HIV Monitoring

Annual Report 2016

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Annual report 2016, approved by the Stichting HIV Monitoring Governing Board on 11 May 2017.

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Art Direction and DTP: Studio Zest, Wormer, the Netherlands

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Foreword

In 2016, Stichting HIV Monitoring continued its important task of monitoring the HIV epidemic in the Netherlands. The solid and well-established collaboration with the 26 appointed HIV treatment centres in the Netherlands has allowed SHM to continue to collect and analyse data on relevant health outcomes, including non-communicable co-morbidities and viral hepatitis co-infections, from people living with HIV (PLWH) in clinical care. These analyses enable SHM to provide a truly representative and nationwide picture of the outcome of care for those living with HIV in the Netherlands. In 2016, in particular, they allowed SHM to monitor and report on the effectiveness of the novel combinations of direct acting antivirals against hepatitis C. Analyses are described in detail in the 2016 HIV Monitoring Report, the key findings of which are included in this annual report.

In addition, during 2016, 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.

SHM continues to be closely involved in various European and other more global HIV observational cohort collaborations, contributing in terms of both data and knowledge. Through these and other research collaborations, SHM contributed to 57 publications and nearly 80 conference presentations in 2016. It is only through such collaborations that the scientific community can address questions that cannot be answered by individual cohorts alone. Such collaborations are therefore vitally important in ensuring optimal care for PLWH and their findings regularly lead to modifications in HIV treatment guidelines.

During the course of 2016, the Data & QC unit has been working very hard towards replacing the present data entry system, Oracle Clinical. The new system is currently being built and tailored to SHM's specific requirements and will go live early 2018. Once it is operational, the new system should make the data collection process more efficient and future-proof. Another move towards improving data collection efficiency has been the expansion of LabLink, the direct electronic link between hospital laboratories and SHM's database. In 2016, LabLink went live in OLVG and, as a result, SHM now receives laboratory data from over 60% of registered PLWH in the Netherlands through LabLink. We hope that 2017 will see further implementation of LabLink in the remaining hospitals.

The important work carried out by SHM would not be possible without the tireless 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 learn how we may continue to improve their care.

Prof. Peter Reiss, MD, PhD

Director

Amsterdam, 11 May 2017

Message from the governing board chair

As I enter my last year as chair of Stichting HIV Monitoring's governing board, I look back on the last eight years serving the SHM board with a strong sense of appreciation and respect for the organisation and its work. During this time I have accompanied SHM through a number of significant changes, including a new director in 2013 and the implementation of an ambitious digitisation strategy.

Throughout this time, SHM has remained dedicated to the goal of collecting high-quality data from people living with HIV and in care in the Netherlands. This collection of data allows SHM's researchers to report on the HIV epidemic in the Netherlands in the annual Monitoring Report, highlighting important trends and changes in the epidemic. For example, the 2016 Monitoring Report confirmed the earlier suggestion that the number of new HIV diagnoses is declining, but also highlighted the large proportion of people who are still presenting late for care. SHM's data collection has also facilitated a rapid monitoring response to the new direct-acting antiviral agents for hepatitis C virus infection. The latest Monitoring Report revealed that these new agents are highly effect in reducing the number of HIV/HCV co-infected individuals requiring treatment for HCV, but also brought to light the issue of HCV reinfection. Such valuable and timely observations are only possible through SHM's comprehensive data collection that affords the Netherlands a unique position worldwide in terms of insight into the national HIV epidemic.

2016 saw SHM embark on another project designed to further improve the quality of the data collection, namely the replacement of the data entry system. This ambitious and demanding project, which should come to fruition at the beginning of 2018, has involved a rigorous overhaul of the entire data collection and entry process and will result in a new data entry system that is more efficient, less sensitive to errors and has the capacity to adapt to future digital developments within treatment centres.

Through its monitoring work and the centre-specific reports made available to treatment centres in the Netherlands for certification purposes, SHM plays a key role in improving the medical care provided to individuals living with HIV in the Netherlands. At the same time, SHM also makes an important contribution to the wider understanding of the HIV epidemic through ongoing involvement in national and international scientific research collaborations. The outcomes of such collaborative research can subsequently be used as the basis for treatment and healthcare policy guidelines.

It remains to me to once again 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. Finally, I would like to thank the members of the board for their work on behalf of SHM and, in particular I would like to express my appreciation to departing board member Loek Elsenburg for his contribution during his term.

Dr Frank Kroon

Chairman of the governing board

Amsterdam, 11 May 2017

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-positive 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 individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

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

This section provides an update of SHM's activities carried out in 2016. In addition to a list of all certified HIV treatment centres in the Netherlands as per 31 December 2016, 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 Collection & Quality Control unit in 2016 and updates on the registration and monitoring of HIV-positive individuals by SHM and the Amsterdam Cohort Studies, which receive funding through SHM. Finally, the progress report provides an overview of SHM's national and international collaborations and describes SHM's main communication activities during 2016.

