Annual Report 2015

HIV Monitoring

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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 all relevant aspects of HIV infection, including comorbidities and co-infections, such as viral hepatitis, in HIV-positive persons in care in the Netherlands.

www.hiv-monitoring.nl

Annual report 2015, approved by the Stichting HIV Monitoring Governing Board on 9 May 2016.

We would like to thank Daniela Bezemer, Daniëlle de Boer, Udi Davidovich, Arianne van der Doelen, Catriona Ester, Luuk Gras, Mireille Koenen, Maria Prins, Henk van Noort, Ard van Sighem, Colette Smit, Melanie Sormani, Brenda Tuk and Sima Zaheri for their contributions.

Requests for copies: The Annual Report is only published online and can be downloaded as a PDF from our website: www.hiv-monitoring.nl. For further information please contact the communications department by email: shm-communicatie@amc.uva.nl or by telephone: +31 20 5664172.

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HIV Monitoring

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Foreword

In 2015, Stichting HIV Monitoring continued its important task of monitoring the HIV epidemic in the Netherlands. The solid and well-established collaboration with the 27 appointed HIV treatment centres in the Netherlands has allowed SHM to continue to effectively collect and analyse data concerning people with HIV in clinical care. The outcome of these analyses enables SHM to provide a truly nationwide picture of the outcome of care for those living with HIV and is described in the 2015 HIV Monitoring Report. The key outcomes of the 2015 HIV Monitoring Report, summarising the current situation in terms of HIV care in the Netherlands, are included in this annual report. In addition, during 2015 SHM continued to provide individual treatment centres with regular updates of their own centre-specific data. These centre-specific reports enable the centres to critically review and improve their performance where necessary and are also required for formal certification of the centres. In this way, SHM makes a significant contribution to the quality of care provided to HIV-positive individuals in the Netherlands.

As treatment of HIV becomes increasingly effective, individuals living with HIV are now surviving into older age. SHM therefore also invests much time and effort in monitoring non-AIDS co-morbidities. Furthermore, in 2015, SHM continued the efforts to expand and improve the data collection for viral hepatitis B and C co-infections in HIV-positive individuals. This investment in a high-quality collection of data on hepatitis C co-infection allowed efficient and up-to-date monitoring of, and reporting on, the effectiveness of the novel combinations of direct acting antivirals against hepatitis C that became available in the Netherlands during the course of 2015.

In the past year, SHM has continued to make an important contribution to various European and other more global HIV observational cohort collaborations, in terms of both data and science. Such a contribution makes it possible to tackle scientific questions that cannot be answered by any individual cohort alone, and outcomes of this research regularly result in modifications to HIV treatment guidelines. In particular, last year SHM was instrumental in re-addressing the issue of how to estimate total HIV populations. On behalf of the European Centre for Disease Prevention and Control (ECDC), SHM developed a tool to estimate the total number of HIV-positive individuals, including those not yet diagnosed. This tool has led to a revised estimate of the number of individuals living with HIV in the Netherlands and is now also being implemented by various other European countries.

During 2015, efforts to identify a replacement for Oracle Clinical, the system on which SHM's data warehouse is currently based, were continued. Following a rigorous selection phase, requirements for a replacement have been drawn up that will ensure the new system is more efficient and also more compatible with the electronic patient record systems now in use throughout many of the HIV treatment centres. The final selection will be made in 2016. Other technological changes within SHM during 2015 were marked by the move to no longer publish the Monitoring Report as a printed book. Instead, in line with SHM's policy to reduce its impact on the environment, the Monitoring Report was made

available online as a searchable and interactive PDF. This move will be continued in 2016, with the digital publication of all subsequent reports, including the present Annual Report.

The important work carried out by SHM would not be possible without the concerted and ongoing efforts of numerous people from different fields. I would therefore like to take this opportunity to thank all these individuals, in particular the SHM staff, the HIV treatment teams, the members of SHM's governing board, advisory board and working group, and all those involved in the ATHENA cohort. Finally, I would once again like to sincerely thank all those living with HIV who are in clinical care for allowing us to capture their data, store blood samples and to learn how we may continue to improve their care.

Prof. Peter Reiss, MD, PhD

Director

Amsterdam, 9 May 2016

Message from the Governing Board Chair

The latest Monitoring Report, published online by Stichting HIV Monitoring (SHM) in November 2015, illustrated the important contribution made by SHM to the quality of care provided to HIV-positive people throughout the Netherlands. As well as reporting that approximately 18,355 HIV-positive people are in care in the Netherlands, the report revealed that, using a novel and more reliable method, the estimated number of HIV-infected individuals not yet in care was considerably lower than previously predicted. Similarly, the number of new diagnoses appeared to be declining. Nonetheless, while this is encouraging news, the observation that around 1,000 persons with new diagnoses entered care in 2015 and that 44% of these people presented late for care, continues to give cause for concern. Moreover, these and other findings presented in the Monitoring Report highlight the importance of continuous monitoring of HIV and its treatment, as carried out by SHM, to ensure that HIV-positive individuals are identified and treated at a very early stage of infection and remain linked to medical care. Not only is this in the interest of the individual living with HIV, but it will also benefit the wider population by slowing down the epidemic.

SHM also provides HIV treatment centres in the Netherlands with centre-specific data that support the centres in the certification process. This certification of treatment centres ensures optimal, well-structured patient care in the Netherlands. However, the data collected by SHM not only benefit national monitoring and HIV care, but also contribute to national and international research projects and collaborations. The outcomes of such collaborative research can subsequently be used as the basis for treatment and healthcare policy guidelines.

The Netherlands holds a unique position both within Europe and worldwide in terms of insight into the national HIV epidemic. This is largely due to the scope and detail of the monitoring work carried out by SHM. Therefore, I would once again like to thank all the SHM employees for their dedication and hard work over the past year. In addition, I would like to express my gratitude to the healthcare professionals and patients for their ongoing and essential contributions.

Sadly, at the beginning of 2016 we lost an esteemed colleague and board member, Han Fennema. Representing GGD Nederland, Han had been a valued member of SHM's board since 2010 and will be sorely missed.

Dr Frank Kroon

Chairman of the Governing Board

Amsterdam, 9 May 2016

Progress report

Introduction

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 SHM is 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 27 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 collectors in cooperation with the responsible HIV physician. Patient data are collected anonymously and then entered into the registration database for storage and analysis.

This section provides an update of SHM's activities carried out in 2015. In addition to a list of all certified HIV treatment centres in the Netherlands as per 31 December 2015, it also provides an overview of the organisation's structure and staffing. The progress report further includes a comprehensive overview of the activities carried out by the Data and QC unit in 2015, and updates on the registration and monitoring of HIV-positive patients by SHM and on the Amsterdam Cohort Studies, which receives its funding through SHM. Finally, the progress report provides an overview of SHM's national and international collaborations and describes SHM's main dissemination activities during 2015.

HIV treatment centres

The monitoring of HIV-infected adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 27 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 recognised as paediatric HIV treatment centres.

In 2015, 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. Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA) — Amsterdam
4. HIV Focus Centrum (DC Klinieken) — Amsterdam
5. Onze Lieve Vrouwe Gasthuis (OLVG)* — Amsterdam
6. Sint Lucas Andreas Ziekenhuis* — Amsterdam
7. MC Slotervaart — Amsterdam
8. Medisch Centrum Jan van Goyen (MC Jan van Goyen) — Amsterdam
9. VUmc — Amsterdam
10. Rijnstate — Arnhem
11. HagaZiekenhuis, locatie Leyweg — Den Haag
12. MCH-Bronovo — Den Haag
13. Catharina Ziekenhuis — Eindhoven
14. Medisch Spectrum Twente (MST) — Enschede
15. Admiraal De Ruyter Ziekenhuis — Goes
16. Universitair Medisch Centrum Groningen (UMCG) — Groningen
17. Spaarne Gasthuis — Haarlem
18. Medisch Centrum Leeuwarden (MCL) — Leeuwarden
19. Leids Universitair Medisch Centrum (LUMC) — Leiden
20. MC Zuiderzee — Lelystad
21. Maastricht UMC+ (MUMC+) — Maastricht
22. Radboudumc — Nijmegen
23. Erasmus MC — Rotterdam
24. Maasstad Ziekenhuis — Rotterdam
25. St. Elisabeth Ziekenhuis — Tilburg
26. Universitair Medisch Centrum Utrecht (UMC Utrecht) — Utrecht
27. Isala, locatie Sophia — Zwolle

Centres for the treatment and monitoring of paediatric HIV were:

A. Emma Kinderziekenhuis (EKZ), AMC-UvA — Amsterdam
B. Beatrix Kinderziekenhuis (BKZ), UMCG — Groningen
C. Erasmus MC-Sophia — Rotterdam
D. Wilhelmina Kinderziekenhuis (WKZ), UMCU — Utrecht

** In October 2015, OLVG and St Lucas Andreas Ziekenhuis underwent a merger. For the purpose of this report, they will be considered as two separate treatment centres. In future reports they will be listed as a single treatment centre, under the name of OLVG.*

SHM has contracts with each centre or subcentre for the collection of demographic, epidemiological, clinical, virological, immunological, and pharmacological 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, in collaboration with, and upon the request of, the Red Cross Blood Bank in Willemstad, Curaçao, SHM provides assistance in collecting data from HIV-infected persons seen by HIV-treating physicians at the St. Elisabeth Hospital in Curaçao (SEHOS).

Stichting HIV Monitoring mission

During 2015, Stichting HIV Monitoring updated its mission statement and objectives to reflect recent developments in the kind of data collected, the research carried out using these data, and our role in the field of HIV care and research.

Our mission

Stichting HIV Monitoring's mission is to further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections, such as viral hepatitis, in HIV-positive persons in care in the Netherlands.

Objectives

- To monitor and report trends in all aspects of HIV infection by collecting high-quality, nationwide data from HIV-positive persons in care.
- To inform all relevant stakeholders, including healthcare providers, government, researchers, and the community of people living with HIV, about national trends in all aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.
- To develop models that accurately predict future trends in the overall HIV epidemic and in the clinical course of HIV-positive persons in care in the Netherlands.
- To monitor and report on the quality of HIV treatment and care in the Netherlands, thereby contributing to the national HIV quality of care standards and formal certification of HIV treatment centres in the Netherlands.
- To contribute to national and international collaborative scientific research.
- To act as a national knowledge centre for information on trends in all relevant aspects of HIV infection and in the clinical course of HIV-positive persons in care in the Netherlands.

Stichting HIV Monitoring organisation

Stichting HIV Monitoring (SHM) is overseen by a governing board that includes members who represent academic and general hospitals, health insurers, the Netherlands HIV Association (*Hiv Vereniging Nederland*, *HVN*), the Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, *NVHB*) and the Academic Medical Center of the University of Amsterdam (AMC-UvA). The board members approve SHM's budget and the content of the annual report. In addition, SHM has an advisory board that reviews SHM's activities from a strategic perspective and advises the director and the governing board.

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 for scientific purposes. Consequently, the working group is also responsible for reviewing research proposals submitted to SHM.

SHM's director has the final responsibility for the organisations' day-to-day activities. SHM's primary activities are carried out by two units, one for the collection of patient data and quality control (Data and QC unit) and the other for data processing and analysis (Data Analysis, Reporting and Research unit). In addition to these units, SHM has a Communications unit and a Human Resources, Office and Finance unit.

The Data and QC unit includes the following departments: Patient Registration and Data Collection, Data Management, and QC and Protocol Management. The Patient Registration and Data Collection department is responsible for administering patient registrations (new registrations and discontinued registrations) and for assigning an anonymous identification code to each registered patient. It also includes the data collectors employed by SHM. In 2015, the average number of FTEs for this department was 17.04. The QC and Protocol Management department is staffed by the data monitors and, in 2015, had an average of 7.24 FTEs.

The Data Management department (1.58 FTEs) carries out data management activities, some of which are also outsourced to the Clinical Research Unit (CRU) of the department of Clinical Epidemiology and Biostatistics at the AMC-UvA. At least twice a year, in February/March and in May/June, a data freeze takes place to produce a dataset for data processing and analysis. During 2015, the total average number of FTEs for staff in the Data and QC unit was 25.86. The Data and QC unit is managed by Sima Zaheri (0.8 FTEs).

The Data Analysis, Reporting and Research unit is staffed by researchers in the field of epidemiology, HIV medicine, statistics, mathematical modelling of HIV and modelling of transmission networks. Together, these researchers implement the HIV monitoring programme, the results of which are presented in the annual SHM Monitoring Report published near the time of World Aids Day. The researchers also contribute to publications involving analyses of the collected data in peer-reviewed international scientific journals. This unit supports and collaborates nationally with researchers in the HIV treatment centres, and internationally with research groups working with comparable observational cohorts in the field of epidemiology and treatment of HIV. This group also organises support for research applications by national and international researchers, both during the preparatory phase and after approval. In 2015, the unit had one assistant researcher participating in a PhD programme. This programme involves mathematical modelling of the impact of various interventions to control the HIV epidemic in the Netherlands. This unit also supports another PhD programme that focuses on the optimisation of quality of care for HIV-positive patients receiving care at HIV treatment centres in the Netherlands. In 2015 an average of 4.53 FTEs were assigned to the Data Analysis, Reporting and Research unit. This unit is led by Peter Reiss (0.95 FTE), director of SHM.

The Communications unit, which had an average of 0.6 FTE in 2015, is led by Catriona Ester (0.75 FTE).

The primary activities of SHM are supported by the Human Resources, Office and Finance unit, which includes the secretariat, financial and personnel administration and financial management. In 2015, the average number of FTEs for the office staff was 2.42. The office staff are supervised by SHM's human resources, office and finance manager, Daniëlle de Boer (0.6 FTE).

As of 31 December 2015, SHM had an average total of 36.51 FTEs. In addition, SHM covers the costs for a total of 9.2 FTEs for data collectors and data entry staff who are employed by the HIV treatment centres and who are not on the SHM staff.

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

Stichting HIV Monitoring's Data and QC unit has four main activities:

- Data collection and data entry;
- Source data verification;
- Help desk and protocol management;
- Data management.

In addition to these four core activities, various projects have been undertaken since 2012 to ensure both efficiency in data collection and quality of the data in SHM's database. These projects are carried out on the basis of a quality management system (QMS), which is based on the principles of the PDCA (plan-do-check-adjust) cycle, ISO 9000 QMS standards, and scientific knowledge of data quality.

Standardisation, automation and steps for improvements

In 2015, SHM continued to improve its data production processes in line with its QMS. The key priorities for 2015 were:

- To standardise and improve data collection, data quality management and data processing;
- To improve the infrastructure for information and communications technology (ICT) and data management processes;
- Where possible, to centralise the collection of data by specially-trained SHM staff;
- To centralise the collection of specialised data and data relating to specific focus areas by specially-trained SHM staff;
- To establish an automated link that allows laboratory data from hospital computer systems to be entered directly and anonymously into the SHM database (LabLink);
- To replace and improve SHM's data entry system, as part of the innovation programme launched in 2013 that aims to maximise digitalised data collection and minimise manual input;
- To intensify the quality control of collected data by concentrating on information that is essential for the output and on consistency within patient data;
- To coach and train data collectors and data quality staff (data monitors).

The results achieved in 2015 are described in the paragraphs below.

Improvement and standardisation of manual data collection

In 2015, various sections of the data collection protocols were evaluated and improved. This review resulted in changes in the collection of data on HIV-infected children and on pregnancies in HIV-infected women.

In 2013, a help desk system was implemented to support the data collectors in extracting data from the information sources in the HIV treatment centres, and in coding and entry of data into the national SHM database in accordance with SHM protocols. This system was evaluated in 2015. To further improve help desk efficiency, efforts were undertaken in 2015 to identify a suitable software package that would improve the work flow. After comparing various candidates, a software package has been selected and will be implemented in 2016. During 2015, the help desk received 361 queries from data collectors, 186 of which could be resolved immediately by the responsible data quality staff member. In 2015, a total of 369 queries were resolved, 36 of which stemmed from 2014 and required longer-term solutions. The help desk queries led to 170 code changes and 61 protocol amendments in 2015.

Centralised data collection

The efficiency and quality of data collection and data entry in the treatment centres appears to be linked to the availability of data collectors in these centres. This can be improved through centralisation of data collection, which requires the mobile deployment of specially-trained staff from SHM's head office (central data collectors). In 2015, local data collectors in UMC Utrecht, Spaarne Gasthuis, St Elisabeth Ziekenhuis and Erasmus MC were assisted by the central data collectors to ensure that these HIV treatment centres remained up to date and to resolve discrepancies in the data. Moreover, central data collectors carried out both prospective and retrospective data collection and entry into the national SHM database of hepatitis-related data from the following two patient groups:

- HIV-infected patients with viral hepatitis C infection (HCV) in all HIV treatment centres (n=2,429);
- Patients with chronic HBV mono-infection (n=860) who are being followed as part of an SHM collaboration with UMC Utrecht and Rijnstate (as part of the approved research proposal entitled *Harmonic: Comparison of the natural course, morbidity and mortality, and effects of treatment in patients with HBV mono-infection and HIV/HBV co-infection*).

In addition, as part of two national approved research proposals (Fib 4 and Predict), central data collectors supplemented the laboratory data from a number of HIV treatment centres with additional laboratory measurements. This increased the data analysis possibilities for the researchers involved in these studies.

Improvements in data entry software

In May 2014, the Clinical Research Unit (CRU) of the Academic Medical Center (AMC) announced that SHM's data entry system, Oracle Clinical, would be phased out over the next three years. SHM therefore put together a project brief ('Oracle Clinical replacement') to identify a suitable alternative to Oracle Clinical. The plan also includes new opportunities for modernising and future-proofing SHM's data collection process in line with ICT developments taking place within the electronic patient record systems in HIV treatment centres. The first steps involved drawing up a statement of requirements, identifying potential candidates and selecting the best application. The company Furore has been requested to provide support in this process.

The statement of requirements was drawn up in September 2014. This was subsequently followed by a market survey to identify candidate replacement systems that also have the capacity to encompass future innovations and to allow possible coupling with electronic patient records in the future. This led to a long-list of seven options. The suppliers of these systems were all sent the statement of requirements; after studying the statement of requirements, four of the approached parties withdrew from process. The three remaining candidates on the short-list were given additional information about the data processes and anonymised patient scenarios. In 2015, these candidates presented their solutions to SHM, after which the products were compared. A preferred supplier was selected and reference visits took place. Following these visits, a proof of concept was carried out in September 2015, in which, together with the CRU and AMC's General ICT Service (ADICT), the feasibility of the proposed solution was investigated. The proof of concept was completed with a positive outcome and led to a requirements analysis. In 2016, subsequent steps will be planned on the basis of the specified requirements, the product description and costs of the system.

Patient reports, graphs and standard data queries

Each centre has access to Microsoft Report Builder, in which treatment teams can view and download for use reports, graphs and queries relating to their own centre. In 2015, these reports, graphs and other standard data queries were maintained, further developed where needed, and improved. Thirty-nine additional reports were built to enable the data collectors and data quality staff to work more effectively and efficiently, such as:

- Overviews of new registrations, discontinued registrations, and patients lost to follow up;
- Overviews to monitor both the LabLink process and the LabLink data (LabLink is the automated link by which laboratory results are transferred directly from the hospital computer system in an anonymised form to the SHM database);
- Overviews of hepatitis-related data from patients infected with both HIV and viral hepatitis and from patients with chronic hepatitis B mono-infection.

LabLink

LabLink is the automated link that allows laboratory data from hospital computer systems to be entered directly and anonymously into the SHM database. LabLink is part of SHM's innovation programme, launched in 2013, to maximise the digitalisation of data collection and reduce manual data entry as far as possible.

Implementation of LabLink

The move to standardise LabLink was continued in 2015. Based on the standard LabLink protocol that was developed in collaboration with the CRU and ADICT for sending laboratory results as HL7 messages (an international standard for electronic data exchange between healthcare information systems), LabLink has been extensively discussed and tested in OLVG and UMCG. The launch of LabLink has, however, been postponed due to implementation of the new electronic patient records system in the OLVG. In fact, implementation of new electronic record systems was the main reason why LabLink could not be set up in the remaining hospitals in 2015. However, once LabLink is launched in OLVG, it will be possible to centralise the transfer of laboratory results from the OLVG East site, the OLVG West site, MC Jan van Goyen, HIV Focus Centrum, Flevoziekenhuis and MC Zuiderzee. In total, 12 treatment centres now use LabLink, representing laboratory data from 53% of the patients included in the SHM database. The expectation is that this figure will rise markedly following the launch of LabLink in OLVG and associated hospitals in 2016. Finally, in 2015, the AMC continued to transfer results directly to SHM from the laboratory computer system using an internal connection.

Harmonisation of LabLink data

A LabLink 'mapping tool' has been developed by the CRU in Microsoft Access. This tool receives and standardises laboratory results from different treatment centres with different terminology. In 2015, 1,924 combinations of laboratory terms and accompanying samples were harmonised using this tool.

Centre-specific reports

Standard reports for each centre are presented twice a year on a password-protected area of the SHM website to provide treatment teams in the treatment centres with an overview of developments, trends and issues within their own patient populations. In 2015, these centre-specific reports were updated and presented to the HIV treatment centres on two occasions.

Improvements to data warehouse and data processing

SHM's data warehouse is located on an SQL (structured query language) server in the AMC, and extracts data from all SHM source systems. The data warehouse is updated daily with data that were manually entered into the national SHM database on the previous day, and with data sent by treatment centres via LabLink. The clear distinction between the production environment and the acceptance test environment allows efficient generation of data views for data analyses and reports, while maintaining quality. In 2015, the data

warehouse contained 344 data views that provided daily overviews of SHM data and made these data available for analysis and presentation to treatment centres in table and report form. A data freeze takes place twice a year, after which the raw data tables from the data warehouse are processed to yield tables suitable for data analysis. The data are cleaned, clustered, and coded according to the standard protocols of various national and international collaborations and the Anatomical Therapeutic Chemical (ATC) classification.

