient decline. To fully curb the epidemic, testing and treatment need to be scaled up, whilst reductions in sexual risk behaviour are expected to have a much greater impact on the number of new infections.

Treatment outcomes

HIV-infected adults

Response to cART

CD4 counts at the time of cART initiation have increased since 2007, reaching a median of 320 cells/mm^3 in 2012. CD4 cell counts at the start of cART were lower amongst men from sub-Saharan Africa and amongst women. Normal CD4 cell counts may be reached after 8 years of continuous HIV suppression, providing that patients start cART before CD4 cell counts fall below 350 CD4 cells/mm^3. For patients to start cART on time, HIV testing rates still need to be improved, especially in women and sub-Saharan African men. Suppression of plasma viral loads to below 50 HIV-RNA copies/ml is important, since high-level viraemia, as well as longer periods of low-level viraemia, are associated with smaller increases in CD4 cell counts and higher probability of treatment failure and development of resistance.

1 This section of the Annual Report is based on the "Monitoring Report 2012 – Human Immunodeficiency Virus (HIV) Infection in the Netherlands" published by SHM on 1 December, 2012.

Currently, almost half of the patients remain on their initial cART regimen for 3 years. Toxicity associated with the drugs used in the combination is still the main reason for changing the regimen, although the incidence of toxicity-driven changes has halved since the introduction of cART in 1996. The treatment-limiting adverse events most frequently recorded have shifted from lipodystrophy, rash or renal insufficiency in 2006 to nausea and diarrhoea at present, also indicating that the toxicity profile of antiretroviral drugs has improved.

The risk of virological failure has declined over time, but it is increased in patients who start cART with higher CD4 cell counts, who are younger and who are heterosexually infected from sub-Saharan Africa, the Caribbean and South America. Patients from sub-Saharan Africa, the Caribbean and South America continue to be at high risk of failure on second-line regimens. Measures to improve adherence in these patients are warranted. For instance, more individualised therapy strategies might help to reduce the risk of treatment-limiting toxicity.

Virological failure is less common in the treated HIV-infected population in 2012 than it was in 2000, thanks to an improved availability of treatment options. This appears to be true even for patients pre-treated with mono- or dual therapy who now have the same rates of virological failure as patients who were previously therapy-naive. Nevertheless, because of a growing volume of treated HIV-infected patients, approximately 250 patients per year still experience virological failure.

Resistance

Resistance patterns in sequences obtained at approximately the time of virological failure seem to indicate that in one quarter of previously therapy-naive patients the failure is the result of patients not taking their prescribed medication, which could be due to, for instance, drug-related toxicity. In patients with a sequence obtained whilst failing on a protease inhibitor (PI)-based or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen, overall levels of drug resistance are similar. However, PIs appear to be more resilient to the development of drug resistance than NNRTIs, most likely as a consequence of the larger number of mutations necessary to render the virus fully resistant. In patients on a PI-based regimen, resistance to lamivudine (3TC) and emtricitabine (FTC) is most commonly observed, whereas in patients on NNRTI-based regimens, resistance to NNRTIs and, to a lesser extent, to 3TC/FTC is most frequent.

Unfortunately, *Pol* sequences are available for only approximately 30% of the patients with virological failure. This makes it difficult to draw firm conclusions on the prevalence of resistance, since a thorough understanding of the conditions under which sequences are available is needed. Also, for some patients, virological failure may be caused by resistance to integrase or entry inhibitors, but sequences of the genes involved in this type of resistance are not yet routinely collected. To determine the true prevalence of resistance in treated patients with virological failure, SHM is investigating the possibility of developing a study

to obtain sequences and plasma drug concentrations at the time of failure in a randomly selected sample of patients.

Meanwhile, less than 2% of patients are infected with a virus that is already resistant to antiretroviral drugs prior to the start of treatment. This may indicate that HIV still does not need resistance to survive in a population with easy access to antiretroviral treatment. If most new infections are caused by HIV-infected individuals who are not yet treated and who may not even be aware of their infection, as shown to be the case amongst MSM in the Netherlands, resistance as a survival mechanism would be unnecessary.

Conversely, the low prevalence of transmitted drug resistance indicates that transmission from the pool of resistant patients is limited. If, however, a resistant virus would be transmitted from the pool of patients on PI-based regimens, this would most likely be a virus with resistance to lamivudine and emtricitabine caused by an M184V mutation in reverse transcriptase. As this mutation comes at great cost to viral fitness, such a virus would quickly revert back to wild-type and defy detection at the time of diagnosis. On the other hand, new infections with a resistant virus arising from patients on NNRTI-based regimens would mostly involve resistance to NNRTIs and, to a lesser extent, to 3TC/FTC. Mutations that play a role in resistance to NNRTIs also negatively impact the fitness of the virus, but at more moderate levels than M184V. In particular, K103N causes only a modest disadvantage in fitness compared to wild-type virus and may remain the dominant viral quasi-species in newly infected patients. As a result, viruses with K103N may have the potential to establish themselves as a subepidemic. Further studies and monitoring of resistance are necessary to confirm if this is already happening in the Netherlands.

AIDS- and non-AIDS-defining events

The incidence of AIDS-defining conditions has decreased dramatically in the last 15 years and is currently similar for men and women. After correction for changes in the ages of men and women with HIV-1 infection, the incidences of renal insufficiency, non-AIDS-defining malignancies and liver disease for both men and women, as well as cardiovascular disease and diabetes mellitus for women, have remained stable during the last 10 years. During this period, the incidence of diabetes mellitus and cardiovascular disease has decreased for men, whilst the incidence of osteoporosis has risen for men and women. The incidences of non-AIDS-defining malignancies and osteoporosis for women were not significantly different from those in an age-matched sample from the general population, but were higher for men. The incidence of diabetes mellitus was lower for men and higher for women than in age- and gender-matched samples from the general population. It was not possible to compare the incidences of cardiovascular disease, renal insufficiency, or liver disease with those in the general population.

Similar proportions of men and women who have lived with HIV-1 infection for at least 20 years have been diagnosed with diabetes mellitus, cardiovascular disease, renal insufficiency, or a non-AIDS-defining malignancy. However, more HIV-1-infected women

have been diagnosed with liver disease or osteoporosis. Further research is needed to determine whether the prevalence of these conditions is higher amongst persons with HIV-1 infection than amongst the general population and whether it is higher between groups of men and women who have lived with HIV infection for longer or shorter periods.

Mortality and loss to follow-up

The death rates for both men and women with HIV-1 who did not start combination antiretroviral therapy (cART) and died before becoming eligible for cART are similar and have fallen in the last 10 years. These rates are currently low and comparable to those amongst age- and gender-matched samples from the general population. This may suggest that HIV-1 infection is being increasingly diagnosed earlier in its course and patients are better able to start cART before HIV-associated immunodeficiency has progressed. The death rates for both men and women who have started cART and the proportion of those dying of AIDS have also fallen in the last 15 years. In the group of those who have started cART, the death rate is higher and the time to death shorter for men than women. In addition, the death rates for men and women are still higher than in gender- and age-matched samples from the general population. The rate of men and women becoming lost to follow-up before or after the start of cART is much higher for patients born outside the Netherlands than in this country. Even after correction for differences in age and the proportion born in the Netherlands, the women who started cART between 2007 and 2010 were more likely to become lost to follow-up than men.

HIV-infected children

Results of the monitoring of HIV-infected children in paediatric care have shown a substantial decline in mother-to-child transmission in the Netherlands since the introduction of national pregnancy screening. However, despite the high uptake of this pregnancy screening, a risk of mother-to-child transmission will always remain amongst women who become infected during the last two trimesters of their pregnancy. A limited number of vertical transmissions have occurred since the start of national screening. A second pregnancy screening in mothers at high risk of HIV infection may be beneficial in effectively increasing even further the prevention of mother-to-child transmission.

The majority of HIV-infected children in care are receiving cART. Exposure to cART will be lifelong, and therefore, virological failure and the development of drug-resistance during childhood may limit future treatment options. Although we observed a poorer early virological response in vertically infected children 0 to 1 year old at the time of cART initiation, the long-term virological response was comparable to that in older children. In addition, the early response to cART improved over calendar time, probably as a result of the introduction of improved regimens. For children with data on resistance testing, we found that 36% had high-level resistance mutations, and these were mainly children who experienced virological failure.

The survival of children benefits from this successful and improved response to cART.

We observed low mortality in HIV-infected children in care in the Netherlands. A large proportion of the children have survived into adulthood and are now in care at one of the adult HIV treatment centres. All patients who have survived into adulthood are currently alive.

All HIV-infected children will face lifelong treatment with cART. For these children, it will be a challenge to maintain lifelong adherence to cART and achieve lifelong virological suppression. Monitoring these HIV-infected children during their adolescence and into adulthood will be important in helping to take up that challenge.

HIV-infected individuals with hepatitis B and/or hepatitis C co-infection

Since 2000, the number of hepatitis C virus (HCV) diagnoses in the Dutch HIV-infected population has increased. Most of these infections have developed in homosexual men. The increase in HCV diagnoses coincides with an increase in acute HCV infections in the same population. The acute HCV infections in homosexual men are probably caused by sexual transmission. The number of hepatitis B virus (HBV) diagnoses has remained stable over time.

Patients co-infected with HIV and HBV or HCV are at increased risk for the development of chronic liver disease. In the HIV-infected population, we have observed a slow but steady increase in hepatocellular carcinoma (HCC) in patients with a chronic HBV or chronic HCV co-infection. Besides the impact of HBV and HCV on progression to liver disease, cART may have a protective effect on progression to liver fibrosis, but it may also enhance liver disease by drug-related hepatotoxicity. Screening for the presence of chronic HBV and chronic HCV infections and optimal management of HBV and HCV co-infection in individuals with HIV are needed to limit the impact of co-infection in the progression to severe chronic liver disease.

From July 2012 onwards, SHM data collection on hepatitis and liver-related disease has improved, and extended data on hepatitis and liver morbidity are now being collected on a regular basis.

A substantial decrease in HBV DNA levels has been observed. As a result of the long-term control of HBV replication, 16% of the patients with HIV treated for HBV co-infection showed hepatitis B surface antigen (HBsAg) clearance.

The current treatment of HCV with a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) has been found to clear HCV infection in 40% of the treated patients. The uptake of anti-HCV treatment in the HCV co-infected population was low, and a considerable number of patients dropped out early in the course of treatment.

As a result of the limited success rates of the current treatment with PEG-IFN and RBV, a large number of patients co-infected with HIV and HCV remain untreated. Two new, direct-acting PIs, boceprevir and telaprevir, have been recently licensed for the treatment of HCV in the Netherlands. When added to PEG-IFN and RBV, sustained rates of virological response have improved substantially in patients with a chronic hepatitis C genotype 1 infection. However, both telaprevir and boceprevir have pharmacologic interactions with antiretroviral therapy that need to be taken into account when treating HCV co-infection in HIV-infected patients.

Other direct-acting anti-HCV drugs are being developed and will result in new therapeutic strategies that may provide new options for patients co-infected with HIV and HCV and, in the long term, may reduce development of severe chronic liver disease. Monitoring of HIV-infected patients who are co-infected with HCV or HBV will become increasingly important. In addition to our extended data collection on liver-related morbidity and mortality, SHM will monitor responses to new therapeutic anti-HCV and anti-HBV strategies.