HIV treatment centres

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

In 2016, the following health institutes were involved as centres or subcentres for adult HIV care (in alphabetical order by town):

1. Noordwest Ziekenhuisgroep — Alkmaar
2. Flevoziekenhuis — Almere
3. Academic Medical Center of the University of Amsterdam (AMC-UvA) — Amsterdam
4. Hiv Focus Centrum-DC Klinieken Lairesse — Amsterdam
5. OLVG — Amsterdam
6. MC Slotervaart — Amsterdam
7. Medisch Centrum Jan van Goyen (MC Jan van Goyen) — Amsterdam
8. VUmc — Amsterdam
9. Rijnstate — Arnhem
10. HagaZiekenhuis (Leyweg site) — Den Haag
11. HMC (Haaglanden Medisch Centrum) — Den Haag
12. Catharina Ziekenhuis — Eindhoven
13. Medisch Spectrum Twente (MST) — Enschede
14. Admiraal De Ruyter Ziekenhuis (ADRZ) — Goes
15. Universitair Medisch Centrum Groningen (UMCG) — Groningen
16. Spaarne Gasthuis — Haarlem
17. Medisch Centrum Leeuwarden (MCL) — Leeuwarden
18. Leids Universitair Medisch Centrum (LUMC) — Leiden
19. MC Zuiderzee — Lelystad
20. Maastricht UMC+ (MUMC+) — Maastricht
21. Radboudumc — Nijmegen
22. Erasmus MC — Rotterdam
23. Maasstad Ziekenhuis — Rotterdam
24. ETZ (Elisabeth-TweeSteden Ziekenhuis) — Tilburg
25. Universitair Medisch Centrum Utrecht (UMC Utrecht) — Utrecht
26. Isala — 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), UMC Utrecht — Utrecht

SHM has contracts with each centre or subcentre for the collection of demographic, epidemiological, clinical, virological, immunological, and pharmacological data for HIV-positive individuals 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-positive persons seen by HIV-treating physicians at the St. Elisabeth Hospital in Curaçao (SEHOS).

Stichting HIV Monitoring mission

Background

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

Mission

Our 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 fulfil our mission, we aim to:

- monitor and report trends in all aspects of HIV infection by collecting high-quality, nationwide data from HIV-positive persons in care.
- 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.
- 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.
- 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.
- contribute to national and international collaborative scientific research.
- 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.

SHM organisational structure

Governing board

The members of Stichting HIV Monitoring's (SHM) governing board represent academic and general hospitals, health insurers, the Dutch HIV Association (*Hiv Vereniging*), the Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB), the national organisation of Public Health Services (*GGD GHOR Nederland*), and the Academic Medical Center of the University of Amsterdam (AMC-UvA). An overview of the board members in 2016 is provided in the appendix. The governing board convenes twice a year. The board's duties include approving SHM's budget and the content of the annual report; board members receive no remuneration for this work.

Advisory board

A scientific advisory board has been established by the governing board to provide the board and SHM's director with strategic advice regarding the registration and monitoring of data from HIV-positive individuals in care in the Netherlands, as well as the use of these data in research. The advisory board comprises national and international experts from the field, as well as a representative of the Hiv Vereniging. The advisory board convenes once a year.

Working groups

In 2016, two working groups were active within SHM:

- *SHM working group*, which reviews scientific research proposals involving the data stored in the national HIV database and advises the director on executive matters regarding such research proposals;
- *hepatitis working group*, which works together with the NVHB and assesses scientific research proposals involving data stored in the national HIV database that relate specifically to HIV/hepatitis co-infection.

Management team

SHM's management team (MT) consists of the director (chair of the MT), the Data & Quality Control (QC) manager, the Communications manager, and a senior researcher representing the Data Analysis, Reporting and Research unit. The director is appointed by, and reports to, the governing board. The director is responsible for day-to-day operations and is primarily responsible for representing the organisation externally. The MT establishes SHM's strategic objectives by common agreement and is responsible for the day-to-day implemention of this strategy. The MT convenes once a week and is advised by the organisation's financial controller and HR advisor.

Business units and support

Business units

SHM has three main business units that carry out the organisation's primary activities:

- Data & QC,
- Data Analysis, Reporting & Research,
- Communications.

Data & QC unit

The Data & QC unit is led by the Data & QC manager and comprises the following departments: Patient Registration & Data Collection, QC & Protocol Management, and Data Management.

Within the Data & QC unit, the following five core activities are carried out:

- *Patient registration*. This involves the registration and de-registration of HIV-positive individuals. This patient registration system is used to assign a pseudonymised code to each registered individual.
- *Data collection and data entry*. This involves the collection of patient data from source documents and entry of these data into SHM's database. The activities are carried out by data collectors according to strict data collection protocols.
- *Quality control*. This activity is carried out by data quality staff (data monitors) to safeguard the validity and reliability of the collected data entered into SHM's database.
- *Helpdesk and protocol management*. This involves keeping protocols up to date, and drafting regular helpdesk products such as mailings, protocol updates and FAQ sheets.
- *Data management and reporting*. This core activity is carried out by data managers and involves checking, cleaning, standardising, combining and documenting data. Some of these tasks are outsourced to the AMC's Clinical Research Unit (CRU) of the Clinical Epidemiology and Biostatistics department and the AMC's general IT service (ADICT).