In 2015, these data processing steps resulted in data sets for centre-specific reports, the *Co-morbidity and Aging with HIV (AGEhIV)* study and ZiZo (*Zichtbare Zorg*, Visible Care). In addition, data processing and data set generation was carried out for four international collaborations, D:A:D, COHERE, EPPIC and BEEHIVE.

Volume of data collection

Figures 1 and *2* summarise the results of the data collection. An important first observation is that the total volume of manual data collection increased by 15% in 2015 compared with 2014 (*Figure 1A*). This increase in manual data collection is the logical result of the increase in the number of patients in follow up and the collection of additional chronic hepatitis B virus mono-infections at UMC Utrecht and Rijnstate. *Figures 1B-F* show the volume of the manual data collection for each data collection topic, according to patient population. Despite the implementation of LabLink in 12 HIV treatment centres, the largest proportion of manually collected data points in all patient groups, with the exception of HIV-exposed children (*Figure 1C*), remains laboratory results. This observation further supports SHM's automation strategy, which aims to improve efficiency through nationwide implementation of LabLink.

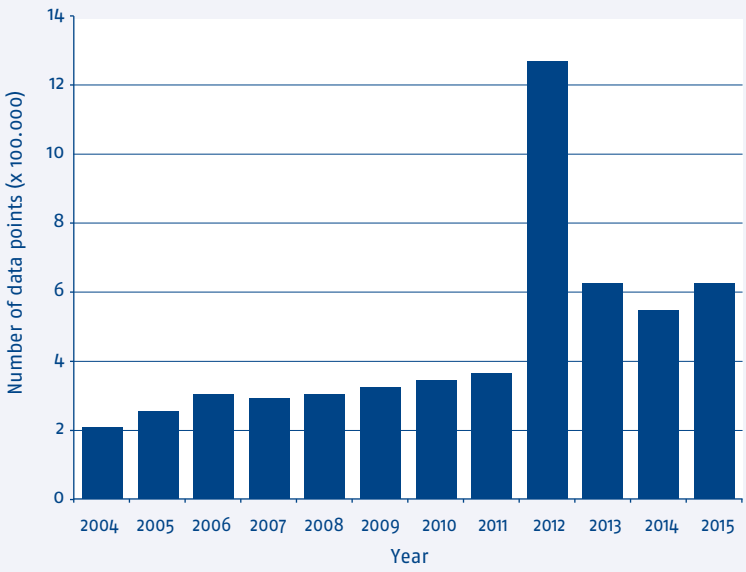
The volume of manually collected data from HIV-infected children decreased further in 2015 (*Figure 1D*). This reduction can be explained by the marked reduction in the number of new diagnoses among children, as well as by the fact that as HIV-infected children become older, their treatment shifts to an adult HIV treatment centre.

The total volume of manually collected data on viral hepatitis in patients infected with both HIV and hepatitis decreased in 2015 (*Figure 1E*). This decrease is associated with the completion of the retrospective collection of HIV and hepatitis co-infection data. In terms of viral hepatitis co-infection, the collection of follow-up data from this patient group appears to consist mainly of laboratory data. Figure 1F shows that the volume of data collected retrospectively from patients with a chronic HBV mono-infection, who are being followed as part of an approved research proposal in UMC Utrecht and Rijnstate, has increased (the *Harmonic* study). The collection of data for the *Harmonic* study was completed in 2015. As in other patient populations, *Figure 1F* shows that laboratory data make up a large proportion of the manual data collection in this group of patients infected with hepatitis.

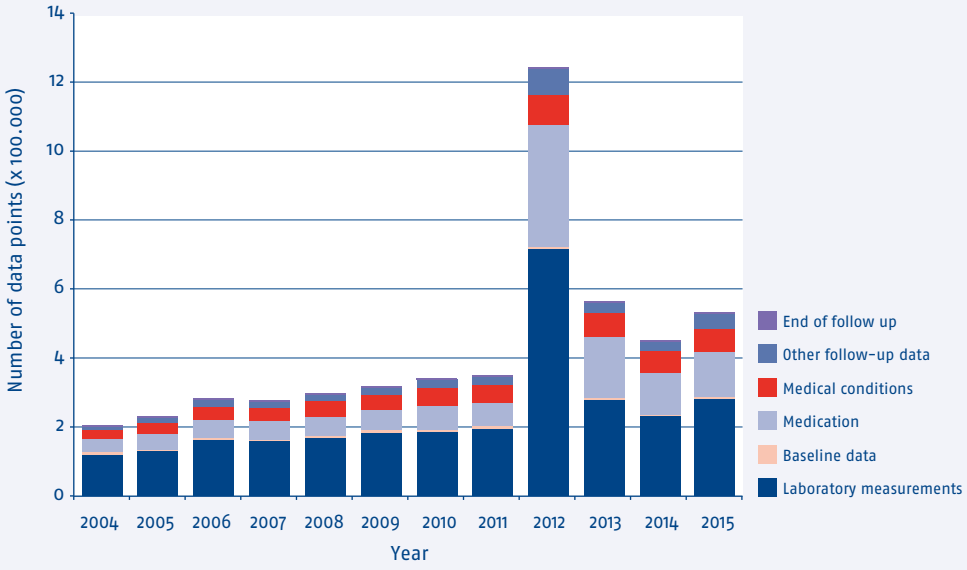
Figure 2 represents the proportion of laboratory data points collected through LabLink compared to laboratory data points collected manually. As expected, the number of data points collected with LabLink increased further in 2015.

Figures 1A–F: *Data collection results from 2004–2015.*

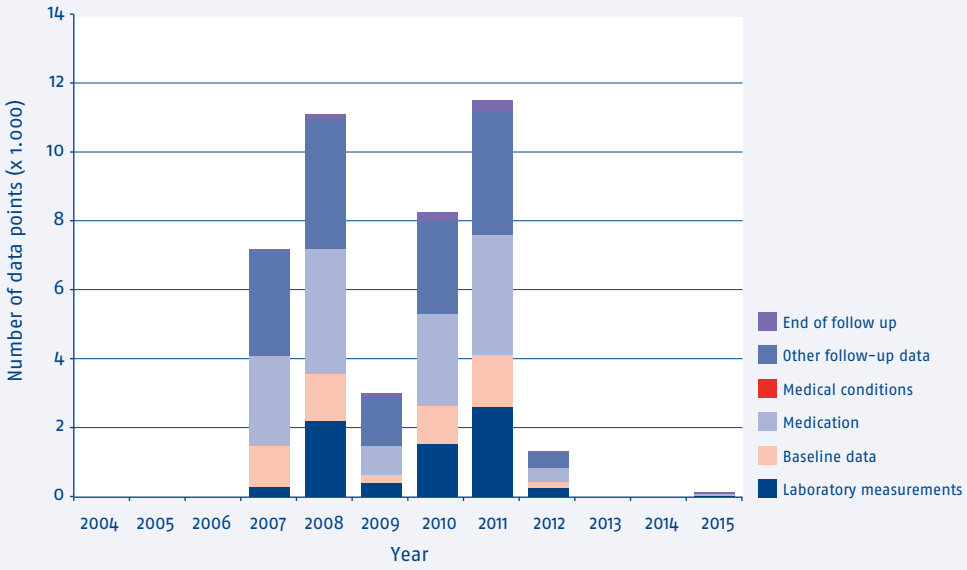
A: *Results of manual data collection from 2004–2015.*



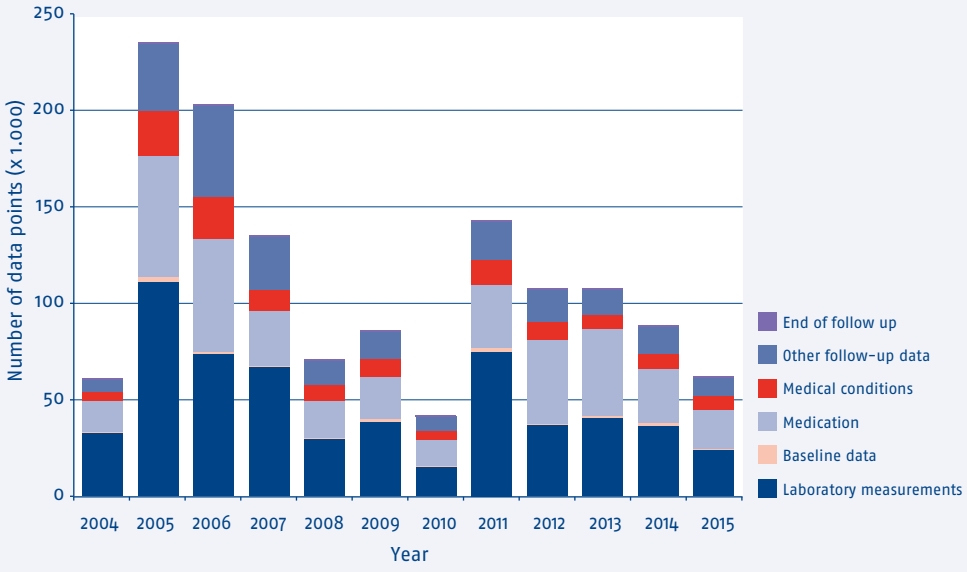
B: Number of manually collected data points per data collection topic for HIV-infected adults from 2004-2015.



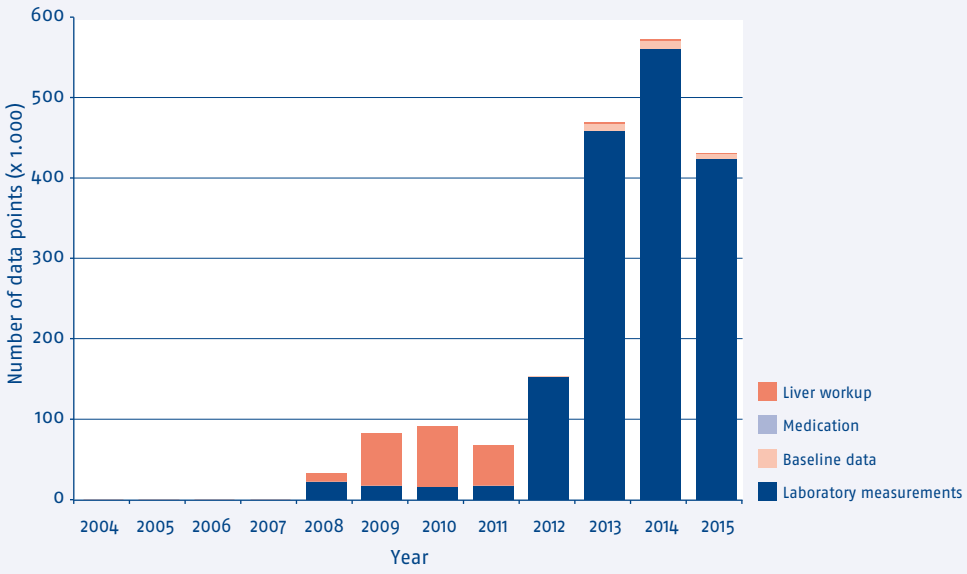
C: Number of manually collected data points per data collection topic for HIV-exposed children from 2004-2015.



D: Number of manually collected data points per data collection topic for HIV-infected children from 2004-2015.



E: Number of manually collected data points per data collection topic for HIV-infected adults with a viral hepatitis co-infection from 2004-2015.



F: Number of manually collected data points per data collection topic for viral hepatitis mono-infected adults from 2004-2015.

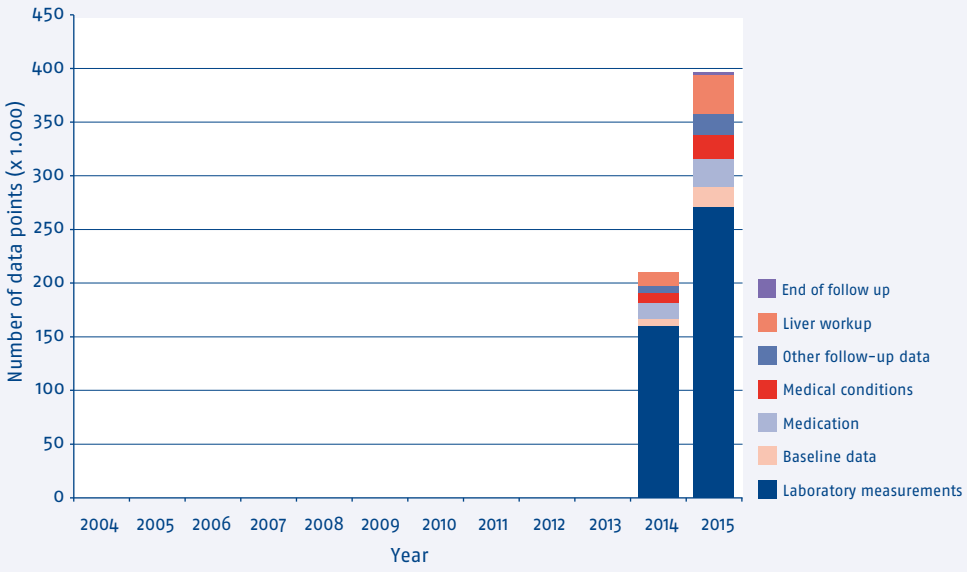
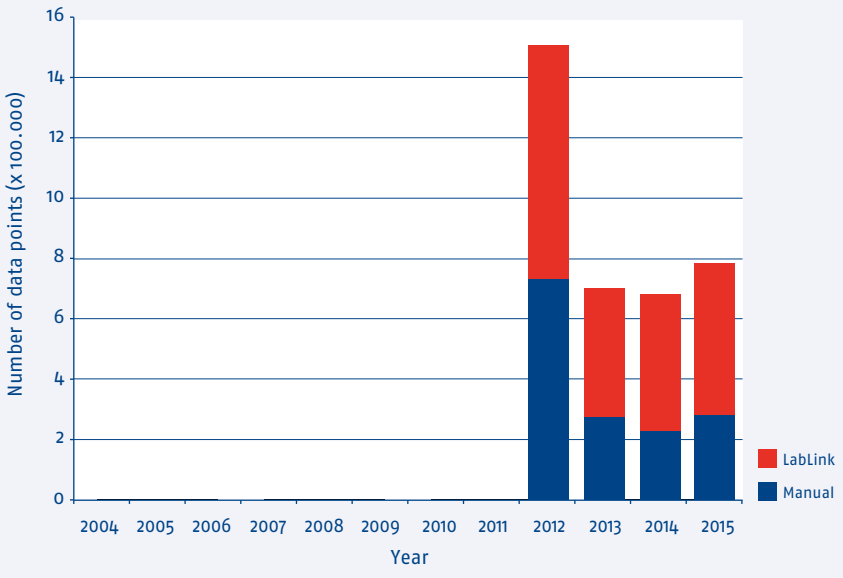


Figure 2: Manual versus automated data collection of laboratory measurements per year.



Data collection backlog

Table 1 presents the percentage of patients with delays in data collection (backlog) at each HIV treatment centre. A distinction is made between an estimated backlog of more than 365 days (long-term backlog) and one of less than 365 days (short-term backlog). The estimate is based on the difference between the predicted time and the actual time between the most recent patient visit and the next visit. The predicted time is calculated on the basis of the frequency of visits in the year prior to the most recent visit. A difference of 180 days or less is not considered a delay.

The average short-term backlog in 2015 was low for most centres. In those centres with a short-term backlog above 10%, data collection is not carried out by a data collector employed by SHM. In 2015, the average long-term backlog in data collection remained at 0%, while the average short-term backlog decreased by 1%. This is a good outcome given that, in 2015, the data collectors not only focused on collecting and entering follow-up data, but also focused strongly on resolving discrepancies and improving the quality of existing data. Furthermore, new study-specific items were introduced, such as HBV mono-infection data. The reduction in the backlog of data collection was also partly due to ongoing efforts to train data collectors in efficiently organising the data collection process, where individual patient reports and standard data queries are used to monitor backlogs and establish priorities.

Table 1: Percentage of patients followed in each treatment centre with an average data collection backlog of more than, and less than, 365 days.

		>365 days		<365 days	
HIV treatment centre	**Location**	**2015**	**2014**	**2015**	**2014**
MCA	Alkmaar	1%	0%	5%	0%
Flevoziekenhuis	Almere	1%	0%	4%	11%
AMC	Amsterdam	0%	0%	5%	5%
HIV Focus Centrum	Amsterdam	0%	0%	2%	1%
MC Jan van Goyen	Amsterdam	0%	0%	4%	6%
OLVG	Amsterdam	0%	0%	1%	2%
MC Slotervaart	Amsterdam	1%	2%	3%	4%
Sint Lucas Andreas Ziekenhuis	Amsterdam	0%	0%	0%	0%
VUmc	Amsterdam	1%	0%	8%	1%
Rijnstate	Arnhem	0%	0%	3%	1%
HagaZiekenhuis – Leyweg	Den Haag	0%	0%	0%	0%
MCH – Bronovo	Den Haag	0%	0%	6%	4%
Catharina Ziekenhuis	Eindhoven	0%	0%	7%	14%
MST	Enschede	0%	0%	0%	0%
Admiraal De Ruyter Ziekenhuis	Goes	0%	0%	4%	7%
UMCG	Groningen	0%	0%	14%	11%
Spaarne Gasthuis	Haarlem	0%	0%	14%	11%
MCL	Leeuwarden	0%	0%	8%	14%
LUMC	Leiden	0%	0%	10%	4%
MC Zuiderzee	Lelystad	0%	0%	7%	8%
MUMC+	Maastricht	0%	0%	7%	21%
Radboudumc	Nijmegen	0%	0%	1%	1%
Erasmus MC	Rotterdam	1%	0%	8%	9%
Maasstad Ziekenhuis	Rotterdam	0%	0%	1%	1%
St. Elisabeth Ziekenhuis	Tilburg	0%	2%	0%	9%
UMC Utrecht	Utrecht	0%	0%	11%	8%
Isala – Sophia	Zwolle	1%	0%	0%	1%
Mean		**0%**	**0%**	**5%**	**6%**

Quality control

In 2015, automated quality checks were carried out to support the manual quality checks by data quality staff and to further improve efficiency. *Table 2* presents the results of the automated quality checks in 2015. In total, 166 validation rules were defined and 12,416 records with discrepancies were selected and checked by the data collectors. These records were made available to the data collectors through user-friendly online reports. The number of records with discrepancies dropped by 30% in 2015. This highlights the effectiveness of automated quality checks and the resulting improvements in data quality compared to the previous year.

LabLink quality controls

Both automated and manual checks, developed in 2013, were also carried out on the LabLink data in 2015. One-off checks for acceptance of new LabLink connections with a laboratory were carried out on data in an acceptance test environment, while structural checks on LabLink data were performed three times on LabLink data in the production environment. The LabLink data were specifically checked for following points:

- Anonymisation of HL7 messages from within the HIV treatment centre;
- Completeness of the HIV treatment centre's patient population for which HL-7 messages are to be sent;
- Completeness of the selected components and time-span of laboratory results, in line with expectations and agreements made with the HIV treatment centre;
- Accuracy of messages transmission frequency, based on agreements with HIV treatment centre;
- Correct format of HL-7 messages;
- Accuracy and completeness of transmitted laboratory results, based on a random selection and comparison with laboratory results in the electronic patient records (carried out by the data collectors).

Table 2: Number of automated validation rules per criterion and number of records sent to data collectors for verification.

Selection criteria for quality checks	2015		2014		2013		2012	
	Validation rules (n)	Records (n)	Validation rules (n)	Records (n)	Validation rules (n)	Records (n)	Validation rules (n)	Records (n)
Consistency checks								
Missing and/or inconsistent baseline data	24	198	24	881	26	1,698	25	2,759
Missing and/or inconsistent demographic data	11	167	11	245	12	247	7	431
Missing and/or inconsistent adverse events data	8	99	8	93	8	178	6	522
Missing and/or inconsistent antiretroviral medication data	17	4,277	18	2,549	16	3,626	15	20,697
Missing and/or inconsistent CDC event data	5	53	5	64	5	126	6	161
Missing and/or inconsistent data on viral hepatitis infection	5	34	6	137	7	291		
Missing and/or inconsistent co-medication data	4	116	4	144	4	202	4	337
Missing and/or inconsistent laboratory data	31	4,027	32	5,522	26	2,986		
Missing and/or inconsistent end of follow-up data	10	696	10	359	10	610	10	1,297
Cross comparisons based on HICDEP[a]	51	2,749	52	7,526	48	11,565		
Total number quality checks	**166**	**12,416**	**170**	**17,520**	**162**	**21,529**	**73**	**26,204**

[a] *HICDEP: HIV Cohorts Data Exchange Protocol*

Manual quality control

Table 3 shows the results of the manual quality checks performed by the SHM data quality staff in 2015. These manual checks focus on collected data that are essential for SHM's output, on a random selection of new items for which data were collected in 2015, on complex data that can be used as training material for personal coaching of data collectors, and on consistency within the data.

In 2015, data from 618 patients were randomly selected and checked. Data related to cause of death and comorbidity, defined as 'endpoints', continued to be checked in 100% of cases in 2015. Additional data were also collected and classified for data analysis. To detect potentially missed comorbidities, data checks were carried out on 951 patients. In 2015, these checks targeted missed cases of myocardial infarction. In this way, 31 missed diagnoses of myocardial infarction were efficiently identified and could subsequently be added to the SHM database.

As part of the personal coaching programme for those data collectors who required support, an average of three patient files from each data collector was selected in 2015. The results of the quality checks were discussed with the responsible data collector and item-specific training was provided.