Summary and conclusions

Trends in the life expectancy and health of people living with HIV in the Netherlands have not changed substantially since our last report and overall remain favourable. More than 70% of patients receiving cART achieve viral suppression within 9 months after starting, and near normal CD4 cell counts are reached within 8 years, provided cART is started when CD4 counts are still above 350 cells/mm^3. However, a substantial proportion of patients are diagnosed late in the infection and thus start cART late. Moreover, 41% of those who are diagnosed in time start cART late. Regular testing for HIV and, when the results are positive, the timely start of antiretroviral therapy still need attention.

Discontinuation of treatment occurs in three quarters of the population undergoing treatment; drug toxicity is the main reason for switching medications, followed by regimen simplification. Over calendar time, a larger proportion of patients continue longer on their first-line regimen. Frequency of virological failure of cART is relatively low and largely the result of declining adherence. However, when virological failure occurs, the risk of repeated failure on second-line cART is high. In almost 40% of those with virological failure whilst on cART, high-level resistance to at least one of the antiretroviral drugs used in the regimen is found. Monitoring of the effect of cART in individual patients and on the population level remains crucial for our understanding of trends in the development of resistance.

"Test and treat", aimed at early detection of HIV infection so that cART may be started at an early stage, is an emerging strategy. Currently, cART is started at CD4 cell counts higher than ever before, indicating that HIV has been diagnosed earlier in the infection and testing strategies have improved amongst those at risk for HIV. An increasing proportion of the recently diagnosed population starts cART with CD4 cell counts above 350 cells/mm^3, and more than 20% of those with 500 CD4 cells/mm^3 or higher start cART within 6 months of diagnosis.

With “test and treat”, the number of people with HIV receiving cART will increase again. This rise in the number of those being treated early in infection and without symptoms of HIV may increase the risk of reduced adherence over the long term and of treatment interruption and subsequently the risk of high-level resistance. This underlines the need for resistance measurement when virological failure occurs.

From 2009 onwards, the number of new HIV diagnoses has remained stable at approximately 1100 new diagnoses per year, indicating that the increase in frequency of testing and in the proportion of patients diagnosed early in the course of their infection has not yet been sufficient to have resulted in a significant reduction in the number of new infections and, thus, the number of new diagnoses. More worrying is the increase over calendar time of both the number and the proportion of diagnoses amongst young MSM. Changing risk behaviour in this group should remain a major goal in prevention policies.

To a certain degree, large-scale cART may help contain HIV spread, especially when adherence is high and “test and treat” becomes the preferred approach. On the assumption that HIV adapts itself continuously to be optimally transmitted, early treatment may change the virus’s fitness towards a shorter window of transmission with higher transmission potential. We have reported that over calendar time HIV-RNA loads at setpoint (i.e., 9 to 24 months after the estimated date of infection) have increased. Such an increase could change the course of the HIV epidemic, and we are currently studying viral factors that could explain this change in viral load over time. Together with the uncertainties regarding adherence to lifelong cART and its toxicity and potential to increase resistance, these factors stress the need for continuing high quality standards of HIV care and monitoring of HIV.

Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV and AIDS started amongst men who have sex with men (MSM) in 1984 and amongst drug users (DU) in 1985. The original aims were to investigate the epidemiology, psychosocial determinants, natural history, and pathogenesis of HIV-1 infection and AIDS and to evaluate the effect of interventions in HIV-negative and HIV-positive men and women. In the past decade, the focus has broadened to include the epidemiology and natural history of blood-borne and sexually transmitted infections (BBI and STI) other than HIV. In recent years, this research has been extended through prospective testing for STI and human papillomavirus infection.

From the beginning, research in the ACS has taken a multidisciplinary approach. The collaborating institutes within the ACS framework are Sanquin Blood Supply Foundation, the Public Health Service of Amsterdam (GGD Amsterdam), the Academic Medical Centre of the University of Amsterdam the University Medical Centre Utrecht, the Jan van Goyen Medical Centre in Amsterdam and Stichting HIV Monitoring (SHM). The ACS infrastructure is financed through a contribution of the National Institute for Public Health and the

Environment (RIVM), and each ACS institute also contributes to the basic support and costs for coordination, management assistance and accountancy. The scientific studies have been predominantly undertaken by PhD students financed separately through external funding.

The ACS is unique because it allows for 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 GGD Amsterdam, whereas HIV-infected persons in the ACS are still followed mostly through HIV care and through monitoring by SHM. In addition to the provision of care, research material has been provided and stored for specific immunologic and virological studies. This includes material from persons who were initially HIV-negative and were infected during follow-up or are still at risk for HIV, as well as those who began participating in the ACS after being infected but subsequent to the study design in 1984-5.

As of 31 December 2012, 2,511 MSM and 1,661 injecting DU were included in the ACS. In total, the GGD Amsterdam was visited 51,503 times by MSM and 27,009 times by DU since the start of the ACS. In 2012, 575 MSM, of which 76 were HIV-positive, were followed at the GGD Amsterdam. Thirty-eight of them had been newly recruited since January 2012, and none of the participants had died. Of the 290 DU (31 HIV-positive) that were followed at the GGD Amsterdam in 2012, 3 had their first study visit in 2012. The HIV-incidence in 2012 was 0.7 per 100 person-years among MSM, and there were no HIV-seroconverters among DU.

Collaborations

National collaborations

AMC–UvA

SHM collaborates with the Academic Medical Center (AMC) of the University of Amsterdam (UvA) on various projects. The Co-morbidity and Aging with HIV (AGEhIV) cohort study, led by Prof. Peter Reiss (Department of Global Health, AMC, Amsterdam; Director SHM from 1 February 2013) and supported amongst others by a grant from Zon-Mw, aims to assess the incidence and prevalence of a broad range of co-morbidities and known risk factors for these co-morbidities in HIV-infected patients. SHM collaborates with the AMC in this study by providing the data collection infrastructure for monitoring the incidence and prevalence of a number of these co-morbidities. The results obtained from this research may be used to inform and adapt national and international guidelines for prevention and management of co-morbidities in aging HIV-infected individuals.

In a separate project, named Bridging the Epidemiology and Evolution of HIV in Europe (BEEHIVE), the AMC and SHM collaborate with Imperial College, London and the British Sanger Institute on a study of viral whole-genome association. The aim of this study is to identify viral virulence factors, which could ultimately shed new light on the pathogenesis of the HIV-1 virus.

In addition to these activities, SHM collaborates with the AMC, together with the Onze Lieve Vrouw Gasthuis (OLVG) and Leiden University Medical Center (LUMC) on the Quality of Care program. The program has received a grant from the Aids Fonds and in April 2012 research was started under the direction of Suzanne Geerlings (AMC). The aim of this research is to investigate the determinants (patient, medical professional and hospital-related) that lead to a higher quality of care.

CIb-RIVM

The Centre of Disease Control (CIb, headed by Prof. 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 and other sexually transmitted diseases such as hepatitis B (HBV) and hepatitis C (HCV), as well as infectious diseases such as tuberculosis. The CIb-RIVM and SHM agreed at the beginning of 2009 to exchange data collected through the SHM framework for purposes of surveillance carried out by the CIb-RIVM.

From 1 January 2012, SHM's funding from the Ministry of Health, Welfare and Sport has been routed via the RIVM.

GGD Amsterdam

SHM contributes to the MSM Observational Study of Acute Infection with Hepatitis C (MOSAIC) study coordinated by the Public Health Service of Amsterdam (GGD Amsterdam). The MOSAIC study is a cohort of men who have sex with men (MSM) with chronic HIV infection who have contracted an acute hepatitis C (HCV) infection. The aim of the study is to look at the contribution of this group to the transmission of HIV, to study the driving factors of the HCV epidemic and HIV's role in this, and to study the impact of acute HCV infection, reinfection and treatment on disease progression. SHM and GGD Amsterdam also work together on the Amsterdam Cohort Studies (ACS, reviewed earlier in the report), in collaboration with the AMC-UvA.

International collaborations

ACHI$_E$V$_{2E}$

A Collaboration on HIV-2 Infection (ACHI$_E$V$_{2E}$) was established in 2005 as a collaboration of 13 observational cohort studies or centres 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, a limited number of studies have specifically focused on HIV-2. In particular, the effect of antiretroviral treatment on outcome has not been studied in detail. ACHI$_E$V$_{2E}$ aims to fill this gap by studying different aspects of treated HIV-2 infection.

ART-CC

The Antiretroviral Therapy Cohort Collaboration (ART-CC), coordinated by Prof. Jonathan Sterne, University of Bristol, is a long-standing international collaboration that includes 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-naive patients. In 2012, Prof. Frank de Wolf and Prof. Peter Reiss (Department of Global Health, AMC, Amsterdam) were the principal investigators for this collaboration on behalf of SHM. ART-CC has financial support from the Medical Research Council of the United Kingdom.

An overview of papers published by ART-CC in 2012 can be found in the *Scientific Output 2012* section of this report.

CASCADE

Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) was established in 1997 as a collaboration between 25 cohorts from 15 European countries, Australia, Canada and Africa. CASCADE's main aim is to monitor newly infected individuals and those already enrolled in studies for the entire course of HIV infection. Through pooling data, issues can be addressed that cannot be reliably addressed from single studies alone. The Amsterdam Cohort Studies (ACS) participates in this study.

An overview of papers published by CASCADE in 2012 can be found in the *Scientific Output 2012* section of this report.

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 that the contributing cohorts cannot answer individually and that 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 populations from across Europe, including pregnant mothers, children and adults. Two Regional Coordinating Centres have been established, one in Bordeaux and one in Copenhagen.

SHM also participates in the Pursuing Later Treatment Options (PLATO II) scientific project of COHERE, which focuses on triple class virologic failure.

An overview of papers published by COHERE in 2012 can be found in the *Scientific Output 2012* section of this report.

D:A:D Study

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is a prospective multi-cohort study that focuses on the early recognition of adverse events, amongst which are cardiovascular problems and liver and renal diseases that could result from HIV

treatment with antiretroviral agents. Jens Lundgren (Department of Infectious Diseases, Hvidovre Hospital, Copenhagen) coordinates the study and Prof. Peter Reiss is the principal investigator for SHM/AIDS Therapy Evaluation in the Netherlands (ATHENA).

An overview of papers published by the D:A:D study in 2012 can be found in the *Scientific Output 2012* section of this report.

DIDE

The Department of Infectious Disease Epidemiology (DIDE) is part of the Faculty of Medicine, Imperial College in London. Prof. Sir Roy Anderson, Prof. Christophe Fraser and Dr. Tim Hallett coordinate the collaboration with SHM. DIDE and SHM have collaborated since 2002, focusing on 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 or in a particular population. Techniques that can provide answers to such questions include the study of the qualities of nonlinear differential equations, organisation and management of large-scale field studies into the 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 combination antiretroviral therapy (cART) on the epidemic in the Netherlands and in another model comparing quality of care in the Netherlands. Yet another study focuses on the variation in HIV-1 plasma RNA setpoints, the clustering around those setpoints that maximise the transmission potential and the changes in viral setpoint over time.

In a separate project, Bridging the Epidemiology and Evolution of HIV in Europe (BEEHIVE), the DIDE and SHM collaborate with the AMC-UvA and the Sanger Institute, UK, on a viral whole-genome association study. The aim of this study is to identify viral virulence factors, which could ultimately shed new light on the pathogenesis of the HIV-1 virus.

Frank de Wolf, Director of SHM until 1 December 2012, is Professor of Clinical Retrovirology at Imperial College, London.