Data Analysis, Reporting and Research unit

The Data Analysis, Reporting and Research unit is led by the director of SHM and 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 SHM's annual Monitoring Report. The researchers also contribute to publications involving analyses of the data in SHM's database in peer-reviewed national and international scientific journals. In addition, the Data Analysis, Reporting and Research unit supports and collaborates with researchers in the national HIV treatment centres. The unit also collaborates with international research groups involved in comparable observational cohorts in the field of HIV epidemiology and treatment. SHM's researchers contribute to these collaborations in terms of setting up and carrying out scientific research.

Until mid-2016, two PhD students were also stationed in the Data Analysis, Reporting and Research unit, working on PhD programmes that were co-supervised by SHM's researchers. These programmes were partly funded by external grants and involved the mathematical modelling of the impact of various interventions to control the HIV epidemic in the Netherlands, and a study into optimising quality of care for HIV-positive individuals receiving care at HIV treatment centres in the Netherlands.

Communications unit

The Communications unit, led by the communications manager, actively disseminates information about the HIV epidemic in the Netherlands and provides information about SHM's activities through a wide variety of communication channels. The aim is inform HIV health care providers, HIV researchers, other health care professionals, people living with HIV, the media and other interested parties.

Support

The primary activities of SHM's management team are supported by the human resources, office and finance staff, who report to SHM's director.

Staffing in 2016

In 2016, SHM had an average total of 37.3 FTEs. In addition, SHM covers the costs for a total of 7.92 FTEs for data collectors and data entry staff who are employed by the HIV treatment centres rather than SHM.

A list of members of SHM's governing board, advisory board, working groups and personnel can be found in *Appendix 1: Composition of SHM*.

Data & quality control: improvement projects and core activities

Stichting HIV Monitoring's Data and Quality Control (QC) unit carries out five main activities:

- patient registration,
- data collection and data entry,
- quality control,
- helpdesk and protocol management,
- data management and reporting.

These core activities will be discussed later in this chapter, following an overview of the improvement projects undertaken in 2016.

Improvement projects in 2016

In addition to the above-mentioned core activities, the Data and QC unit implements various projects designed to further improve both the quality and efficiency of processes and data. In 2016, priority was given to the following projects:

- **IT project 'LISA'**
  This project involves the replacement and concomitant improvement of SHM's data entry system. The aims of this project are:
  - to minimise manual input;
  - to standardise and optimise data collection, data quality management and data processing;
  - to improve the infrastructure for information technology (IT).

- **LabLink**
  The aim of this project is to expand hospital use of the automated link that allows laboratory data from hospital computer systems to be entered directly in a pseudonymised form into the SHM database.

- **Centralisation of data collection**
  This project strives, where possible, to further centralise the collection of data by specially-trained staff employed by SHM.

- **Knowledge management**
  This ongoing project aims to train and coach data collectors, data quality staff (data monitors) and data managers.

- **ISO 9001 and ISO 27001 certification**
  This project was set up to implement the International Organization for Standardization (ISO) standards for quality and information security within SHM.

IT project 'LISA'

In May 2014, the Academic Medical Center (AMC) announced that its clinical research unit (CRU) would no longer be able to continue providing SHM with support. This support comprised the following two core activities:

- data warehousing,
- application management and support for SHM's data entry system, Oracle Clinical.

The existing service level agreement with the CRU was therefore terminated as of 1 July 2014. As a result, all data warehousing services supplied by the CRU to SHM ended on 1 January 2015. The CRU will, however, continue to manage and support Oracle Clinical until 1 January 2018.

In anticipation of these developments, a project brief was drawn up in 2014, entitled 'Phasing out of CRU services', with the aim of finding a suitable alternative to the services provided by the CRU. In addition, given the current IT developments within HIV treatment centres in terms of electronic medical record systems, the plan also included new opportunities for modernising and future-proofing SHM's data collection process.

New data warehousing partner

Together with the shift towards electronic medical record systems in various HIV treatment centres, clinical data warehouses are also becoming more common in both academic and non-academic hospitals. As a front runner in setting up clinical data warehouses, the AMC's general ICT service (ADICT) was chosen as the suitable party to take over SHM's data warehouse activities from the CRU as of 24 March 2015.

New data entry system

To replace Oracle Clinical, in collaboration with the company Furore, a statement of requirements was drawn up in September 2014. This was subsequently followed by a market survey to identify candidate replacement systems that also had the capacity to encompass future innovations and allow possible coupling with electronic medical records in the future. This led to a long-list of seven options and 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 in the form of a cooperation between ICT Automatisering and LogicNets, and reference visits took place. Following these visits, a proof of concept was carried out in September 2015, in which, together with 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 being carried out in 2016.