In the course of 2015, data from 2,896 patients were checked manually by SHM data quality staff. In addition, for all patients (n=1,222) for whom data collectors reported cardiovascular disease or other endpoints in the national SHM database in 2015, the data collected from their files were validated and classified. Data on additional diagnostics were also collected, and cause of death was verified and classified for 173 deceased patients. In addition, each HIV treatment centre was visited an average of 20 times by the SHM data quality staff member responsible for that centre.

The number of patients whose files were quality-controlled increased by 61% in 2015 compared with 2014. This increase is due to a more efficient system for manual quality control, a reduction in the administrative burden associated with carrying out the checks and, consequently, an increase in the number of patient files checked by SHM's data quality staff. These efforts have created more data analysis opportunities and facilitate research collaborations into those topics highlighted in the 2015 checks.

Training

In 2015, seven new SHM employees were trained for the role of data collector and were also given training on relevant medical information relating to HIV, data collection protocols and the data entry system.

In addition to the personal coaching of data collectors, a review day was organised in June 2015 for all data collectors. This review day focused on the diagnostic workup for HIV, HBV and HCV infections, and included a talk on the subject by Suzanne Jurriaans, head of HIV diagnostics at the AMC. Attention was also paid to ongoing studies (*Harmonic* and *PREDICT*) and to the additional data collection required for these studies. Furthermore, protocol changes were presented and discussed by SHM's data quality staff. Finally, working in small groups, cases were used to explain how to detect and resolve data discrepancies.

In 2015, three new members of the QC and Protocol Management department were given training on all medical aspects of HIV infection and on how to recognise related data in the electronic patient records. In addition, two new members of the Data Management department were given a tailored training in SQL Server Query Writing and TrainSQL during two internal training days, and a number of staff members from various departments were given an MS ACCESS training to improve work efficiency.

Table 3: Number of patient files checked by data quality staff, according to data selection criterion.

Selection criteria for quality checks	2015	2014	2013
Random selection			
Random selection of adverse event data	0	0	0
Random selection of antiretroviral medication data	0	0	3
Random selection of baseline data	671	0	0
Random selection of CDC event data	0	0	0
Random selection of co-medication data	0	0	0
Random selection of data on pregnancies	0	229	88
Random selection of data on viral hepatitis B infection	8	135	169
Random selection of data on viral hepatitis C infection	2	138	0
Random selection of all patient data	0	0	0
Random selection of data from last year of follow up	0	0	0
Subtotal random selection	**681**	**502**	**260**
Consistency checks			
Inconsistencies in adverse event data	0	0	0
Inconsistencies in antiretroviral medication data	0	0	0
Inconsistencies in baseline data	0	0	0
Priority analysis of baseline data	0	160	0
Inconsistencies in CDC event data	0	0	0
Inconsistencies in co-medication data	0	0	0
Inconsistencies in laboratory data	4	156	0
Subtotal consistency checks	**4**	**316**	**0**
Detection of missed comorbidities, defined as endpoints			
Cardiovascular disease	951		184
Diabetes mellitus	0		280
Chronic liver disease	0		219
Renal disease	0		84
Non-AIDS-defining malignancies	0		36
Subtotal of detected missed co-morbidities	**951**		**803**
Comorbidity and cause of death checks			
Total cardiovascular disease	707	357	652
Myocardial infarction	*(186)*	*(77)*	*(106)*
Invasive cardiovascular procedures	*(135)*	*(98)*	*(131)*
Diabetes mellitus	*(310)*	*(168)*	*(312)*
Stroke	*(76)*	*(14)*	*(103)*
Chronic liver disease	43	32	41
End-stage kidney disease	45	25	85
Non-AIDS-defining malignancies	254	173	332
Cause of death in 100% of cases	173	211	247
Subtotal of comorbidity and cause of death	**1,222**	**798**	**1,357**
Subtotal personal coaching of data collectors	38	184	309
Total number of quality checks	**2,896**	**1,800**	**2,729**
Change (%) per year	**61%**	**-30%**	**175%**

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Number of patient files								
2012	**2011**	**2010**	**2009**	**2008**	**2007**	**2006**	**2005**	**2004**
0	0	0	0	0	2	1	0	0
0	1	0	2	8	3	13	6	0
56	81	0	0	0	52	17	7	1
0	0	0	0	1	2	11	0	0
0	0	0	0	0	0	2	0	0
				1		129		
0	0	1	0	2	1	17	87	118
0	0	0	0	0	0	38	126	203
56	**82**	**1**	**2**	**12**	**60**	**228**	**226**	**322**
32	237	1,147	74	1,056	30	69	1	0
0	2	2	23	209	1	18	3	0
0	11	0	0	116	362	97	161	0
0	0	0	10	0	207	0	0	0
0	1	2	3	257	122	289	0	0
0	0	0	4	2	7	17	0	0
0	1	4	16	93	18	5	0	0
32	**252**	**1,155**	**130**	**1,733**	**747**	**495**	**165**	**0**
186	223	219	167	55	92	151	108	45
(51)	*(38)*	*(46)*	*(36)*	*(16)*	*(17)*	*(31)*	*(33)*	*(14)*
(49)	*(49)*	*(49)*	*(43)*	*(14)*	*(10)*	*(40)*	*(16)*	*(10)*
(54)	*(76)*	*(101)*	*(62)*	*(19)*	*(40)*	*(55)*	*(37)*	*(16)*
(32)	*(60)*	*(23)*	*(26)*	*(6)*	*(25)*	*(25)*	*(22)*	*(5)*
12	23	10	22					
16	34	12	13					
294	137	177	381					
227	185	152	113	108	128	151	27	1
735	**602**	**570**	**696**	**163**	**220**	**444**	**145**	**46**
168	154	124	114	241	268	216	0	0
991	**1,090**	**1,850**	**942**	**2,149**	**1,295**	**1,254**	**536**	**368**
-9%	**-41%**	**96%**	**-56%**	**66%**	**3%**	**179%**	**19%**	

Facts and figures: registration & monitoring of HIV-infected individuals

This chapter provides a summary of the patient population registered in Stichting HIV Monitoring's database as of 31 December 2015.

General

As of 31 December 2015, a cumulative total of 24,439 persons with HIV infection were registered through the Dutch HIV treatment centres by Stichting HIV Monitoring (SHM) (*Table 4*), of whom 1,068 were newly-registered in 2015 (*Table 5*). Of the 24,439 registered persons, 19,536 (80%) were men, and 4,903 (20%) were women. A total of 258 persons were registered with an HIV treatment centre specialising in HIV care for children and adolescents.

Further clinical data were collected for 23,944 cumulatively registered patients. The remaining 495 (2.0%) persons indicated that they opposed the collection of such data.

In 2015, data were collected from 18,758 (78%) persons. Of the 5,681 (22%) persons with no data collected in 2015, 2,463 had died before 2015, 1,299 had moved abroad and 1,919 had disappeared from care for an unknown reason or had objected to the collection of such data. Taking into account those persons who objected to data collection and those who died in 2015, as of 31 December, there remained 18,587 HIV-infected persons in care for whom data were collected in 2015.

Adults

Of the 23,944 persons registered up to and including 2015 and for whom further clinical data were collected, 23,518 were adults at the time of registration, comprising 18,989 (81%) men and 4,529 (19%) women. The most common route of HIV transmission was sexual contact with other men (73%) in men and heterosexual contact (88%) in women. The median age at diagnosis was 37.2 (interquartile range [IQR] 30.2-45.1) years for men and 31.4 (IQR 26.1-39.0) years for women. At the end of 2015, 3% of the group had been aware of their positive HIV status for less than a year, 17% had known for 1 to 5 years, 24% had known for 5 to 10 years, and 45% had known for more than 10 years, while for 0.5% the HIV diagnosis date had not, or not yet, been registered. The remaining 11% of the 23,518 adults had died. The median follow-up duration was 8.6 (IQR 4.2-14.4) years: 8.3 years for men and 9.7 years for women. The total follow up in the adult group was 231,753 person years.

Of the 1,009 HIV-positive adults newly registered in 2015 for whom further clinical data were collected, the main transmission route remained sexual contact with other men (73%) in men and heterosexual contact (88%) in women. The median age at diagnosis was 37.3 (IQR 28.5-47.3) years in men and 33.8 (IQR 26.9-46.5) years in women.

Children

Of the 23,944 persons registered as of 31 December 2015, 426 (2%) were children or adolescents. This group consisted of 202 (47%) boys and 224 (53%) girls. The median age at HIV diagnosis was 2.7 (IQR 0.5-9.1) years for boys and 2.9 (IQR 0.5-14.8) years for girls. In the majority of cases, the route of infection was vertical mother-to-child transmission (73%); in 19% of cases, the route of infection was recorded as sexual transmission. In total, 30% of the HIV-infected children were born in the Netherlands, and 57% were born in sub-Saharan Africa. The median duration of follow up was 9.6 (IQR 4.9-14.2) years: 9.6 years for boys and 9.6 years for girls. The total follow up for the group of children and adolescents was 4,247 person years.

In 2015, 24 children and adolescents (22 children aged between 0 and 12 years and 2 adolescents aged 13-17 years) were newly registered, comprising 11 boys and 13 girls. Eighteen of the 24 children and adolescents came from sub-Saharan Africa.

Pregnant women

The total number of registered pregnancies increased from 2,825 in 2014 to 2,996 in 2015. These pregnancies occurred in 1,708 women. In 56% of the cases, HIV was diagnosed before the start of the pregnancy, and, in 44% of cases, HIV was diagnosed during the pregnancy. The transmission route of HIV in the pregnant women was mainly through heterosexual contact (94%); in 1.5% of the pregnant women, transmission occurred through injecting drug use. The median age during the first pregnancy was 29 (IQR 25-34) years. In 36% of the women, combination antiretroviral therapy (cART) was started before the first pregnancy was diagnosed, and in 50% of the women, cART was started during the pregnancy. In 26% of cases, gestation lasted less than 16 weeks; in those women who were still pregnant after the initial 16 weeks, the median gestation period was 39 (IQR 37-40) weeks. Of the pregnancies, 74% resulted in the birth of a child, 29% of which involved C-section. Despite the introduction of a national HIV screening programme for pregnant women in 2004, nine children have since been infected with HIV through vertical transmission in the Netherlands. In the case of six of these children, the mothers were not diagnosed as HIV-positive until after the birth of the child. In four of these six cases, the mothers had tested HIV-negative during the pregnancy screening and must have become infected with HIV later on in the pregnancy. Another child's mother was known to be HIV-positive during pregnancy, but for unknown reasons was not treated for HIV. In the two remaining cases, whether the mothers were known to be HIV-positive or had undergone pregnancy screening was unknown.

Table 4: Cumulative numbers and percentages of HIV-positive patients registered by SHM and monitored in one of the HIV treatment centres in the Netherlands and in Curaçao on 31 December 2015.

		Total		Alive		Deceased		Objection[a]		Data in 2015[b]		No data in 2015			
												Deceased before 2015[c]		Other reasons[d]	
HIV treatment centre	**Location**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adult															
MCA	Alkmaar	339	1.4	311	91.7	28	8.3	2	0.6	279	82.3	28	8.3	32	9.4
Flevoziekenhuis	Almere	193	0.8	185	95.9	8	4.1	3	1.6	170	88.1	7	3.6	16	8.3
AMC-UvA	Amsterdam	2,878	11.9	2,543	88.4	335	11.6	11	0.4	2,203	76.5	318	11.0	357	12.4
HIV Focus Centrum	Amsterdam	540	2.2	537	99.4	3	0.6	0	0.0	531	98.3	3	0.6	6	1.1
MC Jan van Goyen	Amsterdam	292	1.2	253	86.6	39	13.4	5	1.7	197	67.5	39	13.4	56	19.2
OLVG	Amsterdam	3,392	14.0	2,998	88.4	394	11.6	157	4.6	2,509	74.0	379	11.2	504	14.9
MC Slotervaart	Amsterdam	840	3.5	690	82.1	150	17.9	12	1.4	588	70.0	145	17.3	107	12.7
St Lucas Andreas Ziekenhuis	Amsterdam	426	1.8	377	88.5	49	11.5	0	0.0	340	79.8	47	11.0	39	9.2
VUmc	Amsterdam	638	2.6	549	86.1	89	13.9	8	1.3	463	72.6	84	13.2	91	14.3
Rijnstate	Arnhem	796	3.3	721	90.6	75	9.4	3	0.4	643	80.8	70	8.8	83	10.4
HagaZiekenhuis	Den Haag	729	3.0	627	86.0	102	14.0	31	4.3	492	67.5	97	13.3	140	19.2
MCH - Bronovo	Den Haag	1,064	4.4	980	92.1	84	7.9	47	4.4	792	74.4	83	7.8	189	17.8
Catharina Ziekenhuis	Eindhoven	647	2.7	609	94.1	38	5.9	4	0.6	524	81.0	37	5.7	86	13.3
MST	Enschede	577	2.4	469	81.3	108	18.7	2	0.3	357	61.9	105	18.2	115	19.9
Admiraal De Ruyter Ziekenhuis	Goes	197	0.8	182	92.4	15	7.6	4	2.0	149	75.6	13	6.6	35	17.8
UMCG	Groningen	912	3.8	823	90.2	89	9.8	30	3.3	716	78.5	82	9.0	114	12.5
Spaarne Gasthuis	Haarlem	480	2.0	428	89.2	52	10.8	4	0.8	371	77.3	51	10.6	58	12.1
MCL	Leeuwarden	291	1.2	265	91.1	26	8.9	1	0.3	240	82.5	24	8.2	27	9.3
LUMC	Leiden	704	2.9	641	91.1	63	8.9	37	5.3	539	76.6	59	8.4	106	15.1
MC Zuiderzee	Lelystad	71	0.3	71	100.0	0	0.0	1	1.4	62	87.3	0	0.0	9	12.7
MUMC+	Maastricht	879	3.6	743	84.5	136	15.5	4	0.5	635	72.2	127	14.4	117	13.3
Radboudumc	Nijmegen	736	3.0	649	88.2	87	11.8	20	2.7	587	79.8	82	11.1	67	9.1
Erasmus MC	Rotterdam	2,519	10.4	2,247	89.2	272	10.8	8	0.3	1,909	75.8	260	10.3	350	13.9
Maasstad Ziekenhuis	Rotterdam	725	3.0	672	92.7	53	7.3	6	0.8	605	83.4	51	7.0	69	9.5
St, Elisabeth Ziekenhuis	Tilburg	1,133	4.7	1,063	93.8	70	6.2	17	1.5	926	81.7	66	5.8	141	12.4
UMC Utrecht	Utrecht	1,687	7.0	1,510	89.5	177	10.5	59	3.5	1,313	77.8	174	10.3	200	11.9
Isala - Sophia	Zwolle	496	2.1	462	93.1	34	6.9	17	3.4	391	78.8	29	5.8	76	15.3
Total		**24,181**	**100.0**	**21,605**	**89.3**	**2,576**	**10.7**	**493**	**2.0**	**18,531**	**76.6**	**2,460**	**10.2**	**3,190**	**13.2**

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Table 4 continued

HIV treatment centre	Location	Total		Alive		Deceased		Objection[a]		Data in 2015[b]		No data in 2015			
												Deceased before 2015[c]		Other reasons[d]	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Paediatric															
EKZ, AMC-UvA	Amsterdam	78	30.2	78	100	0	0.0	1	1.3	73	93.6	0	0.0	5	6.4
BKZ, UMCG	Groningen	25	9.7	25	100	0	0.0	0	0.0	24	96.0	0	0.0	1	4.0
Erasmus MC – Sophia	Rotterdam	79	30.6	77	97.5	2	2.5	0	0.0	67	84.8	2	2.5	10	12.7
WKZ, UMC Utrecht	Utrecht	76	29.5	75	98.7	1	1.3	1	1.3	63	82.9	1	1.3	12	15.8
Total		**258**	**100.0**	**255**	**98.8**	**3**	**1.2**	**2**	**0.8**	**227**	**88.0**	**3**	**1.2**	**28**	**10.9**
Curaçao															
SEHOS	Willemstad	978	98.5	815	83.3	163	16.7	1	0.1	547	55.9	161	16.5	270	27.6
SEHOS kinderkliniek	Willemstad	15	1.5	5	33.3	10	66.7	0	0.0	0	0.0	10	66.7	5	33.3
Total Curaçao		**993**	**100.0**	**820**	**82.6**	**173**	**17.4**	**1**	**0.1**	**547**	**55.1**	**171**	**17.2**	**275**	**27.7**

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

[b] *Data in 2015: registered by SHM in 2015, or deceased during or after 2015, or last contact with an HIV treatment centre during or after 2015*

[c] *No data in 2015 – deceased before 2015: patients who are not included in 'data in 2015' and who had died before 2015*

[d] *No data in 2015 – other reasons: patients who are not included in 'data in 2015' because they moved abroad before 2015 or because they had no contact with their HIV treatment centre in 2015 for an unknown reason*

Table 5: HIV-infected patients newly registered in 2015 and monitored by SHM in HIV treatment centres in the Netherlands and in Curaçao.

		Total		Alive		Deceased		Objection[a]	
HIV treatment centre	**Location**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adult									
MCA	Alkmaar	23	2.2	23	100.0	0	0.0	0	0.0
Flevoziekenhuis	Almere	19	1.8	19	100.0	0	0,0	1	5.3
AMC-UvA	Amsterdam	75	7.2	74	98.7	1	1.3	2	2.7
HIV Focus Centrum	Amsterdam	19	1.8	19	100.0	0	0.0	0	0.0
MC Jan van Goyen	Amsterdam	10	1.0	10	100.0	0	0.0	0	0.0
OLVG	Amsterdam	102	9.8	102	100.0	0	0.0	3	2.9
MC Slotervaart	Amsterdam	16	1.5	16	100.0	0	0.0	0	0.0
St Lucas Andreas Ziekenhuis	Amsterdam	26	2.5	26	100.0	0	0.0	0	0.0
VUmc	Amsterdam	29	2.8	29	100.0	0	0.0	0	0.0
Rijnstate	Arnhem	52	5.0	50	96.2	2	3.8	0	0.0
HagaZiekenhuis	Den Haag	23	2.2	23	100.0	0	0.0	0	0.0
MCH – Bronovo	Den Haag	53	5.1	53	100.0	0	0.0	5	9.4
Catharina Ziekenhuis	Eindhoven	39	3.7	39	100.0	0	0.0	0	0.0
MST	Enschede	14	1.3	14	100.0	0	0.0	0	0.0
Admiraal De Ruyter Ziekenhuis	Goes	10	1.0	10	100.0	0	0.0	0	0.0
UMCG	Groningen	51	4.9	50	98.0	1	2.0	11	21.6
Spaarne Gasthuis	Haarlem	30	2.9	30	100.0	0	0.0	0	0.0
MCL	Leeuwarden	13	1.2	13	100.0	0	0.0	0	0.0
LUMC	Leiden	21	2.0	20	95.2	1	4.8	1	4.8
MC Zuiderzee	Lelystad	7	0.7	7	100.0	0	0.0	0	0.0
MUMC+	Maastricht	39	3.7	38	97.4	1	2.6	0	0.0
Radboudumc	Nijmegen	38	3.6	38	100.0	0	0.0	1	2.6
Erasmus MC	Rotterdam	122	11.7	121	99.2	1	0.8	1	0.8
Maasstad Ziekenhuis	Rotterdam	39	3.7	39	100.0	0	0.0	0	0.0
St, Elisabeth Ziekenhuis	Tilburg	65	6.2	65	100.0	0	0.0	3	4.6
UMC Utrecht	Utrecht	75	7.2	75	100.0	0	0.0	4	5.3
Isala – Sophia	Zwolle	36	3.4	36	100.0	0	0.0	3	8.3
Total		**1,046***	**100.0**	**1,039**	**99.3**	**7**	**0.7**	**35**	**3.3**
Paediatric									
EKZ, AMC-UvA	Amsterdam	2	9.1	2	100.0	0	0.0	0	0.0
BKZ, UMCG	Groningen	2	9.1	2	100.0	0	0.0	0	0.0
Erasmus MC – Sophia	Rotterdam	11	50.0	11	10.00	0	0.0	0	0.0
WKZ, UMC Utrecht	Utrecht	7	31.8	7	100.0	0	0.0	0	0.0
Total		**22**	**100.0**	**22**	**100.0**	**0**	**0.0**	**0**	**0.0**
Curaçao									
SEHOS	Willemstad	51	100.0	51	100.0	0	0.0	0	0.0

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

* *Includes 2 of the 24 children newly-registered in 2015*

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Monitoring of treatment

In 2015, 92% of the 23,944 HIV-positive patients had been treated with cART, whereas 7% of the patients had not yet started treatment. No data had yet been registered for 0.6% of patients, and 0.7% were being treated with non-cART regimens.

In total, 85% of the first-line cART regimens initiated in 2015 consisted of tenofovir in combination with emtricitabine as the nucleotide/nucleoside reverse transcriptase inhibitor (NRTI) backbone, and 11% consisted of abacavir and lamivudine. While, in 2013, efavirenz was the most widely-used supplement to this emtricitabine backbone, it was superseded by cobicistat-boosted elvitegravir in 2014 and by dolutegravir in 2015 (*Table 6*).

Table 6: Most frequently-used first-line cART combinations in 2013-2015.