ECDC

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

In 2012, SHM continued its leading role in a collaborative project to better estimate the prevalence of HIV in Europe and within individual European countries. This project was commissioned by the ECDC in Stockholm. SHM collaborates in this project together with Prof. Christophe Fraser from the Department of Infectious Disease Epidemiology (DIDE) at Imperial College in London, Prof. Andrew Phillips from the Department of Population Health at University College London, Dr. Daniela De Angelis from the Medical Research Council Biostatistics Unit at Cambridge University and Prof. Matthias Egger from the Institute of Social and Preventive Medicine at the University of Bern.

EuroCoord

The European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCoord) was established by several of the largest HIV cohorts and collaborations within Europe - CASCADE, COHERE, EuroSIDA and the Paediatric European Network for the Treatment of AIDS (PENTA). The overall aim of EuroCoord is to use the scientific strengths of each collaboration to ensure that the best, most competitive research is performed. It is a large, integrated network with a common virtual database, which currently contains data from more than 250,000 HIV-infected individuals from many different settings within and outside Europe. EuroCoord's multidisciplinary approach allows HIV research into a number of key areas aimed at improving the management and quality of life of HIV-infected individuals, whilst also exploring differences within sub-groups.

SHM also participates in the EuroCoord Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN) project. CHAIN is a large-scale integrated project designed to effectively and durably combat new and existing anti-HIV drug resistance in clinical settings, with a special emphasis on Eastern Europe and in heavily affected resource-poor regions in Africa. The objective is to compare virological, immunological and clinical outcome up to 12 to 16 months after initiation of cART, according to markers of virus variability (specific mutations, subtypes), with relevance to the drugs in the regimen.

EuroSIDA

The EuroSIDA study is a prospective, observational cohort study of more than 16,500 patients followed in 103 hospitals in 32 European countries plus Israel and Argentina. The main objective of the study is to assess the impact of antiretroviral drugs on the outcomes in the general population of HIV-infected patients in Europe. The primary hospital in the Netherlands providing information for this study is the AMC in Amsterdam. At the request of the principal investigator of EuroSIDA, Prof. Peter Reiss (AMC) collects data from the AMC in Amsterdam for EuroSIDA.

An overview of papers published by EuroSIDA in 2012 can be found in the *Scientific Output 2012* section of this report.

HIV-CAUSAL

The HIV Cohorts Analyzed Using Structural Approaches to Longitudinal Data (HIV-CAUSAL) collaboration is a multinational collaboration of prospective studies of HIV-infected individuals from six European countries and the United States. It aims to answer three main questions: when to start antiretroviral therapy, what antiretroviral regimen to use initially, and when to switch to another regimen. Because these questions are unlikely to be answered by a single study, there is a need for this type of collaborative project. The HIV-CAUSAL collaboration pools data collected for clinical purposes within health care systems that have few barriers to access in the populations they serve. The collaboration is designed to inform evidence-based guidelines and planning of clinical trials. In addition, it facilitates the understanding of and training in causal modelling across leading HIV observational research groups in the United States and Europe.

HIV in Europe

HIV in Europe is a pan-European initiative begun in Brussels in 2007. It provides a European platform for exchange of information 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. It has put the issue of earlier diagnosis of HIV on the political agenda and involved the various constituencies. Also, it has been able to initiate specific projects to enhance optimal testing and care. Its overall objective is to ensure that HIV-positive patients enter care earlier in the course of their infection than they are currently and 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 United Kingdom, 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), exploring 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 individualised combination of drugs.

Dissemination

SHM actively disseminates data and information about its activities through a wide variety of communication channels with the aim of providing information to HIV-treated individuals and their physicians, researchers, other health-care professionals, the media and other interested parties.

SHM Website and eNewsletters

In 2011, SHM introduced a new website and distributed the first eNewsletters that link directly through to the website, where they are archived. During 2012, SHM continued to develop the website and sent out four more eNewsletters on topics as diverse as hepatitis, online reporting, quality of care and the Netherlands Conference on HIV Pathogenesis, Prevention and Treatment (NCHIV) conference.

During 2012, the Patient Data and Quality Control unit also introduced two new online reports: Patient Reports, which replace the hospital-specific data sets known as 'site-sets', and the Centre Specific Report, which gives an overview of developments and trends per HIV treatment centre. Both of these password-protected online reports are accessible via the SHM website. Further information related to the reports is available under *Data Collection, Database and Data Quality Management* in this report.

Patient meeting

In June 2012, SHM organised a meeting with patients, "De mens achter de cijfers" (*translation: the person behind the numbers*), with the Dutch HIV Association (HVN) and Poz & Proud. Held at the Rode Hoed in Amsterdam, the event promoted face-to-face discussions between persons with HIV and researchers. Presentations were also given by the HVN, Poz & Proud and SHM. Researchers and HIV-treating physicians from a range of hospitals, together with researchers, data monitors and data collectors from SHM, participated in the event. The feedback from the event was positive with attendees appreciating the relaxed, open atmosphere and the freedom to ask questions from both sides of the table. Many people felt that the afternoon was very worthwhile and should be repeated in the future.

"Monitoring Report 2012 – HIV Infection in the Netherlands"

In addition to the Annual Report, SHM publishes a yearly Monitoring Report around the time of World AIDS Day on 1 December. The Monitoring Report presents major developments in the HIV epidemic in the Netherlands and effects of treatment on the course of the HIV infection and epidemic, with data extending back to 1996.

The Monitoring Report 2012 continued to reflect the encouraging trends that were reported in 2011. Some of the positive developments included evidence of more HIV testing, earlier diagnosis and earlier start of treatment. However, the number of new HIV diagnoses is still not in a convincingly significant decline, either amongst MSM or amongst heterosexuals, indicating that testing and treatment need to be scaled up to fully curb the epidemic. Reductions in risk behaviour should also remain a major goal in prevention policies. Furthermore, uncertainties regarding increases in viral loads at setpoint, adherence to

lifelong cART, and cART's toxicity and potential to increase resistance stress the need for continuing high-quality standards of HIV care and monitoring of HIV.

Scientific output

In addition to its yearly Monitoring Report, SHM's contribution to the knowledge and understanding of the HIV/AIDS epidemic and of the effect of antiretroviral treatment on the course of HIV infection is visible in its scientific output. In 2012, SHM cohort data was included in 40 publications in peer-reviewed international scientific journals and 57 presentations at international peer-reviewed conferences, workshops and meetings. A full overview of scientific output is included in a later section of this report.

NCHIV 2012

SHM's work was also presented at the 2012 Netherlands Conference on HIV Pathogenesis, Prevention and Treatment (NCHIV). This annual conference is organised by SHM in collaboration with the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (CIb-RIVM), the Aids Fonds, the Amsterdam Institute for Global Health and Development (AIGHD), the Academic Medical Centre of the University of Amsterdam (Department of Global Health) and the Dutch Association of HIV-Treating Physicians (NVHB).

Financial Report

Income

Income for regular HIV monitoring activities in the Netherlands

Stichting HIV Monitoring (SHM) is recognized by the Dutch Ministry of Health, Welfare and Sport with a structural subsidy (Health Subsidy Regulation, Chapter II Institute Grants).

The Governing Board established the 2012 budget on 17 October 2011 at € 3,058,324. On 16 January 2012, the National Institute for Public Health and Environment (RIVM), Ministry of Health, Welfare and Support approved the budget. The indexation for the wage-sensitive part of the budget was set on 18 September 2012 at 2.95% (€ 70,058). The material costs were not indexed. The total budget for 2012 allocated by the Ministry of Health, Welfare and Support for the monitoring of HIV in the Netherlands available to SHM was fixed at € 3,128,383.

As of 1 June 2011, 15,856 of the registered patients (15,671 adults and 185 children) were in active follow-up, which represents an increase of 8.48% compared to the number of patients in 2010. However, the actual increase was higher than the recorded increase, largely due to backlogs in the processing of data by some HIV treatment centres as per 1 June 2011.

Income through projects related to HIV monitoring

The participation of SHM in international studies is of great significance for both individual patients and the quality of care. Individual registration and monitoring programs, such as SHM, are often unable to provide a timely answer to certain questions regarding co-morbidity and changes in mortality trends in large-scale HIV treatment which need much larger sample sizes. To efficiently provide insights into some of the long-term effects of HIV treatment, it is necessary to bring large data sets together from different countries through collaboration, thereby answering questions which cannot be addressed by any cohort individually. During 2012, income of € 1,074,679 was obtained from the following four projects related to HIV monitoring resulting in a reduction of € 106,448 (-9.01%) in 2012, in comparison to income earned through projects in 2011.

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, Welfare and Sport subsidised the ACS via the RIVM to the amount of € 500,000 in 2012. The Academic Medical Centre (AMC) of the University of Amsterdam (UvA) and the Municipal Health Service (GGD) of Amsterdam remain available to carry out projects within the ACS. The University 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, which amounted to € 59,139 in 2012. The conditions

for this contribution are still under negotiation between the UMCU and 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, Welfare and Sport 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). The ACS is not invoiced by SHM for administration costs.

2. **Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D):**
D:A:D is a large international collaboration between observational cohorts, with the aim of identifying early severe side effects of treatment with antiretrovirals. SHM is a major partner in D:A:D and collects data on adverse effects of treatment and non-AIDS comorbidities in registered patients for the benefit of the D:A:D study. The validity of major study endpoints is subject to 100% quality control (in contrast to the usual 10%) through source-data verification. The participation of SHM in this study contributes significantly to a higher quality of data for the general monitoring of HIV in the Netherlands. In 2012, SHM contributed for the 13th time to the data merge and received € 428,446 in compensation for this from the Hvidovre University in Copenhagen, the organisation that leads the D:A:D study. In 2011, more data was added retrospectively than in 2012, leading to a reduced fee of € 74,895.

In 2012, SHM was granted an additional € 55,110 from the Hvidovre University Hospital for the registration of specific D:A:D-related events through 31 December 2011. This grant was paid in full by SHM to the HIV treatment centres that report D:A:D-related events. Costs were deducted by SHM in 2012 for the amount of time incurred due to an increase in the number of forms to be completed by SHM data quality staff.

3. **EuroSIDA:**
SHM participates in EuroSIDA, a European clinical cohort study, within the context of the epidemic in Europe. The AMC participates on behalf of the Netherlands in EuroSIDA with SHM delivering the AMC's patient data to the cohort. EuroSIDA carries out comparative studies on the effect of the treatment of HIV among the participating European countries, including a focus on new EU member states. For SHM's participation in the EuroSIDA study group in 2012, it received compensation of € 1,963.

4. **Other projects:**
In 2012, SHM received a contribution of € 30,021 for its participation in the following international projects: Control of the HIV epidemic in the Netherlands (Aids Fonds), Pursuing Later Treatment Option II (PLATO II) for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) and A Collaboration on HIV-2 Infection ($ACHI_EV_{2E}$).

Expenditure

Three different types of expenses for 2012 are outlined below:

1 **Compensation to the HIV treatment centres for anonymous patient data collection and data entry:**

In 2012, in accordance with the approved budget, SHM compensated the HIV treatment centres in the amount of € 71.35 per patient. This compensation is based on the number of patients who were in active follow-up on 31 December 2011 and on the adoption of the budget set by the Ministry of Health, Welfare and Sport. HIV treatment centres with a backlog in data collection received less of the budgeted amount than centres without a backlog. In 2012, by request of 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.

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.

HIV treatment centres also received € 12.81 per patient to cover the costs for sampling and storing patients' plasma. In total, SHM paid the HIV treatment centres € 755,741 in 2012.