Requirements analysis

The requirements analysis took place at the start of 2016. It comprised a number of internal brainstorming sessions involving staff from different departments and resulted in following basic requirements being defined for the system:

- the system should allow optimisation of the data collection logistics;
- the system should increase the efficiency of manual data collection;
- data collection protocols should be integrated into the system;
- the system should be decision-supported;
- where possible, manual data collection should be minimised;
- the potential for errors in manual data entry and data interpretation should be minimised;
- the system should facilitate data quality checks carried out by data quality staff;
- the system should allow data overviews to be created for data collectors, data quality staff and members of the HIV treatment teams at the hospitals;
- it should be possible to monitor back-logs, missing data and inconsistencies;
- it should be possible to assign different roles and create different work processes;
- it should be possible to host the system within the AMC;
- independent functional management of the system by SHM staff should be possible.

The requirements for the system and SHM's wishes were discussed with several specialists from ICT Automatisering and LogicNets, who subsequently translated these requirements and wishes into technical solutions, suggesting alternatives where necessary. The requirements were then classified according to the MoSCoW method (Must haves, Should haves, Could haves and Won't haves). Finally, with the involvement of staff from ADICT who currently support the data warehouse, a cost-benefit analysis was carried out.

During this phase, consideration was also given to the role of the data warehouse. The cost-benefit analysis revealed that to guarantee functionality, maximise the added value of the new system and achieve the desired efficiency, updating the data warehouse would be unavoidable. Therefore, SHM decided to include this in the project and asked LogicNets to include it in their proposal.

Following a thorough analysis and a legal assessment of the proposal, SHM's board approved the development and implementation of the LogicNets system. An important factor in this decision was the decision support feature of the LogicNets system that should allow SHM to organise manual data collection efficiently, while maintaining quality.

It is expected that the system will be implemented within 18 months through a collaborative effort involving LogicNets, ICT Automatisering, ADICT and SHM. The project has been named 'LISA', an acronym of the names of these organisations (**L**ogicNets, **I**CT Automatisering, **S**HM and **A**DICT), and was officially launched on 24 May 2016.

LISA project: approach and progress in 2016

Following the official start of LISA, the project was organised according to the PRINCE2 approach. The project was divided into eight manageable phases of 6 weeks, and the work packages in each phase were defined and planned for all those involved. Careful consideration was given to the dependencies between the different parties when planning the delivery of the products in each phase.

All work packages involved contribute to the products planned for each phase. Globally, the work package tasks have been distributed as follows:

- SHM is responsible for the content, modelling of content in the data entry application and modelling of the application for the data warehouse. In addition, SHM is responsible for the data model and for the migration of historical data to the new data warehouse. SHM's activities in each phase comprise 2 weeks' preparation and 4 weeks' production, including testing the products.
- ICT Automatisering/LogicNets is responsible for the design, development and installation of the data entry application. They are also responsible for training and coaching SHM staff in modelling the data entry application.
- ADICT is responsible for building the IT infrastructure required for the data warehouse and data entry application and for the authentication and authorisation of all end users.

To ensure that the project runs smoothly, various project teams have been set up within SHM. From the outset of LISA, one of these teams (the protocol team) started converting current data collection protocols into decision tree structures. The team has built the decision trees as efficiently as possible to ensure that there are no unnecessary steps or queries. Around 170 decision trees have now been identified, most of which were designed and conceptually tested in 2016. Those responsible for carrying out data analyses within SHM have been given the task of assessing and approving the decision trees on the basis of each person's field of expertise. During the eight phases of the project, the approved protocols will be built in LogicNets and re-tested by the end users (i.e., data collectors, data quality staff and data analysts).

In 2016, the first two phases of the project were successfully completed. At the end of each phase, the results were presented by LogicNets and SHM to all project staff, steering committee members and end user representatives. The final six phases will be planned and implemented during the course of 2017.

LabLink

LabLink is part of SHM's innovation programme that was launched in 2013 to automate data collection as far as possible and, as such, minimise manual data collection. LabLink is the name given to the interface implemented at an HIV treatment centre to allow laboratory data to be collected digitally wherever possible and entered directly into SHM's data

warehouse. Using LabLink, HIV-related laboratory data are selected from hospital information systems and sent to SHM in a pseudonymised form. These data are then entered into SHM's data warehouse by ADICT. In 2012, a standard LabLink protocol 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). All HIV treatment centres with LabLink now send data to SHM according to this standard.

For the pseudonymisation of LabLink data, each hospital maintains a LabLink-specific overview of those individuals who are in care, have left care or have objected to data collection. Laboratory results are only collected for those individuals who are in care and who have not lodged an objection to their data being collected. For each laboratory result, the following data are required:

- pseudonym,
- date of sample collection,
- test carried out,
- result,
- unit,
- material code,
- assay code,
- normal values.