	2013		2014		2015		Total	
	n	%	n	%	n	%	n	%
TDF+FTC+EFV	421	29.0	227	16.1	40	6.0	688	19.5
TDF+FTC+EVG/c	36	2.5	494	35.0	135	20.1	665	18.8
TDF+FTC+RPV	287	19.8	191	13.5	38	5.7	516	14.6
TDF+FTC+DRV/r	268	18.5	155	11.0	50	7.4	473	13.4
ABC+3TC+DTG	0	0.0	59	4.2	224	33.3	283	8.0
TDF+FTC+NVP	130	9.0	35	2.5	5	0.7	170	4.8
TDF+FTC+ATV/r	101	7.0	51	3.6	17	2.5	169	4.8
TDF+FTC+DTG	0	0.0	33	2.3	92	13.7	125	3.5
TDF+FTC+RAL	40	2.8	36	2.6	4	0.6	80	2.3
Other	169	11.6	129	9.1	67	10.0	365	10.3
Total	**1,452**	**100.0**	**1,410**	**100.0**	**672**	**100.0**	**3,534**	**100.0**

Legend: *cART=combination antiretroviral therapy, TDF=tenofovir, FTC=emtricitabine, EFV=efavirenz, EVG/c=elvitegravir/cobicistat, RPV=rilpivirine, DRV/r=darunavir/ritonavir, ABC=abacavir, 3TC=lamivudine, DTG=dolutegravir, NVP=nevirapine, ATV/r=atazanavir/ritonavir, RAL=raltegravir*

In 2015, the median CD4 cell count at the start of cART was 400 (IQR 200-600) cells/mm^3. Of those patients who started cART in 2015, 68% started within 6 months of HIV diagnosis.

Collection of HIV sequence data

In 2015, only six HIV treatment centres provided HIV sequence data. To date, a total of 12,513 reverse transcriptase and protease sequences and 50 integrase gene sequences have been collected.

Hepatitis B and hepatitis C co-infections

Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can cause liver cirrhosis, liver fibrosis and hepatocellular carcinoma (HCC). In combination with HIV, the course of such diseases is likely to be accelerated. Therefore, HBV and HCV are also monitored regularly in the HIV-infected population over time. Chronic HCV co-infection is defined as the presence of HCV RNA for at least 6 months after infection. Based on this definition, in 2015, chronic HCV co-infection was found in 6.1% of the monitored HIV-infected patients. Chronic HBV co-infection was detected in 6.7% of the monitored HIV-infected patients, and chronic co-infection with both HBV and HCV was found in 0.4% of the monitored HIV-infected patients. Of the patients with chronic HBV co-infection, 9.5% had hepatic fibrosis, 9.6% had hepatic cirrhosis, and 0.9% had HCC. In patients with chronic HCV co-infection, these figures were 24%, 15% and 0.7%, respectively. The difference in hepatic fibrosis and cirrhosis prevalence between patients with chronic HBV and chronic HCV co-infection may be due to the fact that 93% of HBV co-infected patients received a cART regimen that included one or more agents active against both HIV and HBV. Moreover, the higher prevalence in HCV co-infected patients may be due to a lower proportion of these patients having been successfully treated for HCV.

Sample collection and storage

Since the start of the AIDS Therapy Evaluation in the Netherlands (ATHENA) project in 1996, an estimated total of 498,825 plasma samples from patients in follow up have been stored in microbiology laboratories at the HIV treatment centres or in laboratories associated with the centres. This sample collection is exceptionally valuable for clinical epidemiologic research into resistance development over time and for research into the response of HIV-1 subtypes, other than the most common subtype B, to antiviral therapy. The outcome of such research carries implications both for the quality of care of individual patients and for public health.

Registration of HIV-positive individuals in Curaçao

The registration and monitoring of HIV-infected persons being followed in the St. Elisabeth Hospital in Willemstad, Curaçao, has continued during the past years. Results from the monitoring in Curaçao were presented in the Monitoring Report 2015. In total, 993 patients were registered, of whom 51 were newly registered in 2015.

Key outcomes and recommendations

Just before 1 December 2015, Stichting HIV Monitoring published its scientific report, 'Monitoring Report 2015 - Human Immunodeficiency Virus (HIV) Infection in the Netherlands'. A summary of the main findings reported in this publication, based on data collected up to 1 May 2015, is presented below.

The HIV epidemic in the Netherlands

HIV-positive patients registered in the Netherlands as of May 2015

As of May 2015, a total of 18,355 persons living with HIV in the Netherlands (18,149 adults, and 206 children and adolescents) were known to be retained in care in one of the 27 designated HIV treatment centres. Of these 18,355, 93% (17,071) had started combination antiretroviral therapy (cART), and of these 17,071, 92% (15,789) had suppressed viraemia to below the level of quantification at the time of their last available HIV-RNA measurement. These results are impressive when compared to figures from other parts of the world.

New diagnoses in 2014

In 2014, the majority (69%) of newly diagnosed infections in adults were in men who have sex with men (MSM), 25% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission. Of note, almost one quarter of all newly-diagnosed patients in 2014 were 50 years or older. Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to approximately 1,000 new diagnoses in recent years. Although this decreasing trend continued in 2014, the projected number of diagnoses may have been underestimated as registration of HIV diagnoses for this year has not yet been finalised. Nonetheless, this decreasing trend appears to be reflected in the MSM population aged 25-44 years, but remains less marked in MSM both 25 years and younger and 45 years and older, as well as in heterosexuals 45 years and older. Finally, overall, over 90 percent of persons newly diagnosed with HIV entered into specialised care within 6 weeks after diagnosis. There is little variation in these figures, regardless of where individuals were diagnosed.

CD4 count at diagnosis and start of cART

The rates of testing for HIV appear to be increasing in certain settings. Interestingly, the proportion of patients with a previously negative HIV test has also increased (73% MSM and 40% heterosexuals had a known previous negative test in 2014). Moreover, fortunately, the proportion of patients who are identified and start cART earlier in their infection (including during primary HIV infection) continues to increase, particularly amongst MSM. This is reflected in the CD4 count, both at diagnosis and at start of cART, gradually having risen over time to a median of 385 and 410 cells/mm^3, respectively, in 2014.

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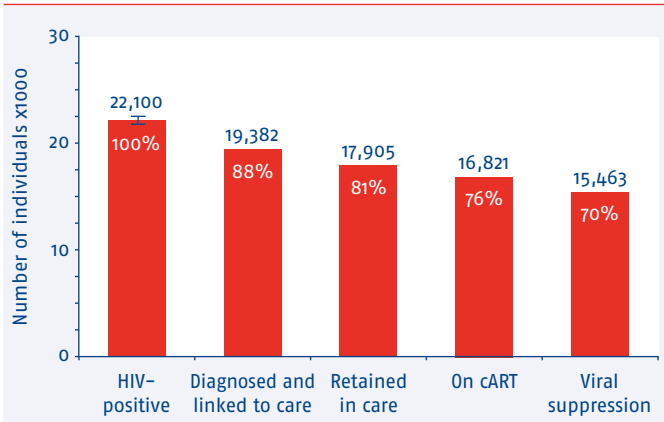
The likelihood of patients starting cART at higher CD4 counts is also reflected in the fact that, while in 2013 49% of patients with a CD4 count of 500 cells/mm^3 had begun cART within 6 months of diagnosis, this proportion rose to 68% in 2014. Nonetheless, far too many patients continue to present late for care. In 2014, 44% of newly diagnosed patients presented late for care, i.e., with AIDS or a CD4 count less than 350 cells/mm^3, and 27% presented with advanced HIV disease, i.e., with a CD4 count less than 200 cells/mm^3 or AIDS. Generally, the likelihood of presenting late for care or with advanced HIV disease was greater for men with heterosexually acquired infection, individuals originating from South and South-East Asia and sub-Saharan Africa, and individuals aged 45 years or older.

Continuum of HIV care in 2014

An important change compared to last year's Monitoring Report is that estimates of the number of people living with HIV, as well as of the number who are not yet diagnosed, are considerably lower than previously reported. The method recently developed by the European Centre for Disease Prevention and Control (ECDC) to estimate the total number of HIV-positive individuals, including those not yet diagnosed, revealed that 22,100 individuals were estimated to be living with HIV in the Netherlands by the end of 2014, of whom 2,700 were still undiagnosed. On the basis of this new estimated number of 22,100 people living with HIV, a continuum of HIV care *(Figure 3)* has been constructed to depict engagement in HIV care in 2014 across a few key indicators, the last one being the number of individuals with suppressed viral load. By the end of 2014, 19,382 patients, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM. In total, 17,905 patients were considered to still be in care. The majority of these patients, 16,821 in total, had started cART, and 15,463 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 70% of the total estimated population living with HIV and 80% of those diagnosed and ever linked to care had a suppressed viral load.

Figure 3: Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2014.



This brings the Netherlands far closer to also reaching the first of the UNAIDS 90-90-90 targets than the less robust UNAIDS estimate used in previous years for constructing the continuum of care. ECDC is currently training public health surveillance staff from European countries to adopt the newly available methodology and use it for constructing their own HIV continuum of care. ECDC is also working together with UNAIDS on how this methodology could also be used for further improving estimates of the global burden of HIV.

Improved transdisciplinary strategies that target all factors sustaining the epidemic continue to be needed to achieve a significant decline in the rate of new infections. The aim of these strategies should be to simultaneously reduce the likelihood of HIV infection in key populations at risk, identify infected individuals early, rapidly link all infected persons to care, and immediately offer them the option of starting combination antiretroviral therapy.

Combination antiretroviral therapy in adults

First-line cART

Guidelines for the choice of first-line cART are closely adhered to in the Netherlands. Most patients who first initiated cART in 2014 did so with a once-daily regimen including tenofovir/emtricitabine as the backbone. Of note a clear shift can be observed towards including integrase strand transfer inhibitors (INSTI) as part of initial regimens. Over one-third of patients first initiating treatment in 2014 did so with the fixed-dose single-tablet regimen of tenofovir plus emtricitabine plus cobicistat-boosted elvitegravir (Stribild®). A similar trend may be expected to become visible in the use of the fixed-dose single-tablet regimen of abacavir plus lamivudine plus dolutegravir (Triumeq®).

Virological response

Virological response to first-line cART continues to improve: over 95% of individuals who first initiated cART with one of regimens recommended in 2014 achieved viral suppression to below the level of HIV-RNA quantification within 9 months. However, individuals <30 years of age, individuals infected through heterosexual transmission (compared with homosexual transmission), and individuals born in sub-Saharan Africa compared with those born in the Netherlands were somewhat less likely to achieve this goal. Importantly, in contrast to earlier periods, patients initiating treatment at CD4 counts >500 cells/mm^3 were no longer less likely to achieve initial suppression, which is an important observation in view of current guidelines recommending cART for all, regardless of CD4 count. Of the patients who first initiated cART from 1999 onwards and were continuously on treatment and still in follow up at 14 years, 99.6% had suppressed viraemia to less than 100 copies/ml.

Virological failure

Overall, 7.2% of the treatment-naive patients who first initiated cART from 1999 onwards have experienced virological failure (defined as time to the first of two consecutive plasma HIV-RNA levels >200 copies/ml after 24 weeks on therapy) to first-line cART. Importantly, the annual proportion of patients experiencing virological failure according to this definition has declined over time to as little as 3%. Nonetheless, as expected, when virological failure does occur, it remains associated with a substantial risk of drug resistance.

Genotypic sequence data are only available to SHM from a suboptimal proportion of patients, both at the time of virological failure as well as at the time of HIV diagnosis prior to first initiating cART. With the introduction of new drug classes in recent years, including integrase and entry inhibitors, the collection of data on sequences needs to be extended to other parts of the viral genome. Increasingly, genotypic sequences of the relevant genes are being obtained during routine clinical care, but insufficient sequences are currently available in the SHM database to give a clear picture of resistance to these new drug classes. The collection of sequencing data needs to be improved to permit more complete monitoring of resistance. The first steps to achieve this have already been taken, and further progress is expected in the near future.

Immunological recovery

The proportion of patients achieving greater immunologic recovery on cART continues to improve year after year. Nonetheless, a substantial number of patients fail to achieve restoration of CD4 cells to levels above which the risk of both traditionally HIV-associated and non-AIDS-related morbidity may no longer be accentuated as a result of the infection. This particularly holds true for those who commence treatment at a more advanced level of immunodeficiency. In 2014, 12% of patients in care had a last available CD4 measurement less than 350 cells/mm^3. The likelihood of achieving normalisation of CD4 counts and CD4/CD8 ratios is clearly dependent on the timely start of cART, and is much greater when treatment is started at a CD4 count greater than 500 cells/mm^3. Together with the results from the START trial, published earlier this year, this reinforces the need to strive for early diagnosis and treatment of HIV infection.

Tolerability of cART

Although tolerability of cART has continued to improve with time and larger numbers of patients remain on their initial regimen for a longer time, drug intolerance or toxicity is still the most common reason for a change of initial treatment. The risk of a toxicity-driven therapy change in those starting cART in or after 2009 was higher in females, when cART was started at CD4 cell counts ≥500 cells/mm^3, and, when cART was started during primary infection, independent of CD4 cell count. When interpreting these findings it is, however, important to realise that, in recent years more proactive switching of regimens for lesser degrees of toxicity and intolerance is occurring because of the increased availability of better tolerated and more convenient fixed-dose combination regimens.

As larger numbers of clinically asymptomatic, newly-identified patients with HIV are expected to start treatment earlier, continued development of even better tolerated, convenient regimens, as well as improvements in individualised patient management remain necessary to improve the durability of initial treatment even further.

Quality of care

Generally speaking, a number of different quality of care indicators showed limited variability across the 27 adult HIV treatment centres. Retention in care and viral suppression rates in the first 6 months on cART, as well as during long-term use of cART, were high across all centres. Across most of the centres, an increasing proportion of patients are starting cART sooner after entering care, a trend we anticipate shall continue in light of the results of the START trial that now definitively supports the current guideline of offering cART to anyone with newly diagnosed HIV, regardless of their CD4 count. More substantial variation was observed regarding repeated screening in groups at risk for HCV. However, this may, to some extent, be explained by centres/physicians applying a policy of targeted screening guided by the presence of incident transaminase elevations. Continued, further monitoring of these trends seems warranted.

Morbidity and mortality

Mortality rates remain low in HIV-infected patients in care in the Netherlands. There has been a sustained decline in death from AIDS, with a shift towards death from other causes. Non-AIDS co-morbidities, including non-AIDS-defining malignancies, cardiovascular disease and chronic liver disease, comprise a sizable fraction of those other causes. Nonetheless, the proportion of patients dying of AIDS (nearly 27%) remained substantial between 2007 and 2014. Once more, this was largely driven by late presentation and late entry into care, and stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

Older age and co-morbidities

Not surprisingly, older age was an important risk factor for co-morbidities that are traditionally associated with ageing, notably cardiovascular disease and non-AIDS malignancies. In this context, it is important to note that the proportion of older individuals with newly diagnosed HIV entering care in the Netherlands is substantial; in 2014, 24% were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 42% currently older than 50 years. Of particular concern is the increasing proportion of patients with multiple co-morbidities, the risk of which appears to be increased in those with HIV, as demonstrated amongst others by data from the *AGEhIV* cohort study, in which SHM collaborates with the Academic Medical Center, the Amsterdam Institute for Global Health and Development and the Public Health Service (*Geneeskundige en Gezondheidsdienst*; GGD) in Amsterdam.

Cardiovascular risk

Despite the increasing age of the HIV-infected population, the proportion at high or very high cardiovascular risk only increased slightly over the period 2000-2014. This suggests that cardiovascular risk management may have improved over time. Significant room for further improvement remains, however, given the suboptimal use of statin therapy, antihypertensive therapy and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit improving, uptake of these medications in the prevention of primary cardiovascular disease.

Non-AIDS malignancies

The crude incidence of non-AIDS malignancies in the Netherlands has remained stable over time, but the absolute number and proportion of deaths due to these malignancies has increased. In men we observed a decline in age-standardised incidence of non-AIDS malignancies, including anal cancer, possibly as a result of a reduction in risk factors such as smoking and a higher proportion of individuals living with higher CD4 cell counts in more recent years. The most common non-AIDS malignancies continue to be lung, anal, head and neck cancers as well as Hodgkin's lymphoma, although the proportion of patients diagnosed with other non-AIDS malignancies increased with increasing age. Collaborative analyses conducted on much larger datasets as part of the D:A:D study showed a signal of protease inhibitor-based cART regimens possibly being associated with an increased risk of non-AIDS malignancies, and invasive anal cancer in particular. No such association was found for non-nucleoside reverse transcriptase inhibitor-based regimens.

Awareness of the role of modifiable, often lifestyle-related risk factors, such as smoking, and their management by both physicians and HIV-positive individuals, particularly those who are older or otherwise at high a priori risk of certain co-morbidities, offers important hope of ensuring a lower comorbidity burden and healthy ageing. This applies not only to conditions such as cardiovascular disease and diabetes mellitus, but also to measures to prevent cancer, chronic kidney disease and bone loss. At the same time there is clear room for improvement in the use of known effective biomedical interventions for primary and secondary prevention according to general guidelines.

Hepatitis B and C co-infections

Screening for hepatitis B (HBV) and C (HCV) co-infection has, with time, increasingly become part of the standard of HIV care in the Netherlands. As a result, the presence or absence of HBV or HCV infection is now documented for virtually all HIV-infected patients in care in the Netherlands. Approximately 12% of patients had evidence of ever having been exposed

to HCV, 6% were documented as having chronic infection and 1.6% had acute infection. Seven percent of patients were shown to have chronic HBV infection.

An estimated 27% of HIV-infected patients overall and 21% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. Although this does represent a reduction compared to our previous report, these findings illustrate the importance of continuing our efforts to increase successful HBV vaccination rates amongst this subgroup of patients.

HCV & direct-acting antiviral agents

HCV genotype 1 infection was the most common genotype in patients with either chronic or acute HCV infection, and most patients with HCV infection were male and from the Netherlands or other European countries. Importantly, the incidence of acute HCV infection observed in 2014 amongst MSM remains high at a rate of 3.7 diagnoses per 1,000 person years (4.2 per 1,000 person years in 2013). This clearly indicates the need for continued preventive efforts in these men, including the use of the novel, highly effective, short-course, well-tolerated and interferon-free combination therapies for HCV which by virtue of their high effectiveness not only benefit the individual patient but may also markedly reduce the risk of onward transmission.

Our data clearly show that, with the advent of novel direct-acting antiviral agents (DAAs) in 2014 and 2015, PEG-IFN-containing regimens are rapidly being replaced in clinical practice by a variety of all-oral DAA-based regimens and more patients with HCV co-infection are being treated. Based on data available up to 15 September 2015, more than 100 patients have received or are currently receiving treatment with regimens including one or more of the currently available novel DAAs sofosbuvir, simeprevir and daclatasvir. Of note, with the exception of one patient, all patients who completed their treatment with these new DAAs had a negative HCV RNA test result at the end of treatment, and 95% of all patients with sufficient follow-up data to calculate an SVR were found to have been cured. These results are markedly better than what was thus far feasible with previous PEG-IFN alpha-containing regimens. Very importantly, these developments have already resulted in a lower total number of HCV-co-infected patients who remain in need of effective treatment compared to last year's report (876 patients in 2014 vs. 907 in 2013), in spite of an increase in the total number of patients with HCV co-infection currently retained in care (1260 in 2014 vs. 1187 in 2013).

Overall, patients with HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. For patients with chronic HBV diagnosed after 2000, liver-related deaths have been significantly reduced, likely as a result of increasingly effective treatment for HBV through the use of tenofovir-containing cART. The rapidly expanding availability of novel interferon-free regimens for HCV, together with optimised screening for HCV co-infection with time, will hopefully similarly limit the impact of HCV co-infection on long-term liver-related morbidity and mortality. In addition, when combined with additional preventive measures, it may be expected to contribute to reducing the rate of incident HCV infection among the key affected population of MSM.

HIV in pregnant women and in children

Pregnant women

Universal first trimester screening for HIV in pregnant women and the increasingly effective use of cART during pregnancy has made perinatal transmission of HIV extremely rare in the Netherlands, although cases of incident HIV infection following a negative first trimester screen have been documented later during pregnancy.

Together with the observation that approximately 10% of HIV-infected pregnant women do not have fully suppressed viraemia around the time of delivery, this indicates the need for continued vigilance to ensure zero vertical transmissions of HIV.

Children & adolescents

Treatment outcomes for children living with HIV in the Netherlands and receiving care in one of the four designated paediatric treatment centres are generally favourable. These outcomes include long-term immunologic responses to cART, particularly in vertically-infected children who started treatment below two years of age. More and more of these children, however, are transitioning into adult care. Almost 30% of the children who have transitioned into adult care and are retained in care currently do not have fully suppressed viraemia.

This illustrates that optimisation of long-term care for this particularly vulnerable and difficult-to-manage group of young individuals is sorely needed.

HIV on Curaçao

SHM continues to provide assistance to Stichting Rode Kruis Bloedbank with data collection and monitoring of patients with HIV in care at the St Elisabeth Hospital in Willemstad on the Caribbean island of Curaçao. In recent years, HIV-positive patients in Curaçao appear to be diagnosed increasingly earlier in their infection, as shown by a declining proportion of patients presenting late for care. As a consequence, cART is being started at increasingly higher CD4 cell counts. The quality of monitoring and treatment offered to HIV-positive patients has also improved considerably. However, adherence to treatment and retention in care do remain suboptimal.

Amsterdam Cohort Studies

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

From the outset, 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 (*Geneeskundige en Gezondheidsdienst Amsterdam*; GGD Amsterdam), the Academic Medical Center of the University of Amsterdam, the University Medical Centre Utrecht, the Jan van Goyen Medical Centre, the HIV Focus Centrum, and Stichting HIV Monitoring (SHM). The ACS infrastructure is financed primarily through a contribution from the National Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu*, RIVM), and each participating institute also makes a financial contribution. The scientific studies are funded separately by external sources.