2 **Personnel costs:**

Personnel costs were once again the largest expenditure for SHM during 2012. As per 31 December 2012, SHM had a total of 42 employees (30 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.

In the framework of the SHM's European collaborations, it has carried out activities for Eurocoord, PLATO II and the European Centre for Disease Prevention and Control (ECDC). The fees amounting to € 73,039 for these studies are used primarily as compensation for salary costs of HIV monitoring. No personnel have been appointed specifically for these studies.

3 **Material costs:**

In addition to staff expenses in 2012, there were structural costs made in relation to database licenses, maintenance of the national HIV monitoring database, data management and operations.

Earmarked reserves

In 2005, money was set aside for the Host Genetics project. The project was developed in collaboration with the AMC. In 2012, € 2,400 was released due to a beneficial result.

In 2007, € 2,000 was set 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 Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (CIb-RIVM), the Aids Fonds, the Amsterdam Institute for Global Health and Development (AIGHD), the AMC-UvA (Department of Global Health) and the Dutch Association of HIV-Treating Physicians (NVHB). The earmarked sum of € 2,000 was maintained in 2012.

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

Operating result

The operating result of SHM's activities shows that the total expenditure for 2012 remains within SHM's income.

The bulk of the addition to SHM's general reserves, amounting to € 552,012, is from projects related to HIV monitoring.

The operating result for HIV monitoring in the Netherlands shows a negative result of € 10,457. This is mainly caused by the significantly higher and increasing number of patients actually monitored compared to the number used in calculating the budget for HIV monitoring. The salary costs associated with this monitoring increased in 2012 by 8.4%, whereas the allocated budget increased to a lesser extent (6.4%).

The interest income for 2012 amounted to € 16,095. SHM conducts a very conservative but accurate treasury policy, yielding a positive financial result of € 5,638 for HIV monitoring in the Netherlands.

Reserves

The total financial reserves of SHM (including continuity reserve, general reserve and earmarked reserves for investment) amounted to € 2,776,323 on 31 December 2012.

1. **Continuity reserve:**
   The continuity reserves amounted to € 36,114 on 31 December 2012. This amount includes the 2012 result of HIV monitoring in the Netherlands. The continuity reserve is thus about 1% of the 2012 budget.

2. **General reserve:**
   From 2002 through 2007, SHM built a general reserve of € 382,205. The continuity reserve and the general reserve are held to guarantee the continuity of the organisation for a certain period of time.

3. **Earmarked reserves for investment, HIV-related projects:**
   As per 31 December 2012, a total of € 2,358,001 has been reserved for HIV-related projects. SHM has committed to participating in these projects for three years.

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 2012 equalled approximately 13% of the budget.

Balance sheet as of 31 December

Assets	31-Dec-12 (€)	31-Dec-11 (€)
Fixed assets		
Tangible fixed assets	30,616	6,026
Total fixed assets	**30,616**	**6,026**
Current assets		
Debtors and accrued assets	764,570	254,901
Cash	3,329,058	3,156,523
Total current assets	**4,093,628**	**3,411,424**
Total assets	**4,124,244**	**3,417,450**

Liabilities	31-Dec-12 (€)	31-Dec-11 (€)
Capital and reserves		
Continuity reserve	36,114	30,476
General reserve	382,205	382,205
Earmarked reserves for investment	2,358,001	1,805,989
Total reserves	**2,776,320**	**2,218,670**
Short-term liabilities		
Short-term liabilities and accrued expenses	1,347,924	1,198,780
Total short-term liabilities	**1,347,924**	**1,198,780**
Total liabilities	**4,124,244**	**3,417,450**

Profit and Loss Account

	2012 (€)	2011 (€)
Profits		
Total subsidies	4,203,062	4,121,497
Other profits	73,089	90,177
Total net revenue	**4,276,151**	**4,211,674**
Operating costs		
Personnel expenses	2,064,944	1,870,860
Depreciation on tangible fixed assets	7,165	6,677
Other operating costs	383,565	425,945
Compensation HIV treatment centres	755,741	754,838
Compensation D:A:D-events	0	110,477
Compensation Amsterdam Cohort Studies	559,139	557,505
Compensation NCHIV	8,056	14,706
Compensation COBRA project	533	0
Total operating costs	**3,779,143**	**3,741,008**
Operating result	497,008	470,666
Financial income and expenses	60,642	42,398
Total operating result	**557,650**	**513,064**
Year Result	**557,650**	**513,064**

Scientific Output 2012

In 2012, 5 requests by researchers in the Netherlands were made for access to Stichting HIV Monitoring's (SHM's) cohort data. During the year, 40 papers including SHM cohort data were published in peer-reviewed journals. Furthermore, 57 abstracts were accepted for presentation at 14 meetings and conferences (32 oral and 25 poster presentations). An overview of research projects, publications and presentations can be found on our website, *www.hiv-monitoring.nl*.

Completed Research Projects

I05511 Influence of HIV-1 co-receptor usage on the clinical course of infection under HAART and the outcome of antiretroviral therapy

Gijsbers EF, van Sighem A, Harskamp AM, Welkers MRA, de Wolf F, Brinkman K, Prins JM, Schuitemaker H, van 't Wout AB, Kootstra NA.

Date of approval: October 2005

In 2012, the data analysis was completed and a prepared manuscript was submitted to AIDS journal in January 2013. The abstract of the submitted manuscript follows.

Objective: The emergence of CXCR4-using HIV variants (X4-HIV) is associated with accelerated disease progression. However, the effect of X4-HIV variants on the treatment response remains unclear. Here we determined whether the presence of X4-HIV variants influenced the time to undetectable viral load and $CD4^+$ T cell reconstitution after initiation of cART.

Methods: The presence or absence of X4-HIV variants was determined by MT-2 assay prior to cART initiation for 732 patients. Viral load and $CD4^+$ T cell counts were analyzed at baseline and every three to six months during a three-year follow-up to assess the effect of cART. Kaplan-Meier and Cox proportional hazard analyses were performed to compare time to viral suppression.

Results: A delayed time to undetectable viral load after initiation of cART was independently associated with high viral load (>4.5 $\log^{10}$ copies/ml) and the presence of X4-HIV variants at baseline. The absolute $CD4^+$ T cell counts were significantly lower in patients harboring X4-HIV variants at all time points during follow-up, but no differences were observed in the increase in $CD4^+$ T cell numbers upon treatment initiation.

Conclusion: The presence of X4-HIV variants prior to start of cART is an independent predictor of delayed viral suppression. $CD4^+$ T cell counts in patients with X4-HIV were significantly lower during follow-up, whereas the increase in $CD4^+$ T cells after start of cART was comparable. Therefore, patients carrying X4-HIV may benefit from earlier treatment initiation in order to obtain a faster reconstitution of the $CD4^+$ T cell population to normal levels.

Manuscript title: The presence of CXCR4-using HIV variants prior to start of combination antiretroviral therapy is an independent predictor of delayed viral suppression.
Authors: Gijsbers EF, van Sighem A, Harskamp AM, Welkers MRA, de Wolf F, Brinkman K, Prins JM, Schuitemaker H, van 't Wout AB and Kootstra NA.

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

Reiss P, Schuitemaker H, van 't Wout A, Gras L, van Manen D.

Date of approval: April 2009

In 2012, the data analysis was completed and the results written up. The resulting manuscript is currently under review with Clinical Infectious Diseases. The abstract of the submitted manuscript follows.

Background: HIV-positive persons have increased rates of coronary artery disease (CAD). The relative contribution of genetic background, HIV-related factors, antiretroviral medications, and traditional risk factors for CAD has not been fully evaluated in the setting of HIV infection.

Methods: In the general population, 23 common single nucleotide polymorphisms (SNPs) were shown to be associated with CAD through genome-wide association analysis. Using the metabochip, we genotyped 1875 HIV-positive, white individuals enrolled in 24 HIV observational studies, including 571 participants with a first CAD event during the 9-year study period and 1304 controls matched by gender and cohort.

Results: A genetic risk score built from 23 CAD-associated SNPs contributed significantly to CAD (P=2.9x10-4). In the final, multivariable model, participants with an unfavourable genetic background (top genetic score quartile) had a CAD odds ratio (OR) of 1.47 (95% confidence interval, 1.05-2.04). This effect was similar to hypertension (OR=1.36; 95% CI, 1.06-1.73), hypercholesterolemia (OR=1.51; 95% CI, 1.16-1.96), diabetes (OR=1.66; 95% CI, 1.10-2.49), >1 year lopinavir exposure (OR=1.36; 95% CI, 1.06-1.73) and current abacavir treatment (OR=1.56; 95% CI, 1.17-2.07). The effect of the genetic risk score was additive to the effect of non-genetic CAD risk factors and did not change after adjustment for family history.

Conclusions: In the setting of HIV infection, the effect of an unfavourable genetic background was similar to traditional CAD risk factors and certain adverse antiretroviral exposures. Genetic testing may provide prognostic information complementary to family history of CAD.

Manuscript title: Contribution of genetic background, traditional risk factors and HIV-related factors to coronary artery disease events in HIV-positive persons.

Authors: Rotger M, Glass TR, Junier T, Lundgren J, Neaton JD, Poloni ES, van 't Wout AB, Lubomirov R, Colombo S, Martinez R, Rauch A, Günthard HF, Neuhaus J, Wentworth D, van Manen D, Gras LA, Schuitemaker H, Albini L, Torti C, Jacobson LP, Li X, Kingsley LA, Carli F, Guaraldi G, Ford ES, Sereti I, Hadigan C, Martinez E, Arnedo-Valero M, Egaña-Gorroño L, Gatell JM, Law M; Bendall C, Petoumenos K, Rockstroh J, Wasmuth JC, Kabamba K, Delforge M, De Wit S, Berger F, Mauss S, de Paz Sierra M, Losso M, Belloso WH, Leyes M, Campins A, Mondi A, De Luca A, Bernardino I, Barriuso-Iglesias M, Torrecilla-Rodriguez A, Gonzalez-Garcia J, Arribas JR, Fanti I, Gel S, Puig J, Negredo E, Gutierrez M, Domingo P, Fischer J, Fätkenheuer G, Alonso-Villaverde C, Macken A, Woo J, McGinty T, Mallon P, Mangili A, Skinner S, Wanke CA, Reiss P, Weber R, Bucher HC, Fellay J, Telenti A, Tarr PE, for the MAGNIFICENT Consortium, INSIGHT and the Swiss HIV Cohort Study.

I08196 The effect of Radiotherapy on CD4 cell count in HIV-infected patients

Sankatsing SUC, Gras LA, Verbon A, Prins JM.

JAIDS 2013; Accepted for publication:
Title: Prolonged decrease of $CD4^+$ T lymphocytes in HIV-1 infected patients after radiotherapy for a solid tumor
Authors: Sankatsing SUC, Hillebregt MMJ, Gras L, Brinkman K, van der Ende M, de Wolf F, Stalpers LJA, Prins JM.

I10270 Predictors for Pneumocystis jirovecii pneumonia (PJP) during the HAART era in the ATHENA cohort

van Lelyveld S, Hoepelman A, Gras L, Hermans S.

Publication in 2012:
Lower incidence of *Pneumocystis jirovecii* pneumonia among Africans in the Netherlands; host or environmental factors?
Schoffelen AF, van Lelyveld SF, Barth RE, Gras L, de Wolf F, Netea MG, Hoepelman AI.
AIDS. 2012 Dec 31. [Epub ahead of print]

I11010 The effect of Maraviroc on serum markers

van der Pas V.