Implementation of LabLink

In 2013, all HIV treatment centres were informed about LabLink and sent the standard LabLink protocol so that they could investigate how LabLink could be implemented within their existing IT infrastructure. Between 2013 and 2016, LabLink was set up in 12 hospitals. Further expansion of LabLink to other hospitals was continued in 2016 and, after intensive preparatory work, LabLink was implemented in the thirteenth hospital, namely OLVG. In addition, the scope of LabLink was expanded in UMC Utrecht to include retrospective laboratory results. In the remaining hospitals, LabLink could not yet be set up due, primarily, to the ongoing internal implementation of electronic medical record systems.

In total, 13 HIV treatment centres now use LabLink and, together, deliver laboratory results from 62% of the individuals followed by SHM. This figure is expected to rise substantially in 2017 once LabLink has been implemented in those hospitals that are coupled to the OLVG laboratory computer system (MC Jan van Goyen, Hiv Focus Centrum, Flevoziekenhuis and MC Zuiderzee) and in those where the first steps towards LabLink implementation have already been taken. In 2016, the AMC continued to transfer results directly to SHM from its laboratory computer system using an internal LabLink connection, made possible because SHM is connected to the AMC IT network.

Harmonisation of LabLink data

In 2012, the CRU developed a LabLink 'mapping tool' in Microsoft Access. This tool receives and standardises ('harmonises') laboratory results from different treatment centres with different terminology. In 2016, 2,386 combinations of laboratory terms and accompanying samples were harmonised using this tool.

Centralisation of data collection

The collection of data from all individuals who are in care at an HIV treatment centre in the Netherlands is carried out by data collectors. Most data collectors are centrally employed by SHM, while a smaller number remain locally employed by the HIV treatment centre. However, SHM remains responsible for the training and coaching of all data collectors.

The efficiency and quality of data collection and data entry in treatment centres seems to be linked to the amount of time data collectors have for data collection activities. This appears to be more limited for locally-employed data collectors, who often have other duties besides data collection. One solution is the centralisation of data collection, which requires the mobile deployment of specially trained staff employed by SHM (central data collectors) and has proven to be highly valuable in terms of achieving efficient, timely, and high-quality data collection.

In 2016, central data collectors provided assistance to local data collectors in UMC Utrecht, Spaarne Gasthuis, ETZ (Elisabeth-TweeSteden Ziekenhuis) and Erasmus MC to ensure that data collection in these HIV treatment centres remained up to date and to resolve discrepancies in the data. Moreover, central data collectors also collected prospective and retrospective data on hepatitis and entered these data into SHM's national database. Finally, central data collectors were involved in collecting additional data from a number of HIV treatment centres as part of a national collaboration entitled the NOVA study (part of the H-TEAM project), thereby creating more data analysis opportunities for the researchers involved.

Knowledge management

In 2016, SHM trained four new data collectors, with specific training on relevant medical information relating to HIV, data collection protocols and the data entry system. In addition to the personal coaching of existing data collectors, two review days were organised in March and November 2016 for all data collectors. In March, the review day focused on the results of research carried out by SHM's data analysis team using SHM's data. Moreover, protocol changes were presented in an interactive manner and, finally, the LISA project was introduced, including the new data entry system that data collectors will start using in 2018. An extensive demonstration of this new system followed during the second review day held in November. This review day also covered a research proposal for a study using SHM's data (the IRIS study) and the effect of hepatitis C (HCV) treatment in HIV/HCV co-infected

individuals in the Netherlands. Towards the end of the day, case studies and protocol changes were discussed in the form of an interactive smartphone quiz.

As part of the LISA project, a number of members of the LISA team from the Data & QC unit were trained and gained certification in project management skills based on the Prince2 method. Moreover, a number of SHM staff also received training in LogicNet design.

Other training provided in 2016 included an internal auditor training for three members of staff involved in the ISO certification project and Excel training for a number of data collectors to enable them to work more efficiently.

ISO 9001 and ISO 27001 certification

SHM works with pseudonymised patient information and treats this information with the utmost care. To ensure that SHM can continue to protect patients´ privacy in the current digital landscape, SHM plans expand its existing PDCA-based quality management system (described in detail in the 2015 annual report) by acquiring ISO 9001 and ISO 27001 certification.

ISO 9001 certification comprises requirements for a general quality management system, while ISO 27001 is a standard that is fully focused on the security of company information and confidential information made available to the organisation. This standard also includes the Dutch NEN7510 standard (`Information security in health care´), which is an instrument for managing and continually improving security. SHM´s goals for information security are fully compliant with the requirements set out by the ISO 27001 standard and described in current legislation (including the general data protection regulation that will come into force on 25 May 2018), and the agreements regarding personal data protection as defined in the individual contracts between SHM and HIV treatment centres.

To gain the ISO 9001 and ISO 27001 certification, the following steps have already been taken in 2015 and 2016:

- a baseline assessment was carried out;
- internal processes were defined;
- a framework was put in place for an information security management system;
- a quality management coordinator was appointed;
- a quality manual was set up based on ISO 9001 requirements;
- preparatory work was carried out for internal audits.

In 2017, internal and external audits will be carried out to gain the ISO 9001 and ISO 27001 certification.