The ACS is unique in its follow up of two populations at risk of HIV infection, namely HIV-negative MSM and HIV-negative DU. These populations are followed through the GGD Amsterdam. Following the Scientific Advisory Committee's positive evaluation of the ACS in 2013, the decision was made to slim down the follow up of DU. This process was set in motion in January 2014. Four subgroups are still being followed at bi-annual visits with blood testing and sample collection, as in the years before: all HIV-positive DU, all HCV seroconverters, all HIV-negative and HCV-negative DU who have injected for more than 2 years and who are therefore more likely to have been exposed to HIV and/or HCV (multiple-exposure group), and a small control group of HIV-negative DU (non-multiple-exposure group). The remaining DU visit the GGD Amsterdam once a year to complete questionnaires without testing and blood sampling. At the same time, the group of HIV-negative MSM was expanded by 64 new participants in 2015, with the aim of having approximately 750 HIV-negative participants in active follow up by the end of 2016. The recruitment also included special efforts to include younger MSM in the ACS.

The HIV-infected MSM included in the ACS remain in active follow up. This follow up takes place primarily through the regular HIV medical care and through monitoring by SHM. In addition to the standard medical care, study samples are collected and stored for specific immunological and virological studies. These samples are collected from HIV-negative individuals, HIV seroconverters who became infected during the ACS follow up, and individuals who were already HIV-infected at inclusion in the ACS.

As of 31 December 2015*, 2,713 MSM and 1,680 DU were included in the ACS. Since the start of the ACS, MSM have visited the GGD 56,181 times and DU have visited the GGD 28,002 times. In 2015, 763 MSM, 108 of whom were HIV-positive, were actively followed by the GGD. Of these participants, 64 were newly recruited. A total of 191 DU (24 HIV-positive) were in active follow up at the GGD in 2015; there were no new inclusions in this group in 2015, and 8 participants died that year. The preliminary HIV incidence in 2015 was 0.41 per 100 person years among MSM, and there were no new HIV infections among DU. These figures may still change as collection of data for 2015 is not yet complete.

** Total numbers for 2015 were still being collected and were not yet complete at time of printing.*

Collaborations

Stichting HIV Monitoring (SHM) participates in both national and international scientific research collaborations. An overview of these collaborations is provided below.

National collaborations

AMC–UvA

SHM collaborates with the Academic Medical Centre (AMC) of the University of Amsterdam (UvA) on various projects. Led by Prof. Peter Reiss (Department of Global Health (a subdivision of the Department of Infectious Diseases), AMC, Amsterdam, and director of SHM), the *Co-morbidity and Aging with HIV* (AGEhIV) cohort study 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 compared with non-HIV-infected individuals. Another collaboration closely associated with the AGEhiV cohort study, is the COBRA (*Co-morbidity in relation to AIDS*) programme, which aims to further investigate these issues in collaboration with a number of European partners, for example by identifying reliable biomarkers of comorbidity and ageing in the context of HIV. As a COBRA partner, SHM collaborates with the AMC and provides 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 ageing HIV-infected individuals.

SHM also makes a contribution in terms of expertise in methodology and data management to the *HIV Transmission Elimination Amsterdam* (H-Team) project, led by the Amsterdam Institute for Global Health and Development and the department of Global Health at the AMC. The project is a multidisciplinary and interdisciplinary collaboration involving various stakeholders from preventative and curative HIV care and from other target groups (including Public Health Service Amsterdam (*Geneeskundige en Gezondheidsdienst Amsterdam*; GGD Amsterdam), SOA Aids Nederland, Dutch HIV Association (*Hiv vereniging Nederland*), Amsterdam hospitals, Maastad Ziekenhuis in Rotterdam, Leids Universitair Medisch Centrum, Erasmus MC, and the National Institute for Public Health and the Environment) that aims to reduce the number of new HIV infections in Amsterdam.

In addition to these activities, SHM collaborates with the AMC, together with OLVG and Leids Universitair Medisch Centrum (LUMC), on the Quality of Care programme. This programme, for which SHM was awarded an Aids Fonds grant in 2012, aims to investigate the determinants (patient, medical professional and hospital-related) that lead to a higher quality of care. The Quality of Care programme has been under the direction of Prof. Suzanne Geerlings (AMC) since 2013.

CIb-RIVM

The Centre of Disease Control of the Netherlands National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu*; CIb-RIVM), headed by Prof. Jaap van Dissel, uses data collected by SHM to coordinate data on the registration of new HIV infections within the framework of the national HIV registration and surveillance programme.

SHM's registration activities are closely associated with the CIb with 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 renewed an agreement at the beginning of 2009 to exchange data collected through the SHM framework for purposes of surveillance carried out by the CIb-RIVM.

GGD Amsterdam

SHM contributes to the *MSM Observational Study of Acute Infection with Hepatitis C* (MOSAIC) coordinated by the GGD Amsterdam. The MOSAIC study involves a cohort of men who have sex with men (MSM) with chronic HIV infection who have contracted an acute hepatitis C (HCV) infection. The aims of the study are to look at how this group contributes to the transmission of HIV; to explore the driving factors of the HCV epidemic and HIV's role in it; and to examine 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 this report), in collaboration with the AMC-UvA. The ACS is primarily funded through the CIb-RIVM and, as of 1 January 2015, the funding is included in the structural institute grant awarded to SHM by the CIb-RIVM.

Harmonic

Harmonic is a collaboration launched in 2014 between two HIV/hepatitis treatment centres in the Netherlands, UMC Utrecht and Rijnstate in Arnhem, and SHM to compare patients with a hepatitis B (HBV) mono-infection with those with HIV/HBV co-infection. This retrospective study aims to compare the natural course of HBV, the morbidity and mortality associated with the infection, and the effect of treatment between mono-infected and HIV co-infected patients. SHM contributes to *Harmonic* by making data available on HIV/HBV co-infected individuals registered in SHM's database, and by implementing the data collection of HBV mono-infection at both study sites. Furthermore, SHM provides database management, data sets for analysis, and contributes analytic and scientific support and supervision.

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International collaborations

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 subgroups.

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 combination antiretroviral therapy (cART), according to markers of virus variability (specific mutations, subtypes), with relevance to the drugs in the regimen.

EuroCoord was funded for a period of 5 years from 2011 as part of the European Commission's Framework Programme 7. Funding for EuroCoord and associated collaborations therefore ceased on 31 December 2015.

COHERE

The *Collaboration of Observational HIV Epidemiological Research in Europe* (COHERE) is a unique collaboration of 33 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 to 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. COHERE is part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV.

An overview of papers published by COHERE in 2015 can be found under 'Scientific output in 2015'.

CASCADE

Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) was established in 1997 as a collaboration between 25 cohorts of documented HIV seroconverters from 15 European countries, Australia, Canada and Africa. CASCADE's main aim is to monitor the course of HIV infection from the time of infection onwards. By pooling data, issues can be addressed that cannot be reliably addressed from single studies alone. The Amsterdam Cohort Studies (ACS) participates in this study through their HIV seroconverted participants. CASCADE is part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV.

An overview of papers published by CASCADE in 2015 can be found under 'Scientific output in 2015'.

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 Netherlands is represented through the participation of the AMC in Amsterdam. At the request of the principal investigator of EuroSIDA in the AMC, Prof. Peter Reiss, SHM collects data from the AMC in Amsterdam for EuroSIDA. EuroSIDA is part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV.

An overview of papers published by EuroSIDA in 2015 can be found under 'Scientific output in 2015'.

EPPICC

The *European Pregnancy and Paediatric HIV Cohort Collaboration* (EPPICC) conducts epidemiological research on the prognosis and outcome of HIV infections in pregnant women and children, as well as in children exposed to HIV *in utero*, across Europe. EPPICC currently consists of 13 studies, including the *European Collaborative Study* (ECS). As the number of children infected with HIV in Europe is relatively small, a single network running paediatric trials and cohorts is essential to efficiently answer research questions in this population. EPPICC is part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV. Within EuroCoord, EPPICC is part of the HIV in children collaboration, *Paediatric European Network for Treatment of AIDS* (PENTA).

An overview of papers published by EPPICC in 2015 can be found under 'Scientific output in 2015'.

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

A Collaboration on HIV-2 Infection (ACHIEV2$_E$) 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 found mainly 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 combination antiretroviral therapy (cART) in therapy-naive patients. In 2015, Prof. Peter Reiss and Dr Ard van Sighem represented SHM in the ART-CC steering group. ART-CC has financial support from the Medical Research Council of the United Kingdom.

An overview of papers published by ART-CC in 2015 can be found under 'Scientific output in 2015'.

D:A:D

The *Data Collection on Adverse Events of Anti-HIV Drugs* (D:A:D) is a prospective multi-cohort study that focuses on the potential association between antiretroviral drugs and cardiovascular disease, liver and renal disease, and non-AIDS-defining malignancies. Prof. Jens Lundgren (Rigshospitalet & University of Copenhagen) coordinates the study, and Prof. Peter Reiss is the principal investigator on behalf of SHM/ATHENA.

An overview of papers published by the D:A:D study in 2015 can be found under 'Scientific output in 2015'.

DIDE

The Department of Infectious Disease Epidemiology (DIDE) is part of the Faculty of Medicine, Imperial College in London. Prof. Christophe Fraser coordinates the collaboration with SHM. The 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 HIV.

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 2015, 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 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.

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 healthcare 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.

An overview of papers published by HIV-CAUSAL in 2015 can be found under 'Scientific output in 2015'.

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), as well as other clinical and laboratory factors and response to HIV drug therapy, on the basis of which computational models are developed to help physicians and their patients select the best individualised combination of drugs in situations where resistant measurements are not possible.

Dissemination

SHM actively disseminates data and information about its activities through a wide variety of communication channels. In doing so, we aim to provide information to people living with HIV, their health care providers, researchers, other health care professionals, the media and other interested parties.

Monitoring Report 2015, HIV Infection in the Netherlands

Each year, SHM publishes a monitoring report just before December 1, World AIDS Day. The HIV Monitoring Report is written by SHM researchers, in close collaboration with a small group of reviewers consisting of HIV treating physicians and experts in public health, whose in-depth knowledge on relevant chapter topics is highly valuable in shaping the content of the chapters.

The Monitoring Report presents major developments in the HIV epidemic in the Netherlands and describes the effects of treatment on the course of HIV infection and on the HIV epidemic, with data extending back to 1996. In addition, the Monitoring Report also describes trends in HIV-related and non-HIV-related morbidity and mortality, and includes a chapter dedicated to viral hepatitis. In 2015, this latter chapter presented up-to-date data on the effect of the new direct-acting antiviral agents in the treatment of hepatitis C co-infection in HIV-positive individuals. Another new addition to the Monitoring Report in 2015 was a chapter on quality of care in the 27 HIV treatment centres in the Netherlands, which examined a number of quality of care indicators. The main findings from the 2015 Monitoring Report are described in an earlier section of this report and were also presented at the *Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment* (NCHIV) by SHM director, Peter Reiss.

Online Monitoring Report

In 2015, in keeping with SHM's policy of reducing paper consumption, the decision was made to no longer publish the Monitoring Report as a printed book. Instead, the report was made available online on the SHM website, in a searchable and downloadable PDF that also included all appendix tables and figures. In addition, all figures and tables were made available in the form of a downloadable PowerPoint presentation on SHM's website. The Summary and Recommendations chapter of the report was, however, printed in both Dutch and English and distributed together with the updated infographics factsheet to all those who had previously received the full printed report. In addition, the printed Summary and Recommendations was included in the conference bags at NCHIV and at the national conference on sexually transmitted diseases and HIV (*Nationaal Congres Soa*Hiv*Seks*).

SHM website and eNewsletters

Regular website updates

During the course of 2015, the SHM website was updated on an ongoing basis. For example, news items about SHM or relevant to the field of HIV treatment and research were placed on the homepage at regular intervals, and presentations and publications involving SHM data were also kept up to date, together with approved and ongoing research projects. The website also provides a list of treatment centres and data collectors and data monitors responsible for these centres.

Quarterly eNewsletters

eNewsletters are sent out on a quarterly basis and appear to be well read, with average open rates of 51.3% and 47.3% for the Dutch and English-language newsletters, respectively. In 2015, the eNewsletters featured interviews with a number of national and international experts in the field of HIV, news about research collaborations and other developments within SHM, along with reviews of SHM data presented at international conferences. In 2015, we added a new item to the SHM newsletter, entitled *Spotlight on SHM research*. This item showcases a recent publication involving SHM data and is based on an interview with the first author. The English-language winter newsletter was also printed and distributed at NCHIV 2015. All newsletters are archived on the website and can be accessed via a direct link.

Internal communication

Intranet

In 2015, as part of ongoing efforts to further strengthen cohesion in the organisation, the communications department developed and launched the SHM intranet site in September. This externally accessible, password-protected site provides a central point of information for employees and contains up to date contact details, HR documents, standard templates, and internal news and events. In 2016, the intranet will be further expanded to include support documents for data collectors.

Internal newsletter

In 2015, the internal newsletter, entitled *SHM Positive: a collection of all the internal news*, was published five times and remains well-read. It continues to provide a channel through which all employees, including those working outside the SHM offices in Amsterdam, are kept up to date with internal developments and upcoming events.

Internal meetings

An internal meeting for all SHM employees is held on a bi-monthly basis. During this meeting, any internal developments are discussed and staff are brought up to date on recent scientific developments relevant to SHM's work, either by an invited speaker or one of SHM's researchers. Subjects covered in 2015 include the H-TEAM initiative, the AGEhIV

study, the ECDC tool to estimate HIV incidence, and regional differences in the HIV cascade of care in the Netherlands.

Patient leaflet and fact sheet

A simple explanation of SHM's activities and data collection process is provided in a patient leaflet that was developed in 2014. Produced in both Dutch and English, this leaflet illustrates how anonymous data provided by people living with HIV in the Netherlands help to drive further improvements in HIV care in the Netherlands through national and international research. The leaflet is accompanied by a factsheet insert that uses infographics to simply summarise the key figures from the latest Monitoring Report. Both the leaflet and fact sheet insert are intended for distribution to new patients by HIV treating physicians and HIV nurse consultants. A recent evaluation revealed that HIV treatment teams regard the leaflet and factsheet as a valuable communication tool.

Updated infographics factsheet

In 2015, the infographics insert was updated and distributed with the printed Summary and Recommendations of the Monitoring Report. The 2015 insert and the Summary and Recommendations were also included in conference bags at NCHIV 2015 and at *Soa*Hiv*Seks*. The leaflets and insert are available for download on the SHM website.

Events

During the course of 2015, SHM researchers and collaborators presented their work with SHM data at various international and national conferences and meetings. Further information on these presentations can be found later in the report.

Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV)

In 2015, SHM organised the 9th annual *Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment* (NCHIV), 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 Center of the University of Amsterdam (AMC-UvA) (Department of Global Health), and the Dutch Association of HIV-Treating Physicians (NVHB). NCHIV 2015 was attended by just over 280 participants. During the course of the day, there were 21 presentations, including an update on the HIV epidemic in the Netherlands by SHM director Peter Reiss and four plenary talks by pre-eminent guest speakers on topics such as PrEP, HIV cure research, modelling of HIV incidence and vaccine development. A total of 13 oral abstract presentations were also given on the pathogenesis, epidemiology, prevention and treatment of HIV and HIV/HCV co-infection. In addition, a moderated oral poster discussion took place on the theme of 'Test and PrEP' in which five poster presenters were invited to give a mini-presentation of their poster and subsequently participate in a moderated discussion. During the lunchtime poster session, 41 posters were presented for viewing.

World AIDS Day

On World AIDS Day, 1 December 2015, Stichting HIV Monitoring was present at the *Soa*Hiv*Seks* conference, with a stand providing information about SHM's activities. In addition, Peter Reiss presented highlights of NCHIV and SHM researcher, Ard van Sighem, gave a workshop on regional differences in the HIV cascade of care in the Netherlands.

Social media

During the latter part of 2015, efforts were increased to disseminate SHM news, in particular regarding recent publications, using LinkedIn. This will be continued and expanded in 2016.

Scientific output

In addition to its yearly Monitoring Report, SHM also contributes to the knowledge and understanding of the HIV/AIDS epidemic and the effect of antiretroviral treatment on the course of HIV infection and co-infections, including viral hepatitis, through research projects and scientific publications. In 2015, SHM cohort data was included in 49 publications in peer-reviewed international scientific journals and 75 oral and poster presentations at international and national peer-reviewed conferences, workshops and meetings. A full overview of the scientific output is included in a later section of this report.

Financial report

Income

In 2015, Stichting HIV Monitoring's (SHM) total income was € 4,390,646. The majority of this income came from the structural institute grant that the SHM receives each year from the Centre for Infectious Disease Control of the National Institute for Public Health and Environment (*Centrum Infectieziektenbestrijding van het Rijksinstituut voor Volksgezondheid en Milieu* (CIb-RIVM)) on behalf of the Ministry of Health, Welfare and Sport (*Ministerie van Volksgezondheid Welzijn en Sport* (VWS)). In addition, SHM participates in various national and international collaborations involving observational cohort studies, for which it receives additional funding.

Income for regular HIV monitoring activities in the Netherlands

SHM is a Ministry of VWS-recognised healthcare institute with a structural institute grant (VWS grants policy framework). SHM's governing board established that SHM required a structural institute grant of € 3,227,139 for HIV monitoring in 2015. The RIVM/Ministry of VWS awarded an institute grant of € 3,118,083. During the course of 2015, corrections totalling -€ 11,153 were applied to the wage-sensitive part of the institute grant of previous years. As such, the total structural institute grant allocated in the fiscal year of 2015 by the Ministry of VWS to SHM for monitoring HIV in the Netherlands was € 3,106,930.

Income from HIV monitoring-related collaborations

SHM's participation in international and national collaborations is highly important for both individual patients and quality of care. Individual registration and monitoring programmes (such as SHM) are often too small to adequately address certain questions regarding individual comorbidities and prognosis associated with large-scale HIV treatment. Collaborations that combine data from various cohorts make it possible to answer questions that cannot be addressed by individual cohorts, and are also an efficient way of providing more reliable insight into the long-term effects of HIV treatment. As such, participation in national and international studies is fully in line with SHM's mission and objectives. In 2015, SHM received € 1,218,565 as income from the HIV monitoring-related collaborations listed below. This income is € 26,045 (2.18%) higher than that earned through collaborations in 2014.

1. Amsterdam Cohort Studies (ACS)

SHM has been responsible for governing and administering the Amsterdam Cohort Studies (ACS) since 2005. Since 1984, the ACS has been carrying out multidisciplinary research into the epidemiology, psychosocial determinants, the natural course and pathogenesis of HIV-1 infection and, more recently, other blood-borne and sexually-transmitted diseases. The institutes involved in this collaboration make use of data and body samples provided by HIV-1 infected persons and persons at high risk of contracting HIV. Following approval of research proposals that involve collaboration with one or several ACS partners, external parties can also gain access to the data and stored body samples. The RIVM provides the ACS with an annual institute grant of € 500,000. In addition, the collaborating institutes, including the Academic Medical Centre of the University of Amsterdam (AMC-UvA),

the Public Health Service of Amsterdam (*Geneeskundige en Gezondheidsdienst*, GGD), and SHM make a financial contribution to the coordination, management and financial management costs. The GGD Amsterdam and the AMC-UvA each contribute individually to the storage of patient data and samples.

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 HIV treatment with antiretrovirals. SHM is a major partner in D:A:D in terms of the volume of data collected on adverse effects of treatment and non-AIDS comorbidities in registered patients for the benefit of the D:A:D study. Source data verification ensures that the validity of key endpoints is subject to 100% quality control. In addition, in line with SHM's data quality procedures, source data verification is used to check completeness and accuracy of selected data. As such, SHM's participation in this study contributes significantly to further improving the quality of the entire collection of data on HIV complications and comorbidity in the Netherlands.

In 2015, SHM contributed for the sixteenth time to the data merge and received € 452,012 in compensation for this activity from the organisation that coordinates the D:A:D study, the Rigshospitalet, University of Copenhagen in Denmark. D:A:D has been made financially possible by the Oversight Committee for the Evaluation of Metabolic Complications of HAART to which various pharmaceutical manufacturers of antiretroviral compounds make a financial contribution on request by the European Medicines Agency. The D:A:D funding is based on the number of person years added by SHM.

For the registration and validation of endpoints collected specifically for the D:A:D study, SHM received an additional fee of € 67,813 in 2015. In 2011, a change was made to how HIV treatment centres were compensated for their work in registering D:A:D events. Consequently, as a precaution, a sum was reserved to cover payments that might still have to be made despite this change. This reserved sum of € 110,477 was released in 2015.

3. EuroSIDA

SHM participates in the EuroSIDA study within a European context. EuroSIDA is a collaboration between clinical cohorts and individual treatment centres distributed throughout Europe (including eastern Europe). The Netherlands is involved in this collaboration through the SHM's role in facilitating the provision of data from a small group of patients from the AMC-UvA. EuroSIDA carries out research into a broad range of clinical issues relating to HIV, making it possible to compare specific regional differences between centres throughout Europe. For its participation in the EuroSIDA study in 2015, SHM received a payment of € 1,495. The knowledge that SHM gains through its participation in EuroSIDA is also valuable in terms of improving the national data collection by SHM in the Netherlands.

4. European Centre for Disease Prevention and Control (ECDC)

The ECDC awarded SHM a grant of € 23,333 for the project entitled 'Improving tools to estimate HIV prevalence in EU/EAA countries'. This two-year project (January 2013 through to January 2015), coordinated by SHM, is a collaboration with the University of Bern, Switzerland, University College London, Imperial College, and the MRC Biostatistics Unit, UK. The project developed methods to improve the reliability of estimates of HIV prevalence and incidence in different European countries. This participation also improved the ability to make such estimates in the Netherlands.

5. Aids Fonds

SHM has received a grant from the Aids Fonds for a project entitled 'Controlling the HIV epidemic'. In 2015, the contribution was € 12,500. SHM has appointed a PhD student for this project, with the aim of developing a mathematical individual-based model to describe the HIV epidemic in various risk groups in the Netherlands. This model should provide greater insight into the factors that drive new HIV infections. Furthermore, it will be possible to study the effect of intervention strategies on the prevention of new HIV infections. In this way, this study should improve our understanding of the course of the HIV epidemic in the Netherlands and give insights into how to fight the HIV epidemic in the Netherlands.