Date of approval: 9 February 2011

Poster presentation at NCHIV 2012:
Title: Maraviroc Intensification in Patients with Suboptimal Immunological Recovery Despite Virological Suppressive HAART: a 48-week, Placebo-controlled Trial
Authors: van Lelyveld S, Drylewicz J, Veel E, Otto S, Richter C, Soetekouw R, Prins J, Brinkman K, Mulder J, Kroon F, Tesselaar K, Hoepelman A.

Background: Several trials have investigated whether HAART intensification with the CCR5-antagonist maraviroc (MVC) in patients with suboptimal immunological recovery increases $CD4^+$ T-cell counts and reduces immune activation. Reported results are conflicting, and in most trials follow-up has been limited to 24 weeks. We performed a 48-week, double-blind, placebo-controlled trial to determine the effects of MVC on $CD4^+$ T-cell reconstitution and performed an in-depth analysis of T-cell proliferation and death in a subgroup of patients.

Methods: HIV-infected patients were randomized to add MVC (42 patients) or placebo (43 patients) to their existing HAART regimen for 48 weeks. The major inclusion criteria were $CD4^+$ T cell count <350 cells/μL while at least two years on HAART or $CD4^+$ T cell count <200 cells/μL while at least one year on HAART and viral suppression for at least the previous 6 months. The primary outcome was the change in $CD4^+$ T-cell count. Additional analyses of markers associated with immune activation were performed. To study to what extent T-cell life spans were normalized by MVC treatment, we performed an in vivo labeling study with deuterated water in a subgroup of patients.

Results: Baseline parameters did not differ between the placebo and maraviroc arms. At week 48, the median $CD4^+$ T-cell count had increased significantly by +23 cells/μL in the placebo arm versus +30 in the MVC arm, which was not significantly different between the arms. T-cell activation levels as measured by CD38/HLA-DR or Ki67-expression tended to stay constant or decrease slightly, but there was no significant difference between the arms. The concentration of soluble CD14 at week 48 had significantly decreased by -1.5 and -0.5 μg/L in the placebo

and MVC arms, respectively. The observed increases in $CD4^+$ T-cell counts consisted of approximately equal amounts of memory and naive $CD4^+$ T cells. Despite the relatively small increases in $CD4^+$ T-cell counts in the MVC group, and the above similarities between the placebo and MVC group, deuterated water labeling revealed one large difference between placebo and MVC patients: the average lifespan of naive and memory $CD4^+$ and $CD8^+$ T cells in MVC patients became almost as long as in healthy individuals, while in the placebo group it remained as short as in untreated HIV-infected patients.

Conclusions: After 48 weeks of treatment there was no significant difference in $CD4^+$ T-cell reconstitution between the MVC and placebo arm. Nevertheless, MVC intensification treatment significantly increased the average lifespan of naive and memory $CD4^+$ and $CD8^+$ T cells, suggesting that MVC treatment may have a beneficial effect in the long run.

I11072 Virologic response after initiation of triple-class antiretroviral therapy in patients with primary and chronic HIV infection

Grijsen M.

Date of approval: 6 July 2011

Publication in 2012:
Similar virologic response after initiation of triple-class antiretroviral therapy in primary and chronic HIV infection.
Grijsen ML, Holman R, Wit FW, Gras L, Lowe SH, Brinkman K, de Wolf F, Prins JM.
AIDS. 2012 Sep 24;26(15):1974-7.

I10053 Capture-recapture analysis to estimate the prevalence of HIV and tuberculosis in patients with tuberculosis and HIV-infection, respectively

Van Leth F.

Date of approval: 13 January 2011

Presentation at 16th IWHOD, March 2012, Athens:
Authors: van Leth F, Wit F, Kalisvaart N, Hillebregt M, Verbon A, Verhagen M, Sprenger H, Kiers A, Cobelens F.

TB-HIV co-infected patients have poorer TB-treatment outcomes and a higher risk of death irrespective of ART use. Proper information on the prevalence of TB-HIV co-infection guides the development and implementation of preventive and therapeutic strategies in a programmatic setting.

Current estimates are derived from the Netherlands Tuberculosis Register (NTR) that includes all notified TB patients in the country. Notification systems are potentially biased due to possible selective underreporting.

We assessed the prevalence of TB-HIV co-infection in the Netherlands using a capture-recapture analysis (CR) with data from the NTR and the national surveillance registers on HIV (Stichting HIV Monitoring Foundation [SHM]) between 2000 and 2010. CR analysis estimates the number of patients missing in both of the independent registers that record similar information.

We selected patients from the NTR with TB and a positive HIV result. Patients from the SHM were selected when they had an HIV

diagnosis during TB treatment or before. This restriction was needed to make sure that TB-HIV patients in the SHM could show up in the NTR. TB treatment is the responsibility of the Municipal Health Services (MHSs), while the mandate for HIV treatment lies with the designated HIV treatment centers.

The findings are reported in the following table:

Year	Prevalence NTR (%)	Prevalence CR (%)	Relative under-reporting (%)
2000	4.64	7.52	21.6
2001	4.62	8.95	21.7
2002	4.72	7.52	21.2
2003	5.59	9.44	17.9
2004	4.24	7.17	23.6
2005	5.67	8.23	17.6
2006	4.38	8.05	22.8
2007	3.61	5.82	27.7
2008	3.89	5.94	25.7
2009	3.73	6.00	26.8
2010	4.28	6.45	23.4

There is a marked underreporting of TB-HIV co-infection in the NTR when compared to information available on the NTR, which is an average 24.5% in the study period. The magnitude of underreporting is relatively stable in the study period.

It is unlikely that all underreported patients are being withheld care. It is more likely that poor administration of the co-infection occurs in both databases leading to a relatively large number of 'additional' patients. The emphasis on close collaboration and proper data exchange between the TB and the HIV programmes, as advocated for many developing countries, should also resonate for the Netherlands.

Ongoing Research Projects

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

Reiss P.

The study continues to successfully follow close to 50,000 patients, and has accrued more than 300,000 person-years of follow-up. The ATHENA cohort continues to rank amongst the top contributors to D:A:D. Recently, the decision was reached by the D:A:D Oversight Committee to continue funding for the period 2013-2016, however, at a reduced budget, which will also have implications for the amount of funding SHM will receive. Details will need to be negotiated, but the expectation has to be that SHM funding through D:A:D will be reduced.

The study continues to successfully meet the aim to delineate the relationship between the use of antiretroviral drug classes as well as individual drugs one the one hand, and the risk of myocardial infarction, and the more recently added additional comorbidity endpoints of end-stage renal disease, chronic severe liver disease and non-AIDS malignancies. The results from the study are regularly presented at major international conferences, to be published, and also continue to inform and influence changes in international HIV treatment guidelines.

An overview of publications during 2012 are included later in this section of the report. For additional information, please see *www.cphiv.dk*.

I08115 Proposal for collaboration and data exchange between HMF and RIVM for national HIV/AIDS surveillance and

data transfer to ECDC in the context of EU obligations for reporting on HIV/AIDS

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

Publication in 2012:
Sexually transmitted infections, including HIV, in the Netherlands in 2011.
Trienekens SCM, Koedijk FDH, van den Broek IVF, Vriend HJ, Op de Coul ELM, van Veen MG, van Sighem AI, Stirbu-Wagner I, van der Sande MAB.
RIVM Rapport 201051001

I08044 Primo SHM R5x4 HAART

Grijsen M, Welkers M.

Publications in 2012:
Temporary antiretroviral treatment during primary HIV-1 infection has a positive impact on health-related quality of life: data from the Primo-SHM cohort study.
The Primo-SHM study group.
HIV Med. 2012 Apr 25. doi: 10.1111/j.1468-1293.2012.01020.x. [Epub ahead of print]

No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial.
Grijsen ML, Steingrover R, Wit FW, Jurriaans S, Verbon A, Brinkman K, van der Ende ME, Soetekouw R, de Wolf F, Lange JM, Schuitemaker H, Prins JM; Primo-SHM Study Group.
PLoS Med. 2012;9(3):e1001196. Epub 2012 Mar 27.

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

Bastiaans D, Burger D, van Luin M, Hartwig N.

Date of approval: 1 November 2010

Ongoing

I10021 Uncovering Determinants of eco-evo Pathogen Dynamica with ABCmu

Ratman O.

Date of approval: 28 May 2011

Ongoing

I07252 Study on sexual behaviour among HIV infected homosexual men

Stolte S, Krol A, Prins M, van Eeden A, Groot M, Visser GB, Heijman T.

Date of approval: December 2007

Ongoing

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

Burger D, Blonk M, Wit F, Smit C, Van Luin M, Gelinck L, Sprenger H, Koopmans P.

Date of approval: 11 May 2010

We selected all HIV-infected patients from 5 hospitals (LUMC, Erasmus MC, St Elisabeth, Rijnstate and UMC St Radboud) with a treatment switch from efavirenz (EFV) to nevirapine (NVP) between 2001 until censoring time in February 2012. This cohort was subsequently categorized in two groups based on NVP dosage at start. The Dose-Escalation (DE) group consisted of patients who started with a reduced dose of 200 mg of NVP, which was subsequently increased to a full dose of 400 mg of NVP. The Full Dose (FD) group consisted of patients who started NVP treatment immediately with a full dose of 400 mg per

day. Because data on reduced starting dosages of NVP were not consequently recorded in the database, all starting dosages with FD NVP were verified in the medical record of the patient or the medical history from the community pharmacy. These data are collected in collaboration with the medical physicians and physician assistants in the 5 participating hospitals. Patients with an unknown NVP starting dose were excluded from statistical analysis. In total, 201 HIV-infected patients were included, 20.9% (n=42) started with DE and 79.1% (n=159) with FD NVP. Statistical analysis is ongoing. The project is expected to be completed in 2013 followed by a publication.

I05513 HIV Resistance Response Database Initiative (RDI)

Revell A, Larder B, Wang D, Coe D.

Date of approval: October 2005

The main activities of the RDI during 2012 using ATHENA data were as follows:

Study 1: The development of new computational models that include the newest drugs and replacement of existing models to power HIV-TRePS

Background: The RDI was set up to collect HIV treatment outcome data and use these data to train computational models that predict virological response to antiretroviral therapy, as a free online treatment support tool. The RDI developed its HIV Treatment Response Prediction System (HIV-TRePS) in 2009. The computational models that were used to power the 'with genotype' version during 2011 comprised a committee of five that used a limited number of treatment history variables and a second committee of five that used individual treatment history variables among the input variable sets. The individual treatment history models demonstrated a marginal superiority and in this study a new committee of 10 models was developed using an expanded training data set and individual treatment history models to power the HIV-TRePS system during 2012.

Methods: 7,638 TCEs were identified that met all the criteria for the study. A committee of 10 random forest (RF) models was trained to predict the probability of virological response (follow-up viral load <50 copies HIV RNA/ml) from the following input variables: baseline viral load, baseline CD4 count, baseline genotype (62 mutations), drugs in the new regimen (18 drugs covered), 18 individual treatment history variables; and time to follow-up. The models were developed using a 10x cross validation scheme. Their accuracy was assessed during cross validation, in terms of the area under the receiver-operator characteristic curve (AUC).

Results: The RF models achieved an average AUC of 0.84 (range 0.79-0.88). Overall accuracy was 78% (77-80%), sensitivity 67% (62-72%) and specificity 83% (80-87%).

Discussion: The models achieved a consistent, high level of accuracy in predicting treatment response, which was superior to that achieved by the previous models. It was encouraging that a high level of specificity was achieved, minimising the potential for false positive predictions of virological response. The models were tested and then up-loaded into the HIV-TRePS system in May 2012.