Core activities

Patient registration

Patient registration involves registering and de-registering patients in the registration system, and is carried out separately from the data collection activity. Patient registration takes place centrally because of the need to generate a unique number under which all subsequent data are stored and processed. This approach creates a clear separation between privacy-sensitive data and the pseudonymised data stored in the national database.

In 2016, the registration and de-registration protocol was revised. In addition, validity and reliability checks were carried out on patient registration on a monthly basis. In 2016, 1,806 individuals were registered and 1,048 individuals were de-registered. These numbers include new diagnoses and de-registration due to death of an individual, as well as registration and de-registration due to an individual moving to another HIV treatment centre or abroad.

Data collection and data entry

Manual collection of data from all individuals being followed in any of the HIV treatment centres in the Netherlands is carried out by data collectors. Data are collected straight from either paper or electronic medical records and, based on data collection protocols, standardised, coded and entered into SHM's data entry system.

Volume of data collection

Figures 1 and 2 summarise the results of the data collection. *Figure 1A* shows that the total volume of manual data collection decreased by 6% in 2016 compared with 2015. This decrease in manual data collection is due to the expansion of LabLink, which resulted in a shift from manual to automated collection of laboratory data. *Figures 1B-D* present the volume of manual data collection for each data collection topic, according to patient population and year. The marked increase in data points in 2012 is related to the migration of data collected before 2003 from a Microsoft Access data entry database to the current Oracle Clinical data entry system. Despite the implementation of LabLink in 13 HIV treatment centres, laboratory results still represent the largest proportion of manually collected data points in all patient groups (*Figure 1B*), with the exception of HIV-exposed children (*Figure 1C*). This observation further supports SHM's digitisation strategy, which aims to improve efficiency through nationwide implementation of LabLink.

Figure 1A: Results of manual data collection from 2004-2016.

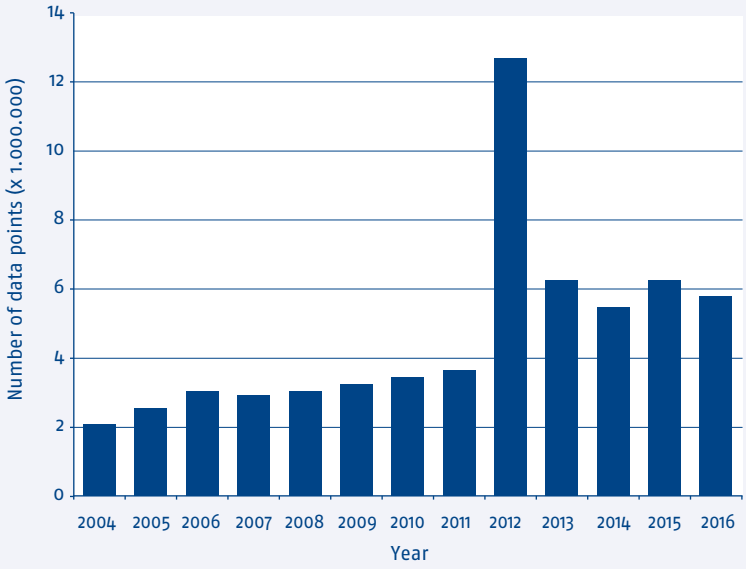


Figure 1B: Number of manually collected data points per data collection topic for HIV-positive adults from 2004-2016.