6. EuroCoord

In 2015, SHM received a sum of € 29,851 from EuroCoord. SHM's participation in EuroCoord improves harmonisation between data from HIV cohorts in Europe, including SHM's data. This, in turn, improves the quality of international collaborations since certain research questions can only be studied by combining databases from several HIV cohorts (including that of the Netherlands).

7. Comorbidity in relation to HIV/AIDS (COBRA)

In 2015, SHM received a payment of € 3,093 from the COBRA study. This project is financed by the European Union's 7th framework programme and SHM is one of the 12 COBRA partners in Europe. SHM's main contribution involves data management and analyses for COBRA. The study focuses primarily on investigating whether the reported ageing-related comorbidities are more common and possibly occur at a younger age in HIV-infected persons compared to non HIV-infected persons. In addition, in-depth research is being done into the various underlying mechanisms, including those associated with HIV infection as well as those associated with the use of antiretroviral treatment. The knowledge acquired from this project will help SHM in establishing priorities for collecting national comorbidity data. Furthermore, the results of the COBRA study may contribute to improving the prevention and treatment of comorbidities in HIV-positive persons.

8. European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

For SHM's contribution to EPPICC, SHM received a sum of € 17,992. EPPICC carries out epidemiological research throughout Europe into the prognosis and outcomes of HIV-infected pregnant women and children, as well as children exposed to HIV *in utero*. Currently, EPPICC comprises 13 studies, including the European Collaborative Study (ECS). Due to the relatively small number of children living with HIV in Europe, it is essential to combine the data within a single network to efficiently address questions arising within this population.

9. Other income

In total, SHM received € 65,151 from other sources of income. Part of this income arose from salary expenses charged (€ 29,742) by SHM to HIV treatment centres to cover the costs of assistance provided by SHM for the collection and entering of anonymised patient data. SHM staff are also involved in organising the Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV) and the associated salary expenses (€ 23,002) are charged to Stichting NCHIV. Finally, data management work carried out on behalf of the H-TEAM project resulted in an income of € 9,221.

Expenditure

In 2015, the total expenses of Stichting HIV Monitoring were € 4,022,448. Three different types of expenses for 2015 are outlined below:

1. **Personnel costs**

   At € 2,280,173, personnel costs once again represented the largest expenditure for SHM in 2015. As per 31 December 2015, SHM had a total of 46 employees (an average of 36.51 FTEs). This number does not include employees of HIV treatment centres that carry out their own data collection and for which the treatment centres receive a payment from SHM.

2. **Material costs**

   In addition to personnel costs in 2015, SHM incurred material costs such as depreciation of automation equipment, database licenses, maintenance of the national HIV monitoring database, data management and other operational costs. In 2015, material costs amounted to € 731,034.

3. **Payments**

   Amsterdam Cohort Studies payments

   In line with the budget, the funding (€ 500,000) assigned by the RIVM to the ACS is transferred by SHM to the GGD Amsterdam and the AMC. SHM does not charge the ACS any management costs.

   Payments to HIV treatment centres

   In 2015, HIV treatment centres received a payment of € 59.08 per patient, based on the number of patients in active follow up on 31 December 2014. In 2015, a number of hospitals requested SHM to provide assistance in data collection. The associated costs were deducted from the payment made by SHM to the hospitals in question for patient data collection and entry. In addition, HIV treatment centres received a sum as a contribution towards the costs of collecting and storing patients' plasma. Sixteen treatment centres have transferred the role of data collection to SHM.

   In total, in 2015 SHM paid the HIV treatment centres € 498,162 for patient data collection and entry and storage of patients' samples.

   D:A:D event payments

   As part of the D:A:D study, physicians are required to complete Cause of Death (CoDe) forms. SHM paid HIV treatment centres € 13,080 for this work.

Operating result

The operating result (€ 400,472) indicates that the total costs in 2015 remained well within SHM's income for 2015. Contributions from the D:A:D study make up a large portion of this addition to the reserves.

Reserves

The total financial reserves of SHM (including the deferred grant revenue, general reserve and earmarked reserves for investment) amounted to € 3,945,515 on 31 December 2015.

1. **Deferred grant revenue**
   The deferred grant revenue amounted to a positive balance of € 170,690 on 31 December 2015. This amount includes the positive 2015 result for HIV monitoring in the Netherlands. The deferred grant revenue is intended to guarantee operational continuity over a certain period of time.

2. **General reserve**
   From 2002 through 2007, SHM built a general reserve of € 382,206. This sum arose through financing from the Healthcare Tariffs Board *(Tarieven Gezondheidszorg)* and, later, the Dutch Healthcare Authorities *(Nederlandse Zorgautoriteit)*.

3. **Earmarked reserves for HIV-related projects**
   As per 31 December 2015, a total of € 3,392,619 has been reserved for HIV-related projects.

Continuity reserves as of 31 December 2015

To cover the financial obligations and risks, SHM must have a sufficiently large continuity reserve. The governing board has decided that, based on SHM's obligations and risks, the target necessary for the continuity reserve should be € 1.5 million.

Risk disclosure

SHM's governing board and director are primarily responsible for avoiding and detecting fraud, ensuring that legislation is adhered to, and identifying any risks that may pose a threat to SHM. It is important that the management of SHM, under the auspices of those responsible for governance, devote the necessary attention to these risks. This approach requires the commitment to develop a culture of integrity and ethical conduct, and can be reinforced by active supervision. As such, SHM's governing board maintains a culture of honesty and ethical conduct and has taken management measures to limit SHM's risk as far as possible.

Risk management measures

SHM strives to foster a culture of respectful and honest conduct; such a culture forms the foundation for preventing fraudulent conduct of any kind. Moreover, SHM has taken certain measures, both soft and hard, to maintain this culture.

One of SHM's core values is respectful conduct towards external parties and between employees themselves. As such, employees are supported in displaying appropriate behaviour, not only through management leading by example, but also by means of various active protocols and procedures. For example, SHM has a code of conduct to which all employees have access and that includes protocols and procedures on issues such as integrity, privacy, IT use, and reporting abuse, or use for private purposes, of SHM property. Furthermore, SHM has an appointed confidential mediator to whom employees can turn with personal concerns and to report incidents, including fraudulent conduct.

This culture and the measures taken to maintain this culture are an important part of SHM's risk management. Moreover, further risk management measures have been taken in response to a number of risks identified by the board. An internal analysis of the most important of these risks has been carried out, and appropriate mitigating measures have been taken for each identified risk to minimise any remaining risk.

2016

Board resolutions

The present database used by SHM for patient data entry is Oracle Clinical. The Clinical Research Unit (CRU) of the Academic Medical Center (AMC) is responsible for the licences and management of the database. In the spring of 2014, the AMC announced that it would be discontinuing some of these services in the near future, including database management. In anticipation of these developments, SHM therefore defined a project to identify a suitable alternative to the Oracle Clinical database.

The project plan sits well within SHM's innovation programme that was initiated in 2013 and, in line with ICT developments taking place within the electronic patient record systems in HIV treatment centres, presents opportunities for modernising and future-proofing SHM's data collection process.

On the basis of recommendations by Nictiz (the government-financed organisation that aims to assist healthcare organisations in improving IT systems), SHM put out a tender in the beginning of 2014 to select an IT service provider to assist in replacing the data entry database. This tender led to the selection of Furore (IT service provider in the field of care, cure and science) and they were tasked with assisting in identifying a suitable replacement for Oracle Clinical. These steps should lead to an improvement in efficiency, in part by reducing manually collected data as far as possible and maximising automated data collection.

During its November 2015 meeting, SHM's board requested the Data and QC unit manager to draw up a business case for the above-described project, detailing considerations, alternatives, benefits and disadvantages, and risks associated with the proposed choice of system, along with the anticipated investment sum, structural costs and efficiency benefits. The risks and associated risk management measures should also be part of the proposal. The board is expected to make a decision regarding the investment in the spring of 2016.

During the period 2015 through to 2017, a total sum of € 1,300,000 has been budgeted for this project. This includes costs of identifying the most suitable system, constructing this system, the migration of historical data and the purchase cost of the new system.

Grants/financial contributions

D:A:D (*Data Collection on Adverse events of Anti-HIV Drugs*) is an international study into the occurrence of adverse events associated with the use of combination antiretroviral therapy. SHM receives a payment on behalf of the D:A:D study to facilitate the addition of data to this European and international scientific collaboration. In addition, SHM receives a financial contribution, paid annually by the University of Copenhagen in Denmark, for each reported D:A:D event.

The contract for these two grants runs until October 2016 and data collection for the purpose of the D:A:D study ended as of 1 February 2016. The 2016 budget includes € 375,000 and € 37,500 for the D:A:D study and D:A:D events, respectively.

Number of staff

The budgeted number of SHM staff for 2016 is equivalent to 41.58 FTEs. Compared with the 2015 budget, this represents an increase of 1.08 FTEs and, compared to the financial statements for 2015, it represents an increase of 5.07 FTEs.

Due to the increasing number of patients, various departments have included vacant positions in their budget: 1.47 FTEs in the department of Patient Registration and Data Collection, 1.55 FTEs in the department of QC and Protocol Management, and 0.38 FTE in the department of Data Management. Furthermore, to ensure optimal support for the growing organisation, a vacancy of 0.4 FTE has been included in the budget for the department of Office and Secretariat.

In total, the 2016 budget includes € 320,897 more for personnel costs than the actual personnel costs in 2015 (€ 2,601,070 in 2016 versus € 2,280,173 in 2015). Compared with the 2015 budget, personnel costs have risen by € 104,059. The increase in the number of staff that was planned in 2015 will be implemented in 2016.

Expenses

Other operational costs in 2016 have been primarily budgeted in line with the actual costs incurred in 2015. The main increase in expenses is the above-described development of the data entry database. The 2016 budget includes € 177,500 for licences. The remaining investment in the project (€ 560,000) will be written off over a period of 5 years and will be included in the depreciation costs from the 4th quarter of 2016 onwards. As part of this project, in 2015, a sum of € 98,500 was paid for the proof of concept, the requirements phase and Furore. The expected total cost of the Oracle Clinical replacement project is € 1.3 million.

The Amsterdam Cohort Studies (ACS) grant of € 500,000 that is paid to SHM by the RIVM/ Ministry of VWS, will be paid out fully to the two organisations that carry out this study, namely the AMC and the GGD.

As of 2015, payments to the HIV treatment centres have been calculated according to a more accurate method. By ensuring that the costs better reflect the actual costs incurred, it has been possible to reduce the payments. For 2015, a payment of € 498,162 will be made and, for 2016, the projected payment is € 487,500.

Balance sheet after appropriation of profits

Assets	31 Dec 15 (€)	31 Dec 14 (€)
Fixed assets		
Tangible fixed assets	9,096	19,175
Total fixed assets	**9,096**	**19,175**
Current assets		
Receivables and accrued assets	229,636	359,923
Liquid assets	4,695,234	4,324,892
Total current assets	**4,924,870**	**4,684,815**
Total assets	**4,933,966**	**4,703,990**

Liabilities	31 Dec 15 (€)	31 Dec 14 (€)
Capital reserves		
Deferred grant revenue	170,690	69,247
General reserve	382,206	382,206
Earmarked reserves	3,392,619	3,093,593
Total reserves	**3,945,515**	**3,545,046**
Provisions		
Sick leave and work disability provision	127,400	0
Short-term liabilities		
Short-term liabilities and accrued expenses	861,051	1,158,944
Total liabilities	**4,933,966**	**4,703,990**

Profit and loss account

Profits	2015 (€)	2014 (€)
Total grants	3,606,930	3,622,335
Financial contributions	718,565	692,520
Other revenue	65,151	59,572
Total net revenue	**4,390,646**	**4,374,427**
Operating costs		
Personnel costs	2,280,173	2,214,179
Depreciation of tangible fixed assets	10,082	11,451
Other operating costs	655,220	729,822
Other project-related operating costs	65,731	17,896
Payments Amsterdam Cohort Studies	500,000	500,000
Payments HIV treatment centres	498,162	654,460
Payments D:A:D events	13,080	14,367
Total operating costs	**4,022,448**	**4,142,175**
Year result	**368,198**	**232,252**
Financial profit and loss		
Interest and similar income	33,362	30,009
Interest and similar expenses	1,088	1,121
Total financial profit and loss	**32,274**	**28,888**
Year result	**400,472**	**261,140**

2016 budget

Profits	2016 (€)
Total grants	3,621,987
Financial contributions	438,160
Other operating revenue	45,000
Total net revenue	**4,105,147**
Operating costs	
Personnel costs	2,601,070
Depreciation of tangible fixed assets	42,981
Other operating costs	824,162
Other project-related operating costs	0
Payments Amsterdam Cohort Studies	500,000
Payments HIV treatment centres	487,500
Payments D:A:D events	20,000
Total operating costs	**4,475,713**
Operating results	**-370,566**
Financial profit and loss	
Interest and similar income	25,000
Interest and similar expenses	1,200
Total financial profit and loss	**23,800**
Year result	**-346,766**

Note: *The 2016 financial results will be influenced by incidental investments and costs related to an IT project.*

Scientific output 2015

In 2015, Stichting HIV Monitoring (SHM) received 12 new requests to make use of SHM's cohort data. During the year, 49 articles were published in international peer-reviewed journals. In addition, 75 abstracts were accepted for presentation at 15 meetings and conferences (48 posters and 27 oral presentations). An overview of research projects, publications and presentations can be found on our website, *www.hiv-monitoring.nl*.

Completed research projects

I13087 Dutch protease for hepatitis C in HIV-infected patients – study (DECIDE-study)

Arends J, Hoepelman A, Brinkman K, van der Meer J, van de Ende I, Richter C, Schippels E, de Vries-Sluijs D, Schinkel J, Smit C.

I13153 Factors associated with late diagnosis of HIV in the Netherlands

Op de Coul E, van Sighem A, Brinkman K, van der Ende M, Geerlings S, Reiss P for the ATHENA national observational HIV cohort.

I14082 HIV testing and counselling in general practices in the Netherlands

Op de Coul E, van den Broek I, Joore I, Reukers D, van Bergen J, van Sighem A.

I15121 Phylodynamic and phylogeographic patterns of sub-subtype F1

Van Laethem K, Vinken L, Pineda-Peña A, Vandamme A, Lemey P, Fransen K, Vancutsem E, Verhofstede C, Ruell J, Debaisieux L, Van den Wijngaert S, Sayan M, Alexiev I, Paraschiv S, Devaux C, Gomes P, Peeters M, Incardona F, Balotta C, Lai A, Bezemer D.

As this research proposal overlapped with Dr Wensing's research programme, an adaptation of the submitted proposal was requested on 17 December 2015. To prevent any further delay, it was decided to complete the study without the inclusion of sequences from SHM.

Ongoing research projects

I04034 The data collection on adverse events of anti-HIV drugs (D:A:D)

Reiss P.

Date of approval: 2000

Background: The study was conceived in 1999 and, since its start in 2000, has continued to successfully follow close to 50,000 patients from 11 cohorts in Europe, Australia and the United States. Currently the study has accrued around 339,000 person years of follow up.

Methods: The study continues to successfully meet the aim to delineate the relationship between the use of antiretroviral drug classes as well as individual drugs on the one hand, and the risk of myocardial infarction, and the additional comorbidity endpoints of end-stage renal disease, chronic severe liver disease and non-AIDS malignancies on the other hand.

Results: The results from the study are regularly presented at major international conferences, published in high-ranking peer-reviewed journals, and also continue to inform and influence changes in national and international HIV treatment guidelines. All presentations and publications, including the most recent, can be found on www.cphiv.dk (under the tab ongoing studies and then D:A:D).

Conclusions: In spite of the study having been highly productive and having generated influential and important findings, it will formally end on 1 February 2016 given the decision by the D:A:D Oversight Committee not to approve continued funding for the study group's proposal beyond this date. Thus, for the moment, the final data merge will be executed this summer on data and validated clinical events accrued up to 1 February 2016.

I005513 HIV resistance response database initiative (RDI)

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

Date of approval: 1 October 2005

The main activities of the RDI during 2015 using ATHENA data were as follows:

1. The development of new global computational models to predict virological response to treatment including the use of genotype.

Background: It is critical that the models used to make the predictions of treatment response in the RDI's online HIV Treatment Response Prediction System (HIV-TRePS) are regularly updated to reflect current clinical practice. Here we developed new models that include a genotype in their input variables to predict response.

Methods: Random forest models were trained to predict the probability of virological response to therapy (<50 copies HIV RNA/mL) following virological failure using the following data from 15,130 treatment change episodes: baseline viral load and CD4 count, baseline genotype (62 mutations in RT and protease taken from the IAS-USA 2014 list) treatment history, drugs in the new regimen (including elvitegravir for the first time), time to follow up and follow-up viral load. The models were assessed during cross-validation and with an independent global test set of 750 cases. The models' accuracy was evaluated in terms of the area under the ROC curve (AUC), sensitivity, specificity, and overall accuracy, using the optimum operating point developed during cross validation as the cut-off for predictions of response and failure. The accuracy of the models as predictors of response was compared to that of genotyping with rules-based interpretation.

Results: The models achieved AUCs of 0.85 - 0.89 (mean of 0.87) during cross validation and 0.84 with the global test set. The sensitivity was 79% during cross validation and with the global test set. Specificity was 79% during cross validation and 74% in testing. Overall accuracy was 79%, 76%. Genotyping with rules-based interpretation achieved AUC values of 0.57 (ANRS), 0.58 (Stanford HIVdb) and 0.55 (REGA).

Conclusions: These are the most accurate models developed to date and for the first time can predict responses to regimens including elvitegravir.

2. The development of two-stage cluster random forest models to improve prediction of virological response to HIV therapy.

Background: Human immunodeficiency virus (HIV) infection is treated with combinations of drugs and when treatment fails, a new combination has to be carefully selected to re-suppress the virus. While drug resistance tests can provide some guidance, machine-learning models trained from large clinical datasets are significantly better predictors of therapy response, even without drug resistance data. However, these have reached a ceiling of around 75% accuracy, independent of dataset size. Here we explored a two-stage cluster modelling methodology in an attempt to improve predictive accuracy.

Methods: We trained standard models using 29,524 treatment change episodes (as described in study 1 above). We then divided the dataset into clusters of similar data and trained additional models from each cluster. For independent test cases, we used a prediction of treatment response from the standard model to allocate them to the appropriate 'cluster model' for a final prediction.

Results: To date the results achieved by this two-stage cluster methodology have not shown any improvement over the 'standard' one-stage random forest modelling. Exploration of this method continues.

I08115 Proposal for collaboration and data exchange between HMF and RIVM for nation HIV/AIDS surveillance and data transfer to ECDC in the context of EU obligations for reporting on HIV/AIDS

Op de Coul E, de Wolf F, Vlugt J, van Sighem A, van der Sande M.

Ongoing.

I10021 Characteristics of HIV-1 transmission among men having sex with men in the Netherlands

Ratmann O, van Sighem A, Bezemer D, Reiss P, de Wolf F, Fraser C, Pettersson A, Schutten M, Bierman W.

Date of approval: 1 May 2010

Background: In the Netherlands, the age at diagnosis amongst men having sex with men (MSM) has been continually increasing from 37 years in 1996 to 41 years in 2013. This challenges the perception that young, high-risk MSM are the predominant source of infection in high-income countries. Using in depth records from the Netherlands' ATHENA HIV observational cohort, we previously identified and characterised 617 transmission events to MSM with evidence for recent infection (12 months) at time of diagnosis. Here, we use this cohort to evaluate the sources of the ongoing MSM epidemic in the Netherlands by age, date of birth, and diagnosis status.

Methods: 903 probable transmitters to 617 recipients with date of diagnosis between 1996 and 2010 were identified through phylogenetic analysis. Demographic and clinical data from the ATHENA cohort were used to characterise these transmission

events in detail. Statistical modelling adjusted for sampling and censoring biases. The proportion of transmissions attributable to age groups was calculated by averaging individual-level viral phylogenetic transmission probabilities across recipients. Limited sequence coverage required us to restrict this multivariate analysis to 509 transmission events between 2004 and 2010.

Results: The estimated proportion of transmissions from young men aged <28 years increased substantially from 2004-2007 to 2008-2010. More than an estimated 80% of the transmissions in 2008-2010 from <28 year olds originated from undiagnosed MSM. We also estimated transmissions between age groups. Transmissions were not concentrated within age groups. Further, transmission dynamics appear to have shifted substantially over calendar time. Men aged <28 years continued to be infected from older men, and transmitted increasingly amongst peers as well as older men.

Conclusions: Young men appear to be increasingly linked within the MSM epidemic in the Netherlands and appear to infect relatively more, older men than previously. The increasing age at diagnosis is a consequence of complex and changing transmission dynamics by age. Sensitivity analyses to validate the estimated contribution of transmissions from different age groups are ongoing.

I12045 An HIV-1 genome wide association study to identify viral determinants of HIV-1 plasma concentration (BEEHIVE)

Fraser C, Cornelissen M, Gall A, Berkhout B, Kellam P, Gras L, van Sighem A, de Wolf F.