Study 2: The development of new computational models to predict virological

response to treatment without the use of genotype for use in resource-limited settings

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 resource-limited settings. Previous RDI studies established that models developed with large data sets, including treatment history information but not genotype data, can predict virological response with only a modest loss of accuracy compared with models trained with genotypes. During 2011 we developed 'no-genotype' models and tested these models with independent test sets from resource-limited settings. The models performed very well with data from 'familiar' western settings where the training data was obtained (AUC of 0.76-0.77). Performance with cases from unfamiliar resource-limited settings was diminished but still comparable to using genotyping with rules-based interpretation as a predictor of outcome (AUC of 0.58-0.65). In 2012 we set out to develop new models using larger training data sets and including some data from resource-limited settings in an attempt to improve this accuracy.

Methods: We identified approximately 40,000 treatment change episodes that fit the criteria for the modelling. Two committees of 10 random forest models are to be trained to predict the probability of response to ART (<50 copies HIV RNA/ml) using the following data: viral load and CD4 count prior to change, treatment history (18 individual variables), drugs in the new regimen, time to follow-up and follow-up viral load. The first committee will be developed to predict responses for patients with undetectable viral load at baseline and the second for those with virological failure. The models will be assessed during cross-validation with the main outcome measure being the area under the ROC curve (AUC). This work continues in 2013.

Annual importation of data from existing contributors: In order to ensure that the RDI database and the data used to train its computational models reflect current clinical practice and include data generated during treatment including the latest drugs, it is essential that the RDI receives new data from its partners on a regular basis. A global programme of data updates and importation was undertaken during 2012. This involved:

1. Liaison with contributing centres
2. Analysis, sorting, ordering and editing prior to importation into the RDI database to ensure compatibility and quality control
3. Importation of the data
4. Identification and resolution of any data inconsistencies
5. Extraction of treatment change episodes (TCEs) for use in subsequent computational modelling
6. Development of basic database statistics

Publications in 2012:

Modelling Treatment Response Could Reduce Virological Failure in Different Patient Populations.
Revell AD, Wang D, d'Ettorre GD, Wolf FDE, Gazzard B, Ceccarelli G, Gatell J, Perez-Elias MJ, Vullo V, Montaner JS, Lane HC, Larder BA on behalf of the RDI study group.
J AIDS Clinic Res 2012; S6:1-6.

The use of computational models to predict response to HIV therapy for clinical cases in

Romania.
Revell AD, Ene L, Duiculescu D, Wang D, Youle M, Pozniak A, Montaner J, Larder BA.
GERMS. 2012;2(1):6-11.

Posters and presentations in 2012:
The development of new computational models for the HIV-TRePS online treatment selection tool.
Revell AD, Wang D, De Wolf F, Gatell J, Ruiz L, Nelson M, Perez-Elias MJ, Lane HC, Montaner JSS, Larder BA on behalf of the RDI study group.
Poster Presentation at: 10th European Meeting on HIV & Hepatitis Treatment Strategies and Antiviral Drug Resistance; Barcelona, Spain, 28-30 March 2012

Models that accurately predict response to HIV therapy are generalisable to unfamiliar datasets and settings.
Revell AD, Wang, Streinu-Cercel A, Ene L, De Wolf F, Gazzard B, Gatell J, Ruiz L, Perez-Elias MJ, Montaner JSG, Lane HC, Larder BA on behalf of the global RDI study group.
Poster Presentation at: International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies; Sitges, Spain, 5-9 June 2012

The development of new computational models for the HIV-TRePS online treatment selection tool.
Revell AD, Wang D, De Wolf F, Gatell J, Ruiz L, Pozniak A, Perez-Elias MJ, Lane HC, Montaner JSG, Larder BA on behalf of the global RDI study group.
Poster Presentation at: XIX International AIDS Conference; Washington DC, USA, 22-27 July 2012

Predicting response to antiretroviral therapy without a genotype: a clinical tool for resource-limited settings.
Larder BA, Revell AD, Wang D, Hamers R, Tempelman H, Barth R, Wensing AMJ, Morrow C, Wood R, De Wolf F, Gazzard B, Lane HC, Montaner JM on behalf of the global RDI study group.
Poster presentation at: XIX International AIDS Conference; Washington DC, USA, 22-27 July 2012

Computational models that predict response to HIV therapy can reduce virological failure and therapy costs in resource-limited settings
Revell AD, Wang D, Alvarez-Uria G, Streinu-Cercel A, Ene L, Wensing AMJ, Hamers RL, Morrow C, Wood R, Tempelman H, De Wolf F, Nelson M, Montaner JS, Lane HC, Larder BA on behalf of the RDI study group.
Late breaker oral O234 presentation at: 11th International Congress on Drug Therapy in HIV Infection; Glasgow, Scotland, 11-15 November 2012

I12045 A HIV-1 genome wide association study to identify viral determinants of HIV-1 plasma concentration

De Wolf F, Cornelissen M, Fraser C, Kellam P, Gall A, Gras L, Van Sighem A, Boucher C, Schuurman R, Claas E.

Date of approval: 16 September 2012

The first phase of the collaboration Bridging the Epidemiology and Evolution of HIV in Europe (BEEHIVE) included the testing of the logistics of stored serum/plasma samples of patients included in the study of virulence factors associated with severity of infection and the efficacy of HIV RNA isolation procedures needed for whole genome sequencing. Procedures have been developed to support these logistics and most

productive and efficient isolation procedures have been selected. Together with the very first sequencing results, the study entered a second phase by the end of 2012, in that the executive operation of locating samples in the associated virology laboratories in the Netherlands has been started and the process of transporting of selected samples to the laboratory for Experimental Virology at the AMC in Amsterdam is in place.

First results are expected in the first quarter of 2013.

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

Rachel O.

Date of approval: 2005

Ongoing

I12001 The rate of mother-to-child-transmission of hepatitis C virus in HIV-1 infected mothers

Van de Ende M, Snijdewind I, Smit C, Schutten M, Hartwig N, de Wolf F.

Date of approval: 9 February 2012

Ongoing

Publications 2012

Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission.
Herbeck JT, Müller V, Maust BS, Ledergerber B, Torti C, Di Giambenedetto S, Gras L, Günthard HF, Jacobson LP, Mullins JI, Gottlieb GS.
AIDS. 2012 Jan 14;26(2):193-205.

Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort.
Van Lelyveld SFL, Gras L, Kesselring A, Zhang S, de Wolf F, Wensing AMJ, Hoepelman AIM, on behalf of the ATHENA national observational cohort study.
AIDS. 2012, Feb 20;26(4):465-474.

Single Nucleotide Polymorphism in Gene Encoding Transcription Factor Prep1 Is Associated with HIV-1-Associated Dementia.
Bol SM, Booiman T, van Manen D, Bunnik EM, van Sighem AI, Sieberer M, Boeser-Nunnink B, de Wolf F, Schuitemaker H, Portegies P, Kootstra N A, van 't Wout AB.
PLoS One. 2012;7(2):e30990. Epub 2012 Feb 7.

Developing a multidisciplinary network for clinical research on HIV infection: the EuroCoord experience.
De Wolf F, Sabin C, Kirk O, Thorne C, Chene C, Porter K.
Clin. Invest. (2012) 2(3), 255–264.

No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial.
Grijsen ML, Steingrover R, Wit FW, Jurriaans S, Verbon A, Brinkman K, van der Ende ME, Soetekouw R, de Wolf F, Lange JM, Schuitemaker H, Prins JM; Primo-SHM Study Group.
PLoS Med. 2012;9(3):e1001196. doi: 10.1371/journal.pmed.1001196. Epub 2012 Mar 27.

HCV coinfection, an important risk factor for hepatotoxicity in pregnant women starting antiretroviral therapy.
Snijdewind IJ, Smit C, Godfried MH, Nellen JF, de Wolf F, Boer K, van der Ende ME.

J Infect. 2012 Apr;64(4):409-16. doi: 10.1016/j.jinf.2011.12.012. Epub 2011 Dec 23.

The clinical interpretation of viral blips in HIV patients receiving antiviral treatment: are we ready to infer poor adherence?
Chun-Hai Fung I, Gambhir M, van Sighem A, de Wolf F, Garnett GP.
J Acquir Immune Defic Syndr. 2012 May 1;60(1):5-11. Epub 2012 Jan 19.

Episodes of HIV Viremia and the Risk of Non-AIDS Diseases in Patients on Suppressive Antiretroviral Therapy
Zhang S, van Sighem A, Kesselring A, Gras L, Smit C, Prins JM, Kauffmann R, Richter C, de Wolf F, Reiss P.
J Acquir Immune Defic Syndr. 2012 Jul 1;60(3):265-272. Epub 2012 Apr 23.

Could better tolerated HIV drug regimens improve patient outcome in the Netherlands?
Smit M, Smit C, Cremin I, Garnett GP, Hallett T, de Wolf F.
AIDS. 2012 Sep 24;26(15):1953-9.

Similar virologic response after initiation of triple-class antiretroviral therapy in primary and chronic HIV infection
Grijsen ML, Holman R, Wit FW, Gras L, Lowe SH, Brinkman K, de Wolf F, Prins JM.
AIDS. 2012 Sep 24;26(15):1974-1977.

Resurgence of HIV Infection among Men Who Have Sex with Men in Switzerland: Mathematical Modelling Study
Van Sighem A, Vidondo B, Glass TR, Bucher HC, Vernazza P, Gebhardt M, de Wolf F, Derendinger S, Jeannin A, Bezemer D, Fraser C, Low N; the Swiss HIV Cohort Study.
PLoS One. 2012;7(9):e44819. Epub 2012 Sep 14.

Increasing sexual risk behaviour amongst Dutch MSM: mathematical models versus prospective cohort data
Van Sighem A, Jansen I, Bezemer D, De Wolf F, Prins M, Stolte I, Fraser C.
AIDS. 2012 Sep 10;26(14):1840-3.

No advantage of quadruple or triple-class antiretroviral therapy as initial treatment in patients with very high viraemia
Grijsen ML, Holman R, Gras L, Wit FW, Hoepelman AI, van den Berk GE, de Wolf F, Prins JM; the ATHENA National Observational Cohort Study.
Antivir Ther. 2012;17(8):1609-1613. doi: 10.3851/IMP2321. Epub 2012 Aug 22.

Temporary antiretroviral treatment during primary HIV-1 infection has a positive impact on health-related quality of life: data from the Primo-SHM cohort study
Grijsen M, Koster G, van Vonderen M, van Kasteren M, Kootstra G, Steingrover R, de Wolf F, Prins J, Nieuwkerk P; Primo-SHM study group.
HIV Med. 2012 Nov;13(10):630-5. doi:10.1111/j.1468-1293.2012.01020.x. Epub 2012 Apr 25.

The VACS Index: An internationally generalizable risk index for mortality after one year of antiretroviral therapy
Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, Nattermann J, Lampe FC, Bucher HC, Sterling TR, Crane HM, Kitahata MM, May M, Sterne JA.
AIDS. 2012 Nov 6. [Epub ahead of print]

Lower incidence of Pneumocystis jirovecii pneumonia among Africans in the Netherlands; host or environmental factors?
Schoffelen AF, van Lelyveld SF, Barth RE, Gras L, de Wolf F, Netea MG, Hoepelman AI.
AIDS. 2012 Dec 31. [Epub ahead of print]

Publications related to collaborations:

ART-CC

The effect of injecting drug use history on disease progression and death among HIV-positive individuals initiating combination antiretroviral therapy: collaborative cohort analysis

Murray M, Hogg RS, Lima VD, May MT, Moore DM, Abgrall S, Bruyand M, D'Arminio Monforte A, Tural C, Gill MJ, Harris RJ, Reiss P, Justice A, Kirk O, Saag M, Smith CJ, Weber R, Rockstroh J, Khaykin P, Sterne J; for the Antiretroviral Therapy Cohort Collaboration (ART-CC).