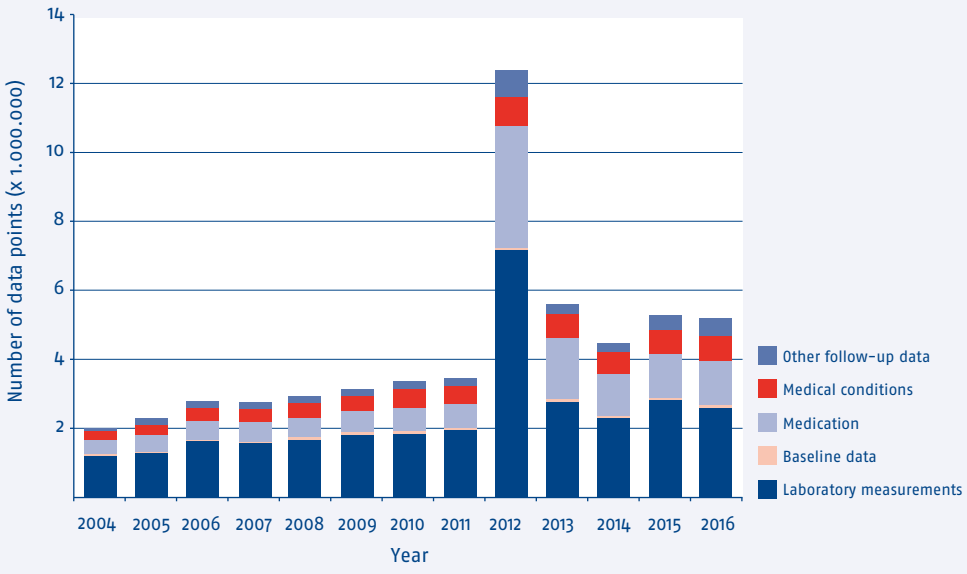
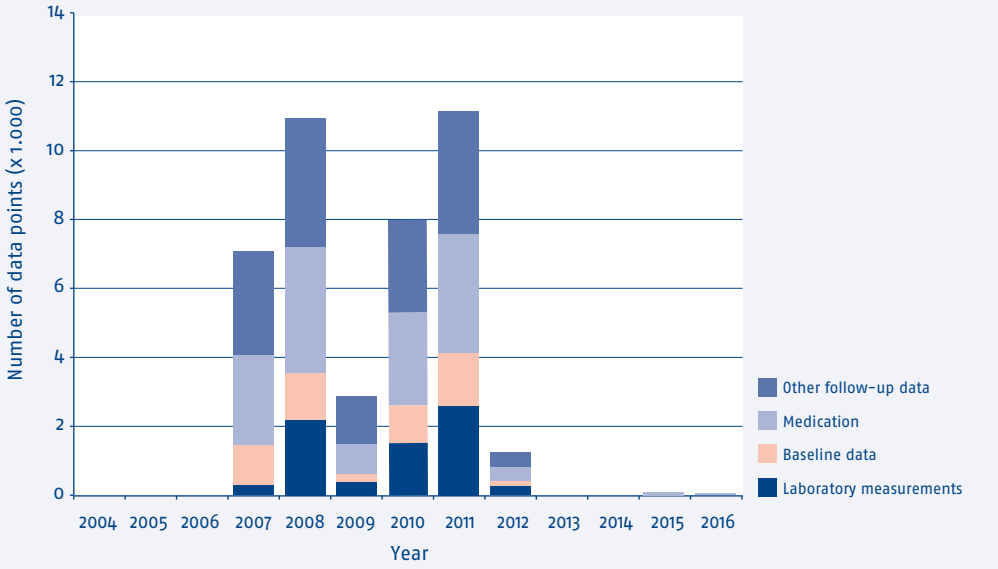


Figure 1C: Number of manually collected data points per data collection topic for HIV-exposed children from 2004-2016.



The volume of manually collected data from HIV-infected children increased slightly in 2016 (*Figure 1D*). This increase is due to efforts to work away the data entry backlog that arose at the Wilhelmina Kinderziekenhuis in 2015.

The total volume of manually collected data on viral hepatitis in individuals infected with both HIV and hepatitis also increased slightly in 2016 (*Figure 1E*). This increase can be explained by an increase in the number of people who were treated with the new agents against HCV infection, which in turn necessitated more HCV RNA measurements. In fact, in this patient population, the collection of follow-up data on viral hepatitis co-infection consisted primarily of laboratory data.

Figure 1D: Number of manually collected data points per data collection topic for HIV-positive children from 2004-2016.

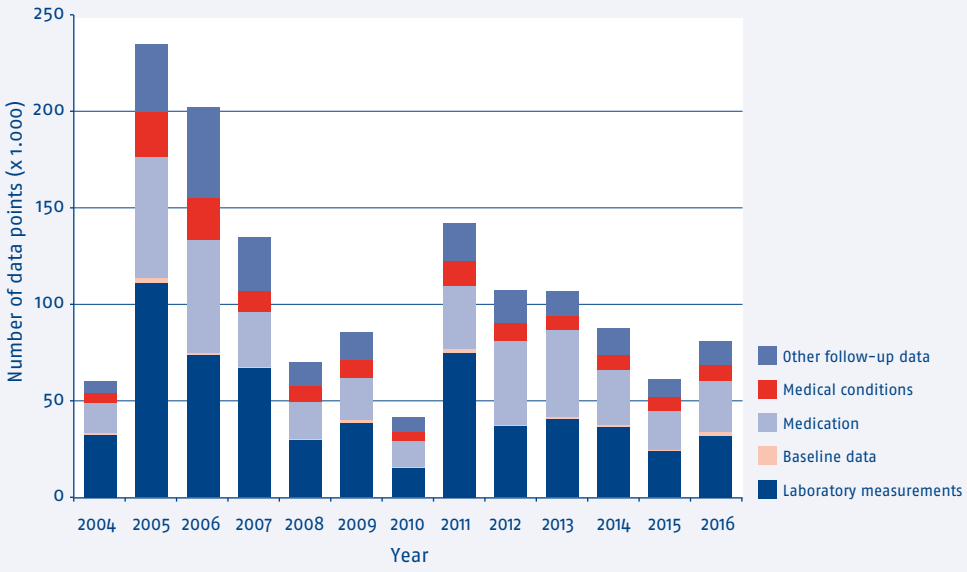


Figure 1E: Number of manually collected data points per data collection topic for HIV-positive adults with a viral hepatitis co-infection from 2004-2016.