Date of approval: 19 September 2012

The first phase of the Bridging the Epidemiology and Evolution of HIV in Europe (BEEHIVE) collaboration included 1) testing the logistics of stored serum/plasma samples from patients selected for inclusion in the study of virulence factors associated with severity of infection and 2) testing the efficacy of HIV RNA isolation procedures needed for whole genome sequencing. Procedures have been developed to support these logistics, and the most productive and efficient isolation procedures have been selected. The very first sequencing results were available at the end of 2012 and, at the same time, the study entered a second phase that continued in 2013. During this second phase, 593 samples from 5 associated virology laboratories in the Netherlands were located and transported. Viral RNA was isolated by the laboratory for Experimental Virology at the AMC in Amsterdam and was subsequently sent to the Wellcome Trust Sanger Institute, where a number of whole genome sequences have successfully been obtained. Progress was made on developing a pipeline for generating whole HIV genomes from the short read output from the sequencing. Construction of a database holding clinical and sequence data was completed. Other international cohorts with samples obtained from individuals with a reliable estimate of moment of infection were asked to join BEEHIVE. A kick-off meeting was held in Greenwich, London, UK, 21-22 October 2014 with investigators from contributing cohorts and experts on phylogenetics, molecular evolution and epidemiology. In 2015, we continued the inclusion of samples from other European cohorts (French cohort (n=441), Swiss cohort

(n=1,053)). At the end of 2015, in total 2,358 isolated RNA samples had been sent to Sanger for sequencing. To detect significant 'motifs' that have a moderate influence on set-point viral load, one of the main objectives of the BEEHIVE study, approximately 2,750 whole viral genomes are needed. Therefore samples from a German cohort (n=361) will be included together with the samples from additional HIV-1 treatment centres in the Netherlands, for which patient's informed consent had to be obtained. Preliminary results with the first 802 whole genomes of HIV isolated from three countries: France, the Netherlands and the UK, resulted in more accurate molecular clock calculations. Results also showed that there is an increasing variance in virulence over time. Dual infections with two strains of HIV were present in 60-80 individuals (7.5-10%); an 18% increase in infectiousness in these patients was seen together with 1.35 years faster disease progression.

I13032 Combined and comparative analysis of virulence trends across multiple cohorts

Herbeck J, Müller V, de Wolf F, Bezemer D.

Date of approval: 25 May 2013

Background: We have shown an increase over time of the HIV plasma concentration at viral set-point. Monitoring of these changes is critical, since such an increase may be indicative for increasing HIV virulence, which in turn would have implications for the treatment and prevention of HIV/AIDS.

Virulence is defined as the severity of disease; the virulence of a pathogen may evolve within a host population as the rates of transmission and host death are balanced. HIV is a unique model system for the study of virulence evolution, as its recent origin and high evolutionary potential suggest that it has adapted to humans rapidly. Whether HIV virulence has evolved, or is evolving still, can inform our understanding about past and possible future patterns of the HIV/AIDS pandemic.

Methods: The HIV Virulence Trends Working Group has been established, within which large scale data analysis together with mathematical modelling aims to inquire about past virulence trends and to predict future virulence trends. The Working Group is an initiative of scientists from the University of Washington School of Medicine, Seattle and Eötvös Loránd University, Institute of Biology, Budapest. In order to accomplish the goal the group will: 1) bring together a collaborative network of HIV cohorts representing US, Europe and Africa to create a database of relevant clinical and epidemiological information; 2) assess whether the HIV virulence has changed over the course of the pandemic; 3) investigate whether variation in regional epidemiology explains discrepancies among previous HIV virulence studies; and 4) use mathematical modelling to predict future trends of HIV virulence, considering the effect of potential interventions, e.g., the effect of widely used HIV antiretroviral therapy. The results of this HIV Virulence Trends Working Group will inform public policy on past and future trends of HIV virulence.

Results: A combined dataset has been compiled. Analyses are currently underway.

I13051 aMASE: advancing migrant access to health services in Europe (EuroCoord work package 14: migrants and HIV) barriers for HIV prevention, testing and treatment service uptake by migrants in the Netherlands

Bil J, Prins M, Zuure F, Burns F, del Arno J.

Date of approval: 22 July 2013

Background: Migrants represent a significant group in the HIV epidemic across Europe. Many remain unaware of their HIV infection and migrants are more likely to be diagnosed late. Existing HIV testing and prevention strategies targeting migrant populations need to be enhanced and new strategies developed for new and emerging migrant populations. This study is part of a European research project (aMASE study within EuroCoord) which aims to prevent HIV infection and improve diagnosis and prognosis in migrant populations living with HIV by providing evidence to support policy development at European level. We aim to determine the likely country of HIV acquisition for migrant populations and identify barriers to HIV prevention, testing and treatment.

In the Dutch study arm we will focus on identification of barriers for migrants living in the Netherlands.

Methods: Data was collected via two surveys: The first targets HIV-infected migrants; recruitment took place at the HIV clinic (i.e., clinical survey). The second survey targets migrants in general, irrespective of their HIV status, and was disseminated via the Internet (i.e., community survey). All participants self-completed a questionnaire. In addition to the questionnaire, in the clinical survey, data about clinical indicators of HIV disease was collected (data source: SHM). The clinical survey is a multi-site study which took place in nine European countries. In the Netherlands, recruitment took place at three sites: 1) Academic Medical Center of Amsterdam (AMC), 2) OLVG in Amsterdam, 3) Medisch Centrum Haaglanden (MCH) in The Hague. In addition to the European study, in the Netherlands we also collected data from native HIV-positive patients to compare the results with those found among the migrant patients. The community survey was disseminated through non-governmental and community-based organisations in nine European countries including the Netherlands.

Results:

Clinical survey

Enrolment took place in three hospitals in the Netherlands. In total 40 migrants and 42 controls (HIV-infected patients born in the Netherlands that met the remaining aMASE inclusion criteria) were recruited and completed the aMASE questionnaire at the HIV outpatient clinic of the AMC in Amsterdam. Recruitment was stopped in the AMC in August 2014. Recruitment continued in the OLVG hospital in Amsterdam and in total 52 migrants and 72 controls were included. Finally, from March 2015 onwards, 32 migrants and 24 controls were enrolled in the Haaglanden Hospital in The Hague. In total 124 migrant and 138 controls patient were included in the three hospitals. Across Europe, a total of 2,117 patients were included.

Community survey
In 2013, the questionnaire for the community survey was developed together with the European partners. Dissemination of the community survey started in May 2014. Recruitment for the community survey involved various approaches, working closely together with these NGOs and the community. Throughout Europe, 1,782 participants were recruited, of which 134 in the Netherlands.

Conclusion: Data are currently being analysed for final publications, and abstracts have been sent for presentation at various conferences. Preliminary results from the European clinical survey show that a substantial proportion of HIV-positive migrants living in Europe acquired HIV after migration (54-62%). Post-migration HIV-acquisition is particularly high among migrant MSM (72%-73%) and injecting drug users (66%-77%), compared to heterosexual men (36%-46%) and women (36%-47%). Preliminary results from the European community survey show that a third of migrants within this sample had never tested for HIV. The most reported reason for not testing was a low risk perception. Missed opportunities for HIV testing continue to exist in primary care and other healthcare settings.

The final European results and the results of the Dutch data for the clinical and community survey are expected to be presented in 2016.

I13059 Clinical, immunological, virological and social outcomes of cART treated HIV infected children after transition into adult health care services (CLIVIA study)

Weijsenfeld A, Smit C, Mutschelknauss M, Pajkrt D.

Date of approval: 7 October 2013

Background: As a result of effective combination antiretroviral treatment (cART) and advanced supportive health care, a growing number of HIV-infected children survive into adulthood. As for adolescents with other chronic medical conditions, the period of transition to adult care is often associated with impaired adherence to treatment and discontinuity of care. We aimed to evaluate virological and social outcomes of HIV-infected adolescents and young adults (AYA) before and after transition, and explore which factors are associated with virological failure.

Methods: We included HIV-infected AYA from the Netherlands who had entered into paediatric care and transitioned from paediatric to adult health care. We used HIV viral load (VL) and cART data from the Dutch Stichting HIV Monitoring database (SHM; 1996-2014). We collected social and treatment data from patients' medical records from all Dutch paediatric HIV treatment centres and 14 Dutch adult treatment centres involved.

Results: HIV virological failure (VF) occurred frequently during the study period (range from 14% to 36%). During the transitioning period (from 18 to 20 years of age) there was a significant increase in VF compared to the reference group (OR 4.26 [CI 1.12-16.28,

p=0.03]). Characteristics significantly associated with VF were low educational degree, lack of autonomy regarding medication adherence at transition and a low level of HIV knowledge at transition.

Conclusions: HIV-infected AYA are vulnerable to VF, especially during the transitional period. Identification of HIV-infected adolescents at high risk for VF might help to improve treatment success in this group.

I13061 Factors associated with time to HIV RNA suppression in women with HIV infection starting antiretroviral treatment during pregnancy

Mudrikova T, van Snippenburg W, Wensing A, Nellen J, Godfried M, Smit C.

Date of approval: 11 July 2013

Ongoing.

I13120 SPREAD Program 3.0 – Surveillance of transmission of HIV-1 drug resistance

Wensing AMJ, Boucher CAB, Brankman K, Richter C, Bierman WFW, van der Ende ME, van Kasteren MEE, Hoepelman IM, Hofstra M (CP).

Date of approval: 19 May 2014

The data of patients newly diagnosed in 2011-2013 in any of the six participating centres of the Netherlands have been received from SHM and have been incorporated in the European SPREAD cohort.

The SPREAD cohort collects data from 28 European countries. Data collection and verification for 2011-2013 has been completed for all countries. Over 4,000 patients have been included for 2011-2013.

A data analysis team has been formed with participants from various European countries, and include Dr A.M.J. Wensing and Prof. C. Boucher of the Netherlands.

First results show that the prevalence of transmitted drug resistance is stable in Europe (9.0% in 2011-2013). However, there are regional differences that will be further investigated. Preliminary results have been presented at the *15th* European AIDS Conference in October 2015, during the best poster discussion session.

In addition to the European analysis, we will now start a specific analysis on the Dutch dataset. Ard van Sighem of SHM will participate in the Dutch SPREAD study team.

I14065 Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients: Implications for screening strategies

Wandeler G, Rauch A, Reiss P, Smit C, van der Valk M, Arends J.

Date of approval: 4 May 2014

Background: Hepatocellular carcinoma (HCC) is a leading cause of death in HIV/hepatitis B virus (HBV)-coinfected patients. Current screening recommendations are based on incidence estimates in untreated HBV-infected patients and might be inadequate for HIV/HBV-coinfected individuals on antiretroviral therapy (ART). We explored the impact of tenofovir (TDF) on HCC incidence in a large collaboration of HIV cohorts including the Swiss HIV Cohort Study, Athena, EuroSIDA and ANRS CO3 Aquitaine.

Methods: We included all HBsAg-positive adults with complete ART history available. HCC incidence was described for the full population and compared between subgroups according to the main demographic and clinical characteristics. We defined the cumulative time off TDF (either without any HBV-active ART or including only lamivudine) as the main HBV therapy exposure variable. A binary variable was created according to the median follow-up (FUP) time on TDF (4 years). Liver cirrhosis was defined according to histology or as an AST-to-platelet ratio index (APRI) >1.5. We evaluated the association between cumulative time off TDF and the incidence of HCC using multivariable Poisson regression, adjusted for sex, ethnicity, hepatitis C virus (HCV) infection and liver cirrhosis.

Results: Of 3,593 HIV/HBV-coinfected patients included, 587 (16.3%) were female, 1,803 (50.2%) men who have sex with men, 2,876 (80.0%) Caucasians and 835 (23.2%) HCV-coinfected. Overall, 40.3% of the cumulative FUP time was spent on TDF, 30.6% on 3TC only and 29.1% on ART without HBV-activity. Over 32,644 patient years (PY), 60 individuals (1.7%) developed an HCC, resulting in an overall incidence of 1.84 per 1,000 PY (95% confidence interval [CI] 1.40-2.37). The incidence of HCC was highest in patients with >4 years of FUP off TDF (incidence rate ratio [IRR] 4.04, 95% CI 2.10-7.70) and in those with liver cirrhosis (IRR 3.04, 95% CI 1.83-5.04). In adjusted analyses, there was a significant increase in the incidence of HCC per year off TDF (adjusted IRR [aIRR] 1.12, 95% CI 1.07-1.17), and patients with cirrhosis remained at higher risk of HCC (aIRR 2.85, 95% CI 1.70-4.79). During TDF therapy, the risk of HCC remained stable per additional year of FUP (aIRR 0.96, 95% CI 0.86-1.05).

Conclusions: Approximately 2% of patients developed an HCC over a median follow-up time of 8.4 years. HCC incidence increased with the length of FUP off TDF and was three times higher in cirrhotic compared to non-cirrhotic patients.

l14067 Predictive value of cardiovascular risk equations in the HIV-infected population receiving care in the Dutch HIV treatment centres

Wit F, van Zoest R, Vaartjes I, Gras L, Arends J, Reiss P.

Date of approval: 3 June 2014

Background: Cardiovascular disease (CVD) is more prevalent among HIV-infected participants than in HIV-uninfected controls. The pathophysiological mechanism is thought to be multifactorial. The current Dutch cardiovascular risk management guidelines recommend risk assessment based on the SCORE-NL risk equation. However, it is unknown whether the SCORE-NL risk equation also accurately identifies HIV-infected patients at increased risk of CVD. The aim of our study is (1) to assess whether the SCORE-NL risk equation correctly estimates the CVD risk of the HIV-infected population in the Netherlands, and (2) to compare various CVD risk equations in the HIV-infected population.

Methods: We received the SHM data set in June 2014. The population that will be used for the current analysis was selected using our predefined inclusion criteria. The baseline date (t_0) has been defined for all study

participants, and all variables have been labelled. The five risk equations we will evaluate in this project have been coded in STATA syntax: SCORE-NL equation, D:A:D risk equation (reduced and full), Framingham risk equation, and Pooled Cohort Risk Equation. Besides, the CVD endpoints have been defined and coded. We have identified the proportion of missing values per variable. Since the number of missing values is very high for some of the variables (family history of CVD, smoking status, total/HDL cholesterol), we have discussed possible ways of dealing with missing data with a team of experts on imputation/missing data working at the Julius Center Utrecht. We are currently at the stage of imputation and implementing the CVD risk equations, after which we are planning to evaluate the different equations.

Results: No results available, analysis ongoing.

Conclusions: No conclusion available, analysis ongoing.

I14087 Clinical experience with rilpivirine (KLIRI study)

Roelofsen E, Burger DM, Touw DJ, Gelinck LBS, Wilms EB, van Sighem AI.

Date of approval: 28 October 2014

Background: Rilpivirine has been available in the Netherlands since 2012. Until April 2014, according to the SHM database, a total of 1,453 patients started rilpivirine. In April 2014, 1,273 patients were still using rilpivirine. Although data on safety and efficacy can be derived from clinical trials, no data is yet available on the experience with rilpivirine outside a clinical trial setting. In an earlier study we developed a pharmacokinetic model for rilpivirine, which predicted that 95% of patients taking rilpivirine would reach a concentration within the therapeutic range. A second study showed (although with limited numbers) that the effect of rilpivirine on eGFR was significant (minus 7,72ml/min/1,73m^2 in switch and minus 13,40 ml/min/1.73m^2 in naive patients). Furthermore rilpivirine is thought to have fewer CNS adverse events than efavirenz and should be well tolerated. However anecdotal experience in clinical practice shows that not all patients who switch from efavirenz get relief from their CNS toxicity. Furthermore efavirenz is the comparison drug in clinical trial and therefore chosen as a comparison drug for efficacy, toxicity and potential decrease in eGFR in this study.

Methods: The primary goal of this nation-wide retrospective cohort study is to describe the clinical use of, and experience with rilpivirine in therapy-naive and therapy-experienced patients in the Netherlands. This research will focus on 6 areas: description of characteristics of the patients who switch to rilpivirine, start/stop/switch characteristics, efficacy and toxicity, potential eGFR decrease, pharmacokinetics, resistance.

Results: In progress.

Conclusions: In progress.

I14096 Primary and recurrent venous thromboembolism in HIV-1 (PREDICT study)

Borjas-Howard J, Rijnders BJA, Rokx C, Tichelaar YIGV, Verbon A, Meijer K.

Date of approval: 21 August 2014

Since August 2014, two students from the UMCG and Erasmus MC have completed case report forms at 12 different HIV treatment centres in the Netherlands. These case report forms contained data on venous thrombotic events and factors associated with the venous thrombotic events. This stage of data acquisition was completed in Spring 2015. Since then, we have queried the data managers to validate venous thrombotic events for which definitive data was missing. This was completed in October 2015.

At this moment, we are performing general data quality checks by cross referencing case report forms completed by the students with SHM patient reports to check for inconsistencies. We are hoping to complete this process and have a definite dataset by April/May 2016. In parallel, final data analysis plans are being made so as to be able to carry out analyses a soon as possible.

l14144 GIS-hiv: Geographical information system to determine high prevalence areas of targeted screening and early case-finding.

Van Bergen J, Joore I, op de Coul E, van Sighem A, Prins J, Geerlings S.

Date of approval: 8 February 2015

Ongoing.

l14145 Evaluation of an evidence-based, Internet-supported self-help program for people living with HIV suffering from mild to moderate depressive symptoms

Garnefski N, Kraaij V, van Luenen S.

Date of approval: 23 September 2014

In 2015, participants were included in the study and data collection started. However, the medical data that we will use from SHM have not yet been obtained. We will obtain this data in 2016/2017.

l14157 Overlap between HIV and HCV networks among MSM with HIV/HCV co-infection

Vanhommerig JW, Bezemer D, Molenkamp R, van Sighem AI, Smit C, Arends JE, Lauw FN, Brinkman K, Rijnders BJ, Newsum AM, Bruisten SM, Prins M, van der Meer JT, van de Laar TJ, Schinkel J, on behalf of the MOSAIC study and the ATHENA national observational cohort.

Date of approval: 8 December 2014

Background: Men who have sex with men (MSM) practicing unsafe sex are at risk of becoming infected with HIV-1 and hepatitis C virus (HCV). MSM infected with HIV/HCV-co-infection may represent high risk core groups and could be drivers of the HIV epidemic among MSM.

Methods: For MSM in the ATHENA observational cohort with an HIV pol sequence available, transmission clusters were selected in the HIV subtype B phylogenetic tree. Results were compared between MSM with or without evidence of HCV co-infection. In addition, HIV and HCV phylogenies of HIV/HCV co-infected MSM were compared for men that had an HCV NS5B sequence available within the MOSAIC study.

Results: We included 5,038 HIV-infected MSM with HIV pol sequences available, 563 (11.2%) of whom were (ever) co-infected with HCV. In total, 118 HIV clusters of >10 sequences included 3,084/5,038 (61.2%)

HIV pol sequences. 97 out of 118 (82.2%) HIV clusters contained ≥ 1 HCV infection. HCV sequences were obtained from 150 HCV infections among 126 MSM from the MOSAIC study, of whom 21 had ≥ 1 reinfection. Ultimately, 19/150 (12.7%) HCV infections showed overlap in HCV and HIV phylogenetic tree topologies.

Conclusions: Our results indicate a generalised HIV epidemic with no evidence for high risk core groups of HIV-infected MSM with elevated risk of HCV infection nor of high risk HIV/HCV co-infected MSM driving the HIV epidemic.

I14201 Failure of donor selection: what can the virus of the donor tell us?

Van de Laar T, Bezemer D, Zaaijer H, van Switen P, van Sighem A, Vlaas E, Compernolle V, Vanderwalle G, de Smet A, van Laethem K, Vandamme A.

Date of approval: 12 February 2015

Background: Risk-behaviour based donor selection is used to reduce the number of potentially infectious donors. Nevertheless, routine donor screening identified 55 HIV-infected donors in the Netherlands and Flanders between 2005 and 2014. During post-test counselling, approximately 25% of HIV-infected Dutch donors disclosed risk factors which, if revealed during the donor selection procedure, would have caused permanent donor deferral.

Methods: HIV is characterised by a high-genetic diversity. The presence of various subtypes is linked to specific geographic areas. However, within HIV-1 subtype B, which predominates in western Europe, transmission clusters can be identified specifically linked to men who have sex with men (MSM), heterosexuals or injecting drug users (IDUs). By comparing HIV-1 donor sequences with sequences from the general population of the Netherlands and Flanders we try to gain more insight into the underlying risk behaviour in HIV-1 infected donors in low-endemic countries. Viral typing was based on the HIV pol gene (1200 bp). Phylogenies were constructed using HIV donor sequences plus HIV pol sequences from the ATHENA cohort (n=8673), the HIV sequence database of Catholic University Leuven and, for each donor sequence, the 10 most related sequences available at GenBank.

Results: Samples were available for 47/55 (85%) of HIV-infected Flemish and Dutch donors. Viral typing revealed the following HIV-1 genotypes: B (68%), CRF02_AG (13%), C (6%), A (2%), D (2%), F (2%), CRF01_AE (2%) and other recombinant forms (4%). HIV subtype B is strongly associated with being male (OR 28.4) and being infected before 2010 (OR 7.4). Phylogenetic analysis shows that 24/26 (92%) of male donors and 0/6 (0%) female donors infected with subtype B were part of MSM-specific transmission clusters. Donors infected with non-subtype B were mostly female and reported heterosexual partners from HIV-endemic areas in Africa. MSM-specific transmission clusters were also identified among HIV-1 non-B subtypes, one male donor with CRF02_AG and one male donor with subtype F were part of MSM-specific networks.

Conclusions: Viral typing is a useful tool to improve our understanding of risk factors in donors with unexpected blood-borne

infections, enabling us to estimate the relative contribution of various risk factors in donors who do not disclose risk behaviour or donors who avoid post-test counselling.

I15004 The impact of combinations of strategies for HIV prevention among men who have sex with man

Xiridou M, van den Bosch A, van Benthem B, op de Coul E, van Sighem A, Stolte I.

Date of approval: 28 January 2015

Background: In the Netherlands, men who have sex with men (MSM) account for most new HIV diagnoses. Despite the availability of successful treatment, there is still ongoing transmission. Research thus far has focused mainly on assessing the impact of individual measures, such as early initiation of treatment or pre-exposure prophylaxis. However, the impact of combined strategies is unknown. In this project we will assess the individual impact of several prevention measures, if implemented individually or in combinations. The impact of these measures on HIV transmission will be investigated, as well as their cost effectiveness.