HIV Med. 2012 Feb;13(2):89-97. Epub 2011 Aug 7.

Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and N. America 2002-2009

Abgrall S; The Antiretroviral Therapy Cohort Collaboration (ART-CC).

AIDS. 2012 Nov 28. [Epub ahead of print]

Heterogeneity in outcomes of treated HIV-positive patients in Europe and North America: relation with patient and cohort characteristics

May MT, Hogg RS, Justice AC, Shepherd BE, Costagliola D, Ledergerber B, Thiébaut R, Gill MJ, Kirk O, van Sighem A, Saag MS, Navarro G, Sobrino-Vegas P, Lampe F, Ingle S, Guest JL, Crane HM, D'Arminio Monforte A, Vehreschild JJ, Sterne JA; Antiretroviral Therapy Cohort Collaboration (ART-CC).

Int J Epidemiol. 2012 Dec;41(6):1807-20. doi: 10.1093/ije/dys164. Epub 2012 Nov 12.

CASCADE

Uptake of combination antiretroviral therapy and HIV disease progression according to geographical origin in seroconverters in Europe, Canada, and Australia

Jarrin I, Pantazis N, Gill MJ, Geskus R, Perez-Hoyos S, Meyer L, Prins M, Touloumi G, Johnson A, Hamouda O, de Olalla PG, Porter K, del Amo J; CASCADE Collaboration in EuroCoord.

Clin Infect Dis. 2012 Jan 1;54(1):111-8. Epub 2011 Nov 21.

Risk of tuberculosis following HIV seroconversion in high-income countries

Lodi S, Del Amo J, d'Arminio Monforte A, Abgrall S, Sabin C, Morrison C, Furrer H, Muga R, Porter K, Girardi E; on behalf of the CASCADE collaboration in EuroCoord.

Thorax. 2012 Oct 31. [Epub ahead of print]

Rate of CD4 decline and HIV-RNA change following HIV seroconversion in men who have sex with men: a comparison between the Beijing PRIMO and CASCADE cohorts

Huang X, Lodi S, Fox Z, Li W, Phillips A, Porter K, Lutsar I, Kelleher A, Li N, Xu X, Wu H, Johnson AM; on behalf of the Beijing PRIMO cohort study and the CASCADE Collaboration in EuroCoord.

J Acquir Immune Defic Syndr. 2012 Dec 6. [Epub ahead of print]

Effect Of HCV Infection On Cause-Specific Mortality Following HIV Seroconversion Before And After 1997

Van der Helm J, Geskus R, Sabin C, Meyer L, Del Amo J, Chêne G, Dorrucci M, Muga R, Porter K, Prins M; CASCADE collaboration in EuroCoord.

Gastroenterology. 2012 Dec 21. doi:pii: S0016-5085(12)01852-5. 10.1053/j.gastro.2012.12.026. [Epub ahead of print]

COHERE

Trends in virological and clinical outcomes

in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study
The Pursuing Later Treatment Option II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Group.
Lancet Infect Dis. 2012 Feb;12(2):119-27. Epub 2011 Oct 9.

Calendar time trends in the incidence and prevalence of triple-class virologic failure in antiretroviral drug experienced people with HIV in Europe
Nakagawa F for the PLATO II group for COHERE in EuroCoord.
JAIDS. 2012 Mar 1;59(3):294-9.

CD4 Cell Count and the Risk of AIDS or Death in HIV-Infected Adults on Combination Antiretroviral Therapy with a Suppressed Viral Load: A Longitudinal Cohort Study from COHERE
The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.
PLoS Med. 2012 Mar;9(3):e1001194. Epub 2012 Mar 20.

All-cause mortality in treated HIV-infected adults with CD4 ≥ 500/mm³ compared with the general population: evidence from a large European observational cohort collaboration
Lewden C, Bouteloup V, De Wit S, Sabin C, Mocroft A, Wasmuth JC, van Sighem A, Kirk O, Obel N, Panos G, Ghosn J, Dabis F, Mary-Krause M, Leport C, Perez-Hoyos S, Sobrino-Vegas P, Stephan C, Castagna A, Antinori A, d'Arminio Monforte A, Torti C, Mussini C, Isern V, Calmy A, Teira R, Egger M, Grarup J, Chêne G voor The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.
Int J Epidemiol. 2012 Apr;41(2):433-445.

Effect of hepatitis C treatment on CD4 cell counts and the risk of death in HIV-hepatitis C co-infected patients; COHERE collaboration
The HCV working group of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.
Antivir Ther. 2012 Jul 24. doi: 10.3851/IMP2263. [Epub ahead of print]

D:A:D Study

Evaluation of HIV Protease Inhibitor Use and the Risk of Sudden Death or Nonhemorrhagic Stroke
Worm SW, Kamara DA, Reiss P, Fontas E, De Wit S, El-Sadr W, D'Arminio Monforte A, Law M, Phillips A, Ryom L, Dabis NF, Weber R, Sabin C, Lundgren JD; on behalf of the D:A:D Study Group.
J Infect Dis. 2012 Feb;205(4):535-9. Epub 2012 Jan 5.

Predicting the short-term risk of diabetes in HIV-positive patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study
Petoumenos K, Worm SW, Fontas E, Weber R, De Wit S, Bruyand M, Reiss P, El-Sadr W, d'Arminio Monforte A, Friis-Møller N, Lundgren JD, Law MG on behalf of the D:A:D Study Group.
Journal of the International AIDS Society 2012, 15:17426.

Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of HBV or HCV co-infection: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

Kovari H, Sabin CA, Ledergerber B, Ryom L, Worm SW, Smith C, Phillips A, Reiss P, Fontas E, Petoumenos K, De Wit S, Morlat P, Lundgren JD, Weber R.
Clin Infect Dis. 2012 Dec 21. [Epub ahead of print]

EuroSIDA

The rate of accumulation of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in patients kept on a virologically failing regimen containing an NNRTI(*)
Cozzi-Lepri A, Paredes R, Phillips A, Clotet B, Kjaer J, Von Wyl V, Kronborg G, Castagna A, Bogner J, Lundgren J; for EuroSIDA in EuroCoord.
HIV Med. 2012 Jan;13(1):62-72. Epub 2011 Aug 17.

Long-term exposure to combination antiretroviral therapy and risk of death from specific causes: no evidence for any previously unidentified increased risk due to antiretroviral therapy
Kowalska JD, Reekie J, Mocroft A, Reiss P, Ledergerber B, Gatell J, d'Arminio Monforte A, Phillips A, Lundgren JD, Kirk O; EuroSIDA study group.
AIDS. 2012 Jan 28;26(3):315-23.

The clinical benefits of antiretroviral therapy in severely immunocompromised HIV-1-infected patients with and without complete viral suppression
Mocroft A, Bannister WP, Kirk O, Kowalska JD, Reiss P, d'Arminio Monforte A, Gatell J, Fisher M, Trocha H, Rakhmanova A, Lundgren JD; the EuroSIDA Study in EuroCoord.
Antivir Ther. 2012;17(7):1291-1300.

Regional differences in AIDS and non-AIDS related mortality in HIV-positive individuals across Europe and Argentina: The EuroSIDA Study
Reekie J, Kowalska JD, Karpov I, Rockstroh J, Karlsson A, Rakhmanova A, Horban A, Kirk O, Lundgren JD, Mocroft A; for EuroSIDA in EuroCoord.
PLoS One. 2012;7(7):e41673.

HCV viremia increases the incidence of chronic kidney disease in HIV-infected patients
Peters L, Grint D, Lundgren JD, Rockstroh JK, Soriano V, Reiss P, Grzeszczuk A, Sambatakou H, Mocroft A, Kirk O; for EuroSIDA in EuroCoord.
AIDS. 2012 Sep 24;26(15):1917-1926.

Benchmarking HIV health care: from individual patient care to health care evaluation. An example from the EuroSIDA study
Podlekareva D, Reekie J, Mocroft A, Losso M, Rakhmanova A, Bakowska E, Karpov IA, Lazarus J, Gatell J, Lundgren JD, Kirk O.
BMC Infect Dis. 2012 Sep 25;12(1):229.

Temporal changes and regional differences in treatment uptake of hepatitis C therapy in EuroSIDA
Grint D, Peters L, Vogel M, Beniowski M, Pradier C, Battegay M, Jevtovic D, Soriano V, Lundgren J, Rockstroh J, Kirk O, Mocroft A.
J Int AIDS Soc. 2012 Nov 11;15(6):18118. doi: 10.7448/IAS.15.6.18118.

HIV-CAUSAL

Impact of Antiretroviral Therapy on Tuberculosis Incidence Among HIV-Positive Patients in High-Income Countries
The HIV-CAUSAL Collaboration.
Clin Infect Dis. 2012 May;54(9):1364-72. Epub 2012 Mar 28.

The effect of efavirenz versus nevirapine-containing regimens on immunologic, virologic and clinical outcomes in a prospective

observational study
The HIV-CAUSAL Collaboration.
AIDS. 2012 Aug 24;26(13):1691-1705.

Other printed materials

Sexually transmitted infections, including HIV, in the Netherlands in 2011
Trienekens SCM, Koedijk FDH, van den Broek IVF, Vriend HJ, Op de Coul ELM, van Veen MG, van Sighem AI, Stirbu-Wagner I, van der Sande MAB.
RIVM Rapport 201051001.

Nederlandse vertegenwoordiging tijdens CROI 2012
Gras LA, van Sighem AI.
HIV Bulletin, nummer 2, 2012, Special CROI.

Presentations 2012

Oral presentations

Tenofovir/emtricitabine versus abacavir/lamivudine
Holman R, Gras L, Prins J, de Wolf F.
Winter meeting NVHB, Amsterdam, Netherlands, 13 January 2012.

HIV prevalence estimates
Van Sighem A.
Annual meeting STI and HIV in EU/EEA, Stockholm, Sweden, 15-17 February 2012.

Non-AIDS defining malignancies (NADM) and immunosuppression: The D:A:D study
Worm SW, Bower M, Reiss P, Grulich A, Fontas E, Bonnet F, Faetkenheuer G, Law M, Phillips A, Furrer HJ, El-Sadr W, Kirk O, Ryom L, Abrams D, D'Arminio Monforte A, De Wit S, Sabin C, Lundgren JD on behalf of the D:A:D study group.
19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 5-8 March 2012.

Estimating HIV prevalence in European countries
Van Sighem A.
HIV in Europe, Copenhagen, Denmark, 18-20 March 2012.

Higher rates of AIDS and death during the first year of therapy among those born outside Europe, the United States, and Canada: the importance of tuberculosis
Shepherd BE, Jenkins CA and Sterling on behalf of ART-CC.
16th International Workshop on HIV Observational Databases, Athens, Greece, 29-31 March 2012.

Effect of hepatitis C treatment on the risk of death in HIV/HCV co-infected patients; European Cohort Collaboration (COHERE) in EuroCoord
Smit C, on behalf of the HCV working group of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.
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16th International Workshop on HIV Observational Databases, Athens, Greece, 29-31 March 2012.

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16th International Workshop on HIV Observational Databases, Athens, Greece, 29-31 March 2012.

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Kesselring A, Wit F, Smit C, van der Valk M, Richter C, Reiss P and de Wolf F.
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Low CD4 in recently-infected individuals and the proportion experiencing rapid progression
Olson A on behalf of the CASCADE Collaboration in EuroCOORD.
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Impact of antiretroviral therapy (ART), viraemia and immunosuppression on lipid levels: the D:A:D Study
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6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.

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Smit C, van der Meer J, van der Ende M, Arends J, van der Valk M, Brinkman K, Schippers E, de Wolf F, Schutten M, Schinkel J, de Vries-Sluijs T, Hoepelman A, Richter C.
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Decreased incidence of Pneumocystis jirovecii pneumonia among sub-Saharan African patients in the Dutch ATHENA cohort; genetic susceptibility or environmental factors?
Schoffelen A, van Lelyveld S, Barth R, Gras L, de Wolf F, Netea M, Hoepelman A.
6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.

An overview of the Dutch pediatric vertically HIV-infected population in the era of cART
Cohen S, Smit C, Pajkrt D, for the Dutch Pediatric HIV Study Group (PHON).
6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.

Appendix 1: Composition of SHM

Governing Board SHM

Name	Position	Affiliation
Dr. F.P. Kroon	Chair	NVHB
Dr. J.S.A. Fennema	Secretary	GGD Nederland
Drs. A.J. Lamping	Treasurer	Zorgverzekeraars Nederland
Prof. R.A. Coutinho	Observer	RIVM (until 16 April 2012)
Drs. P.E. van der Meer	Member	NVZ
Dr. R.J.M. Hopstaken	Member	NFU
Mr. L.M.J. Elsenburg	Member	HIV Vereniging Nederland
Prof. K. Stronks	Member	AMC-UvA
Drs. M.I. Verstappen	Member	AGIS

Advisory Board SHM

Name	Affiliation
Prof. J.M.A. Lange (Chair)	AMC, Dept. of Global Health; AIGHD, Amsterdam
Prof. Sir R.M. Anderson	Imperial College, Faculty of Medicine, Dept. of Infectious Disease Epidemiology, London, UK
Prof. M. Egger	University of Bern, Switzerland / Bristol, UK
Dr. S.E. Geerlings	AMC, Dept. of Internal Medicine, Amsterdam
Prof. D.R. Kuritzkes	Brigham and Women's Hospital, Section of Retroviral Therapeutics, Boston, MA, USA
Mr. C. Rümke	HIV Vereniging Nederland, Amsterdam
Prof. J. Schuitemaker	AMC, Dept. of Internal Medicine, Amsterdam

Working Group SHM

Members

Name	Affiliation
Dr. M.E. van der Ende (chair)	Erasmus MC, Dept. of Internal Medicine, Rotterdam
Prof. C.A.B. Boucher	Erasmus MC, Dept. of Internal Medicine, Rotterdam
Dr. F.C.M. van Leth	KNCV Tuberculosefonds, The Hague
Dr. W.M.C. Mulder	HIV Vereniging Nederland, Amsterdam
Prof. P. Reiss	AMC, Dept. of Global Health, Amsterdam

Reviewers

Name	Affiliation
Dr. N.K.T. Back	AMC, Dept. of Human Retrovirology, Amsterdam
Prof. K. Brinkman	OLVG, Dept. of Internal Medicine, Amsterdam
Prof. D.M. Burger	UMC St Radboud, Dept. of Clinical Pharmacology, Nijmegen
Dr. E.C.J. Claas	LUMC, Clinical Virology Laboratory, Leiden
Prof. G.J.J. Doornum	Erasmus MC, Dept. of Virology, Rotterdam (Emeritus)

Name	Affiliation
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, Clinical Virology Laboratory, Amsterdam
Dr. J.R. Juttmann	St Elisabeth Ziekenhuis, Dept. of Internal Medicine, Tilburg (until September 2012)
Dr. P.P. Koopmans	UMC St Radboud, Dept. of Internal Medicine, Nijmegen
Prof. A.C.M. Kroes	LUMC, Clinical Virology Laboratory, Leiden
Prof. T.W. Kuijpers	AMC, Dept. of Paediatrics, Amsterdam
Dr. W.J.G. Melchers	UMC St Radboud, Dept of Medical Microbiology, Nijmegen
Prof. J.M. Prins	AMC, Dept. of Internal Medicine, Amsterdam
Prof. P.H.M. Savelkoul	AZM, Dept. of Internal Medicine, Maastricht
Dr. G. Schreij	AZM, Dept. of Internal Medicine, Maastricht
Dr. R. Schuurman	UMCU, Dept. of Virology, Utrecht
Dr. H.G. Sprenger	UMCG, Dept. of Internal Medicine, Groningen
Dr. A.M.J. Wensing	UMCU, Dept. of Virology, Utrecht

Hepatitis Working Group

Members

Name	Affiliation
Dr. C. Richter (chair)	Rijnstate, Dept. of Internal Medicine, Arnhem
Dr. C. Smit	Stichting HIV Monitoring, Amsterdam
Prof. K. Brinkman	OLVG, Dept. of Internal Medicine, Amsterdam
Prof. A.I.M. Hoepelman	UMCU, Dept. of Virology, Utrecht
Dr. J. Arends	UMCU, Dept. of Internal Medicine, Utrecht
Dr. M.E. van der Ende	Erasmus MC, Dept. of Internal Medicine, Rotterdam
Dr. T.E.M.S. de Vries-Sluys	Erasmus MC, Dept. of Internal Medicine, Rotterdam
Dr. M. van der Valk	AMC, Dept. of Internal Medicine, Amsterdam
Dr. J. van der Meer	AMC, Dept. of Internal Medicine, Amsterdam
Dr. J. Schinkel	AMC, Clinical Virology Laboratory, Amsterdam
Dr. E.F. Schippers	HagaZiekenhuis, Dept. of Internal Medicine, The Hague
Dr. M. Schutten	Erasmus MC, Dept. of Clinical Virology, Rotterdam

Personnel SHM

Position	Name
Director	Prof. F. de Wolf MD (until 1 December 2012)
Research – Senior	Dr. D.O. Bezemer
	Drs. L.A.J. Gras
	Dr. R. Holman
	Dr. A.M. Kesselring (from 23 November 2012)
	Dr. A.I. van Sighem
	Dr. Ir. C. Smit
Research – PhD students	E. Engelhard MD (external, from 1 April 2012)
	R. van den Hengel MSc (from 1 September 2012)
	Drs. A.M. Kesselring (until 22 November 2012)

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 E.J. Claessen C.W.A.J. Deurloo-van Wanrooij L.G.M. de Groot-Berndsen R. Henstra-Regtop (from 17 April 2012) A.S. de Jong, MSc (from 23 July 2012) C.R.E. Lodewijk R. Meijering, MSc (from 19 July 2012) 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 (until 1 August 2012) R.A. van den Boogaard MSc Drs. S. Grivell Drs. M.M.J. Hillebregt Drs. A.M. Jansen V. Kimmel MSc Dr. Ir. A. de Lang (from 1 September 2012) Drs. B. Lascaris Drs. B. Slieker (until 1 November 2012) N.J. Wijnstok MSc (from 1 September 2012)
Patient Data & Quality Control – Assistent Data Monitors	M.M. Berkhout MSc (from 1 September 2012) P.T. Hoekstra MSc (from 1 September 2012)
Office, Administration, Communications – Manager	D. de Boer
Office	I. Bartels Bsc (from 1 April 2012) M.M.T. Koenen Bsc
Administration – Personnel & Administration	I.H.M. de Boer Drs. H.J.M. van Noort
Communications	L.J. Dolfing-Tompson BVSc Drs. A.P. Nollen (from 1 April 2012)

Appendix 2: Terminology & Definitions

Acute Infection
Any infection that begins suddenly, with intense or severe symptoms, is called acute (or primary). If the illness lasts more than a couple of weeks, it is called chronic.

Adherence
Adherence measures how faithfully a person takes all antiretroviral medications at the right time. Poor adherence is one of the main reasons antiretroviral combinations fail.

AIDS
Acquired Immunodeficiency Syndrome. A disease caused by a retrovirus, HIV (human immunodeficiency virus), and characterized by failure of the immune system to protect against infections and certain cancers.

Antibody
A substance in the blood formed in response to invading disease agents such as viruses, fungi, bacteria and parasites. Usually antibodies defend the body against invading disease agents, however, the HIV antibody does not give such protection.

Antigen
An invading substance that antibodies may target.

Antiretroviral therapy (ART)
A treatment that may prevent HIV from further damaging the immune system by blocking or hampering the reproduction of the HIV virus.

Antiviral
A substance that stops or suppresses the reproduction of a virus.

ATHENA
AIDS Therapy Evaluation in the Netherlands project (ATHENA). Stichting HIV Monitoring was founded in 2001 as a result of the successful ATHENA project.

cART
Combination antiretroviral therapy - a combination of drugs used to keep HIV infections under control.

CD4 (T4) cell
$CD4^+$ T-lymfocyte, or T4-cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by the HIV virus. In the course of the HIV infection the number of CD4 cells may drop from normal levels (+ 500 per mm^3) to dangerously low levels (fewer than 200 CD4 cells per mm^3 of blood).

CIb
Centre for Infectious Disease Control Netherlands, National Institute for Public Health and Environment (*www.rivm.nl/cib*).

DNA
Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert itself into the DNA molecules inside human cells and establish dormant infection.

GGD
Dutch municipal health service (*www.ggd.nl*).

HAART
Highly Active Antiretroviral Therapy, also known as combination antiretroviral therapy (cART).

Hepatitis B virus (HBV)
A viral infection that affects the liver and is transmitted only through blood-to-blood and sexual contact.

Hepatitis C virus (HCV)
A viral infection that is transmitted primarily by blood and blood products, as in blood transfusions or intravenous drug use, and sometimes through sexual contact.

HIV
Human Immunodeficiency Virus; the virus that causes the Acquired Immunodeficiency Syndrome (AIDS). HIV attacks and destroys the immune system by entering and destroying the cells that control and support the immune response system.

HIV Type 1 (HIV-1)
The HIV type responsible for the majority of HIV infections worldwide.

HIV Type 2 (HIV-2)
A virus very similar to HIV-1 that has been found to cause immune suppression. HIV-2 infections are found primarily in West Africa.

MSM
Men who have sex with men.

Person-year
A measure of time used in medical studies. A single person-year is 1 year lived by 1 person.

Retrovirus
A class of viruses which includes HIV. Retroviruses are so named because they carry their genetic information in RNA rather than DNA, and the RNA information must be translated "backwards" into DNA.

Reverse Transcriptase
After infecting a cell, HIV uses an enzyme called reverse transcriptase to convert its RNA into DNA and then replicates itself using the cell's machinery.

RIVM
Dutch National Institute for Public Health and the Environment (*www.rivm.nl*).

Seroconversion
The change from an absence of HIV antibodies in the blood to the presence of those antibodies.

Seroprevalence
The incidence of disease in a given population based on blood serum specimens.

SHM
Stichting HIV Monitoring (the Dutch HIV monitoring foundation, *www.hiv-monitoring.nl*).

Viral load
The number of HIV particles in a millilitre of blood or another body fluid, such as semen or cerebrospinal fluid.

VWS
Dutch Ministry of Health, Welfare and Sport (*www.rijksoverheid.nl*).