Methods: We developed an individual based model that describes the formation of sexual relationships between MSM and the transmission of HIV. Parameters relating to sexual behaviour were estimated from data from the Amsterdam Cohort Study among MSM in Amsterdam. The rate of starting new sexual relationships depends on the average number of partners in the preceding few months and the average number of partners in the preceding few years. The duration of relationships depends on the starting times of relationships and on individual characteristics, such as age or preference for long or short relationships.

Results: The average number of sexual partners in the preceding six months is increasing with age for MSM up to 45 years old and is decreasing with age for MSM older than 45; this result agrees with observational data. Moreover, in the model, the number of partners in the preceding six months has a power-law-like distribution, represented by an almost straight line of the probability density function in a double logarithmic plot. In populations with this property, epidemics arise and propagate much faster and are more difficult to control.

Conclusions: The distribution of sexual partners of MSM is characterised by substantial heterogeneity. The distribution has a form similar to the power-law distribution, indicating that MSM who have had many partners in the past are more likely to have many partners at present. This might explain why the HIV epidemic could propagate so fast in the 1980s and why HIV control among MSM has been so difficult thus far.

I15021 Global resistance following virologic failure with tenofovir +NNRTI containing antiretroviral regimens: a retrospective multi-centre multi-cohort study and meta analysis

Rokx C, Gupta R, Rijnders B, Shafer B, Gregson J, Tang M, Hamers R, Raizes E, Crawford K, Marconi V, Hill A, Hosseinipour M, Clumeck N, Kanki P, Lockman S, de Wit T, Hoffman S, de Oliveira T, Wallis C, Morris L, Hunt G, Dunn D, Blanco JL, Gunthard H, Kumarasamy D, Kaleebu P, Pillay D, Charpentier C, Descamps D, van Damme A, Theys K, Camacho R, Calvez V, Gras L.

Date of approval: 20 February 2015

Background: Analysis of virological failure (VF) and resistance following TDF-based first line regimens including 3TC or FTC and an NNRTI.

Methods: Meta analysis of 45 cohorts/ studies. SHM was one of the contributing parties.

Results: VF on TDF was associated with region (sub-Saharan Africa), use of 3TC instead of FTC, and lower CD4 count. TDF resistance was common, ranging from 20% in high income countries to 60% in low-middle income countries (LMIC). TDF resistance was often accompanied by cytosine analogue resistance (M184V/I).

Conclusions: Drug resistance was common in LMIC and surveillance is necessary.

I15022 Community viral load as a tool for HIV surveillance in the Netherlands and South Africa

Op de Coul E, Bolijn R, Heijne J, van Sighem A, Kretzschmar M.

Date of approval: 22 April 2015

Ongoing – manuscript in preparation.

I15043 Cost-effectiveness of the adherence improving self-management strategies (AIMS) in HIV care: A model-based economic evaluation

De Bruin M, Prins J, Oberjé E, Hiligsmann M, Evers S, van Sighem A.

Date of approval: 17 June 2015

Background: To develop an economic model for evaluating the long-term impact of an effective adherence intervention in HIV care tested in the Netherlands (the Adherence Improving self-Management Strategy, or AIMS), we required longitudinal data from a large sample of HIV patients in routine care.

Methods: A Markov model has been developed comparing the relative risks of the AIMS intervention (intervention versus control), with the SHM data on patient trajectories in routine clinical care. The model also incorporates productivity losses and HIV transmission risks.

Results: The model has been finalised and both the base case and multiple sensitivity analyses reveal that AIMS is dominant to treatment-as-usual in the Netherlands: both cheaper and more effective.

Conclusions: AIMS is a cost-effective intervention and should be considered for adoption in routine clinical care in the Netherlands.

I15065 Comparison of the occurrence of severe HBV-related liver disease and (liver-related) mortality between patients with hepatitis B mono-infection and patients co-infected with hepatitis B and HIV in the Netherlands (HARMONIC)

Arends JE, Richter C, Lieveld FI, Reiss P, Smit C, Spanier M, van Erpecum KJ, Hoepelman IM.

Date of approval: 28 July 2015

Background: Studies comparing mortality and liver-related outcomes between patients with HBV mono-infection and HIV/HBV co-infection are scarce and have reported

inconsistent results. This is a retrospective observational longitudinal cohort study in which we aim to compare liver-related and overall mortality, hepatocellular carcinoma and advanced liver fibrosis between adult patients with HIV/HBV co-infection and adult patients with HBV mono-infection.

Methods: SHM has approved the use of nationwide data from all registered HIV/HBV patients. Data from the HBV mono-infected patients included in UMC Utrecht and Rijnstate hospital have been collected in a separate database by SHM, with collected parameters being similar to the data collected for HIV/HBV patients by SHM. The two groups will be compared on the following outcomes: 1) Death from all causes vs. alive; 2) Liver-related death vs. alive; 3) Advanced liver fibrosis [defined as Metavir scores F3-F4 as determined by liver biopsy or fibroscan results or liver cirrhosis as determined by imaging modalities (echography, CT-scan, MRI)] vs. No to moderate fibrosis [Metavir F0-F2 as determined by liver biopsy or fibroscan results or no liver cirrhosis as determined by imaging modalities]. 4) Hepatocellular carcinoma vs. no hepatocellular carcinoma based on documentation in the patient file by the treating physician. Cross sectional analysis using multivariate logistic regression models and longitudinal analysis using multivariate cox regression models will be performed.

Results: Data collection has been completed as of 29-9-2015. A total of 856 HBV mono-infections have been included, n=518 from UMC Utrecht and n=338 from Rijnstate Hospital. Data from 1444 HIV/HBV co-infections are available through SHM. Currently, comparative analyses between the two groups are being done. First results will be available in February 2016.

Conclusions: Currently, data collection is complete and data analyses are ongoing. Results are expected in February 2016.

I15066 Cost-effectiveness of HIV treatment and care in the Netherlands

Verbon A, Nichols BE, Boucher C, Geerlings S, Reiss P, van Sighem AI, Kroon FP, Postma MJ, Brinkman K.

Date of approval: 24 June 2015

Ongoing.

I15090 Fibrosis progression after acute HCV infection in HIV-infected individuals

Van der Valk M, Kooij KW, Newsum A, Smit C, Reiss P, Prins M, van der Meer J, MOSAIC study group, SHM hepatitis working group.

Date of approval: 27 July 2015

Background: Hepatitis C virus (HCV) infection is common in HIV-infected individuals, due to shared routes of transmission. In recent years, incidence of sexually transmitted HCV among HIV-infected men who have sex with men (MSM) has increased. HIV co-infection decreases the likelihood of spontaneous hepatitis C viral clearance and, when chronic HCV infection is established, may accelerate the progression to liver fibrosis and cirrhosis.

The fibrosis-4 score (FIB-4) is developed in an HIV-HCV coinfected population to reduce the need for liver biopsy, as described by Sterling et al. In this study, a FIB-4 cut-off <1.45 was used to predict absence and a

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cut-off of >3.25 to predict presence of advanced liver fibrosis (Metavir score ≥F3). Using these cut-offs, in 70% of patients in this study advanced liver fibrosis could be confirmed or rejected, with an 87% accuracy compared to liver biopsy. Later studies, performed in HIV-HCV coinfected and HCV monoinfected populations, have confirmed the value of FIB-4 to predict significant fibrosis, advanced fibrosis and/or cirrhosis. These studies used several different cut-offs and show moderate accuracy. A systematic review of studies including HCV mono-infected patients reported a summary sensitivity of 64% and specificity of 68% (cut-off >1.45) for predicting significant fibrosis and a summary sensitivity of 55% and specificity of 92% for predicting cirrhosis (cut-off >3.25).

FIB-4-defined advanced liver fibrosis (FIB-4 >3.25) has prognostic value for the development of liver decompensation and liver related mortality in HCV-infected as well as HIV-HCV coinfected individuals, comparable to that of liver biopsy. Recently, a study reported on a better prognostic value of the FIB-4 compared to liver biopsy in predicting overall death and liver-related events in HIV-HCV coinfected patients; the area under the receiver operator curve (AUROC) was 0.648 for liver biopsy versus 0.742 for FIB-4-defined advanced fibrosis.

Recently, a study among HCV monoinfected patients demonstrated an unexpectedly high rate of fibrosis progression, relatively soon after HCV seroconversion, as measured by the change in FIB-4 score over time. Some studies have indicated that acute HCV infection in HIV-infected individuals may lead to even more rapid development of liver fibrosis. However, these studies were small (case reports) and had relatively short follow up; it is possible that the observed accelerated rate of liver fibrosis progression in those co-infected with HIV with time could stabilise to levels observed in chronic HCV mono-infection. Chronic HIV-HCV co-infected patients are at a higher risk for hepatic decompensation than HCV mono-infected patients, even in the era of modern antiretroviral therapy. However, data on the rate of liver fibrosis progression and its determinants soon after HCV seroconversion in those with underlying HIV infection are lacking.

Methods: 535 acute HCV cases have been identified from the SHM database, based on anti HCV antibody and HCV RNA test results, and from the MOSAIC database.
Additional data for HCV cases treated in hospitals that do not have LabLink have been collected: historic ALT, AST and platelet values have been entered in the SHM database by data collectors. Data sets are being prepared for analysis. Statistical analysis planning is in progress.

Results: None yet.

Conclusions: None yet.

I15148 Model based on clinical parameters to predict the natural history of severe liver fibrosis in HIV/HCV co-infected patients

Arends JE, van der Meer AJ, Smit C, Hansen B.

Date of approval: 15 December 2015

No developments yet.

Publications in 2015

Increased virological failure in naive HIV-1 patients taking lamivudine compared to emtricitabine in combination with tenofovir and efavirenz or nevirapine in the Dutch nationwide ATHENA cohort
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Country of birth does not influence long-term clinical, virologic, and immunological outcome of HIV-infected children living in the Netherlands: a cohort study comparing children born in the Netherlands with children born in sub-Saharan Africa
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Use of surveillance data on HIV diagnoses with HIV-related symptoms to estimate the number of people living with undiagnosed HIV in need of antiretroviral therapy
Lodwick RK, Nakagawa F, van Sighem A, Sabin CA, Phillips AN.
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Favourable SVR12 rates in boceprevir or telaprevir triple therapy in HIV/HCV coinfected patients
Arends JE, van der Meer JTM, Posthouwer D, Kortmann W, Brinkman K, van Assen S, Smit C, van der Valk M, van der Ende M, Schinkel J, Reiss P, Richter C, Hoepelman AIM, on behalf of Stichting HIV Monitoring/Nederlandse Vereniging van HIV Behandelaren, Hepatitis Working Group, and the ATHENA national observational HIV cohort.
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Joore I.
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High alcohol use is associated with non-AIDS-related mortality in the ART-CC
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Higher prevalence of hypertension in HIV-infected individuals partially explained by increased waist-hip ration rather than BMI, other traditional risk factors or markers of systemic inflammation
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Appendix 1: Composition of SHM

SHM board

Name	Position	Representing	Affiliation
Dr F.P. Kroon	Chair	Nederlandse Vereniging HIV Behandelaren (NVHB)	LUMC
Dr J.S.A. Fennema†	Secretary	GGD Nederland	GGD Amsterdam
Dr P.W.D. Venhoeven	Treasurer	Prinses Maxima Centre for Paediatric Oncology	
Prof. K. Stronks	Member	AMC-UvA	AMC-UvA
L.J.M. Elsenburg	Member	HIV Vereniging Nederland	HIV Focus Centrum
Dr R.J.M. Hopstaken	Member	Nederlandse Federatie Universitair Medische Centra (NFU)	AMC-UvA
P.E. van der Meer	Member	Nederlandse Vereniging Ziekenhuizen (NVZ)	Albert Schweizer Ziekenhuis
J. Crasborn	Member	Zorgverzekeraars Nederland	Achmea

SHM advisory board

Name	Affiliation
Prof. D.R. Kuritzkes (chair)	Brigham and Women's Hospital, Section of Retroviral Therapeutics, Boston, MA, USA
Prof. Sir R.M. Anderson	Imperial College, Faculty of Medicine, Dept. of Infectious Disease Epidemiology, London, UK
Prof. G. Chêne	Université Victor Segalen, Bordeaux, France
Prof. M. Egger	University of Bern, Switzerland; University of Bristol, UK
Prof. T.B.H. Geijtenbeek	AMC-UvA, Dept. Experimental Immunology, Amsterdam
P.J. Smit	HIV Vereniging Nederland, Amsterdam
Dr M. van der Valk	AMC-UvA, Dept. Internal Medicine, Amsterdam

SHM working group

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 Tuberculosis Foundation, The Hague; AIGHD Amsterdam
Dr W.M.C. Mulder	HIV Vereniging Nederland, Amsterdam

† *Died 8 January 2016*

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Reviewers

Name	Affiliation
Dr N.K.T. Back	AMC-UvA, Clinical Virology Laboratory, Amsterdam
Prof. K. Brinkman	OLVG, Dept. of Internal Medicine, Amsterdam
Dr D.M. Burger (Pharmacology subgroup)	Radboud UMC, 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)
Dr S.P.M. Geelen	UMCU-WKZ, Dept. of Paediatrics, Utrecht
Prof. A.I.M. Hoepelman	UMC Utrecht, Dept. of Virology, Utrecht
Dr S. Jurriaans	AMC-UvA, Clinical Virology Laboratory, Amsterdam
Dr P.P. Koopmans	Radboudumc, Dept. of Internal Medicine, Nijmegen
Prof. A.C.M. Kroes	LUMC, Clinical Virology Laboratory, Leiden
Prof. T.W. Kuijpers	AMC-UvA, Dept. of Paediatrics, Amsterdam
Dr W.J.G. Melchers	Radboudumc, Dept. of Medical Microbiology, Nijmegen
Prof. J.M. Prins	AMC-UvA, Dept. of Internal Medicine, Amsterdam
Prof. P.H.M. Savelkoul	MUMC+, Dept. of Internal Medicine, Maastricht
Dr R. Schuurman	UMC Utrecht, Dept. of Virology, Utrecht
Dr H.G. Sprenger	UMCG, Dept. of Internal Medicine, Groningen
Dr A.M.J. Wensing	UMC Utrecht, Dept. of Virology, Utrecht

Hepatitis working group

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
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Dr J. Arends	UMC Utrecht, 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-UvA, Dept. of Internal Medicine, Amsterdam
Dr J. van der Meer	AMC-UvA, Dept. of Internal Medicine, Amsterdam
Dr J. Schinkel	AMC-UvA, Clinical Virology Laboratory, Amsterdam
Dr E.F. Schippers	HagaZiekenhuis, Dept. of Internal Medicine, Den Haag
Dr M. Schutten	Erasmus MC, Dept. of Clinical Virology, Rotterdam
Dr A. Vollaard	LUMC, Dept. of Infectious Diseases, Leiden

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SHM personnel

Position	Name
Director	Prof. Dr P. Reiss MD
Data analysis, reporting & research	
Researchers	D.O. Bezemer PhD
	L.A.J. Gras MSc (until 1 September 2015)
	A.I. van Sighem PhD
	C. Smit PhD
	F.W.N.M. Wit MD PhD
PhD candidates	E. Engelhard MSc (external)
	R. van den Hengel MSc
Data & QC	
Manager	S. Zaheri MSc
Data management	M.M.J. Hillebegt MSc (coordinator)
	A.S. de Jong MSc
	Y.M. Tong MSc (until 1 June 2015)
QC & protocol management	
Data monitors	A.M. Jansen MSc (data monitor coordinator)
	S. Grivell MSc (protocol coordinator)
	D. Bergsma MSc
	M.M.Z. Berkhout MSc (until 1 October 2015)
	R. van den Boogaard MSc (until 1 April 2015)
	P.T. Hoekstra-Mevius MSc
	V. Kimmel MSc (until 1 April 2015)
	A. de Lang PhD
	M.S. Raethke MSc
	M.J.C. Rademaker MSc

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Patient registration & data collection	
	L.G.M. de Groot-Berndsen (coordinator)
	M.M.B. Tuk-Stuster (patient registration)
Data collectors	M. van den Akker
	Y.M. Bakker
	M. Broekhoven-van Kruijne
	E.J. Claessen
	A. El Berkaoui
	R. Henstra-Regtop
	J. Koops
	E.I. Kruijne
	C.R.E. Lodewijk
	R. Meijering MSc
	L. Munjishvili
	B.M. Peeck
	C.M.J. Ree
	Y.M.C. Ruijs-Tiggelman
	T. Rutkens
	L. van de Sande MA
	S. Schnörr MSc
	M.J.C. Schoorl MSc
	E.M. Tuijn-de Bruin
	D.P. Veenenberg-Benschop
	S. van der Vliet
	T.J. Woudstra
Human resources, office & finance	
Manager	D. de Boer
Office and secretariat	M.M.T. Koenen
Human resources	I.H.M. de Boer (until 31 December 2015)
	I. Bartels
Finance	H.J.M van Noort MSc
Communications	
Manager	C.J. Ester PhD
	M.J. Sormani

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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 characterised by failure of the immune system to protect against infections and certain cancers.

Antibody
An immune system protein 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 may be the target of antibodies.

Antiretroviral treatment (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.

Baseline
An initial measurement used as the basis for future comparison. For people infected with HIV, baseline testing includes CD4 count, viral load (HIV RNA), and resistance testing. Baseline test results are used to guide HIV treatment choices and monitor effectiveness of antiretroviral therapy (ART).

cART
Combination antiretroviral treatment.

CD4 cell
CD4+ T-lymphocyte, 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).

CDC
US Centers for Disease Control and Prevention.

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

CLB
Central Laboratory for the Blood Transfusion Service (*Centraal Laboratorium van Bloedtransfusiedienst*).

Co-infection
When a person has two or more infections at the same time. For example, a person infected with HIV may be co-infected with hepatitis C (HCV) or tuberculosis (TB) or both.

Comorbidity
When a person has two or more diseases or conditions at the same time. For example, a person with high blood pressure may also have heart disease.

Cross-resistance
After a person becomes resistant to one particular drug, they may develop resistance to similar drugs, without ever having been exposed to these drugs. This is known as cross-resistance.

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.

Epidemiology
The study of the distribution, causes, and clinical characteristics of disease or health status in a population.

Genotype
The genotype is the underlying genetic makeup of an organism.

GGD
Dutch public health service (*Geneeskundige en Gezondheidsdienst*, www.ggd.nl).

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

Half-life
The time it takes a drug to lose half its original concentration or activity after being introduced into the body. Drug half-life is considered when determining drug dosing.

Hepatic
Pertaining to the liver.

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 Africa.

HIV Vereniging Nederland
Dutch HIV patients' association (http://www.hivnet.org).

Immunologic failure
A type of HIV treatment failure. There is no consensus on the definition of immunologic failure. However, some experts define immunologic failure as the failure to achieve and maintain adequate CD4 counts despite viral suppression.

Interferon
Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they don't directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs the half-life of interferon. Pegylated interferon alpha is used to treat chronic hepatitis C infection.

Mono-infection
When a person has only one infection.

Mortality
Mortality rate is a measure of the frequency of occurrence of death among a defined population during a specified time period.

MSM
Men who have sex with men.

Nederlandse Federatie Universitair Medische Centra (NFU)
Netherlands Federation of University Medical Centres.

Non-AIDS events
Diseases and clinical events that are not related to AIDS (i.e. that are not listed as being associated with AIDS by the Centers for Disease Control and Prevention) and include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, cardiovascular disease.

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
Antiretroviral (ARV) HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleoside Reverse Transcriptase Inhibitor (NRTI)
Antiretroviral (ARV) HIV drug class. Nucleoside reverse transcriptase inhibitors (NRTIs) block reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleotide
A building block of nucleic acids. DNA and RNA are nucleic acids.

Nucleotide Reverse Transcriptase Inhibitor
A type of antiretroviral (ARV) HIV drug. Nucleotide reverse transcriptase inhibitors interfere with the HIV life cycle in the same way as NRTIs. Both block reverse transcription and therefore nucleotide reverse transcriptase inhibitors are included in the NRTI drug class.

NVHB
Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*).

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

Perinatal transmission
Perinatal transmission of HIV refers to the passage of HIV from an infected mother to her child during pregnancy, labour and delivery, or breastfeeding (through breast milk).

Protease
A type of enzyme that breaks down proteins into smaller proteins or smaller protein units, such as peptides or amino acids. HIV protease cuts up large precursor proteins into smaller proteins. These smaller proteins combine with HIV's genetic material to form a new HIV virus. Protease inhibitors (PIs) prevent HIV from replicating by blocking protease.

Protease Inhibitor (PI)
Antiretroviral (ARV) HIV drug class. Protease inhibitors (PIs) block protease (an HIV enzyme). This prevents new HIV from forming.

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.

Ribavirin
A type of nucleoside inhibitor prescribed for the treatment of hepatitis C in combination with an interferon. Ribavirin stops the hepatitis C virus from spreading by interfering with the synthesis of viral RNA.

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.

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

Sustained virologic response or sustained viral suppression
The continuous, long-term suppression of a person's viral load (HIV RNA), generally to undetectable levels, as the result of treatment with antiretroviral drugs.

Tolerability
The extent to which a drug's side effects can be tolerated by the patient.

Viraemia
The presence of a virus in the blood.

Virologic failure
A type of HIV treatment failure. Virologic failure occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/mL. Factors that can contribute to virologic failure include drug resistance, drug toxicity, and poor treatment adherence.

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

Viral suppression or virologic control
When antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level. Viral suppression does not mean a person is cured; HIV still remains in the body.

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

Some of the above definitions were taken from www.aidsinfo.nih.gov