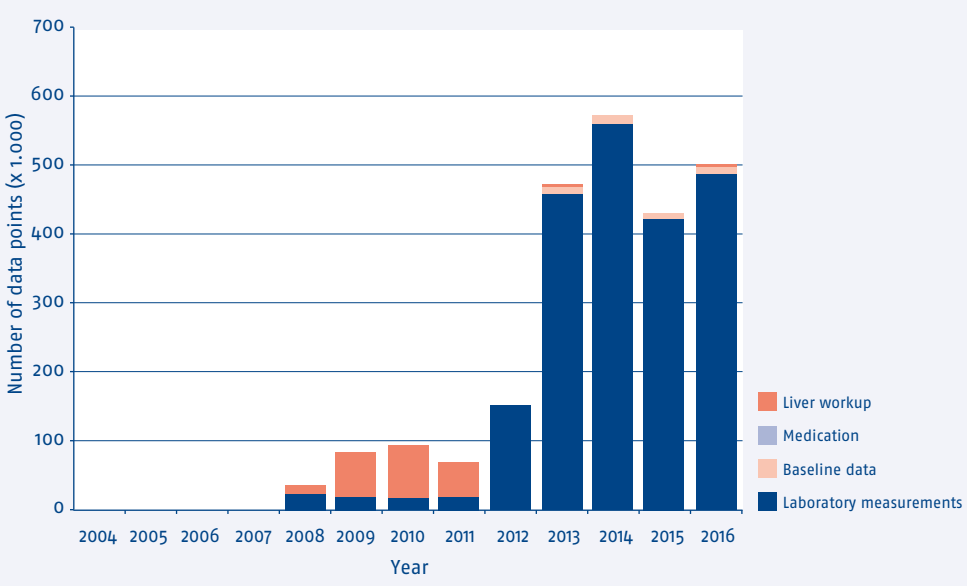
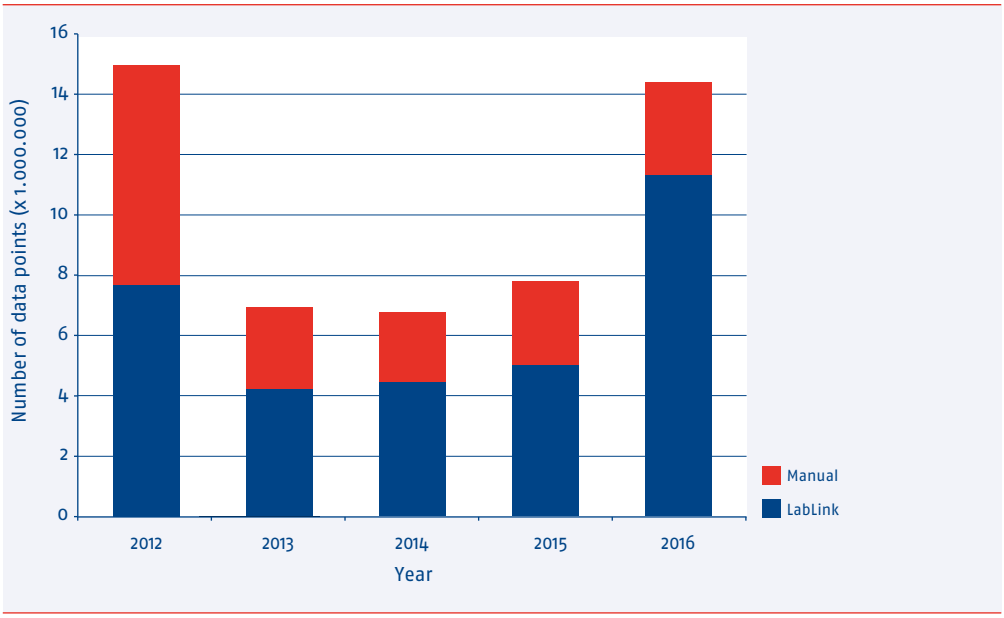


Figure 2 represents the proportion of laboratory data points collected through LabLink compared to laboratory data points collected manually. As expected, the number of data points collected through LabLink increased markedly in 2016. This increase reflects the expansion of LabLink to OLVG, and the transmission of retrospective data from UMC Utrecht.

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 fewer 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 subsequent visit. The predicted time is calculated on the basis of the frequency of visits in the year prior to the last visit. A difference of 180 days or less is not considered a delay.

The average short-term backlog in 2016 was low for most centres and, at 5%, remained the same as in 2015. The average long-term backlog in data collection in 2016 remained 0%. These are good results given that, in 2016, 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. Another factor that has contributed to this outcome is the ongoing training of data collectors in efficient data collection, where individual patient reports and standard data queries are used to monitor backlogs and establish priorities.

These results are expected to improve further once the new data entry system comes into use.

Table 1: Percentage of individuals 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**	**2016**	**2015**	**2016**	**2015**
Noordwest Ziekenhuisgroep	Alkmaar	0%	1%	3%	5%
Flevoziekenhuis	Almere	0%	1%	8%	4%
AMC-UvA	Amsterdam	1%	0%	4%	5%
Hiv Focus Centrum	Amsterdam	0%	0%	5%	2%
MC Jan van Goyen	Amsterdam	0%	0%	5%	4%
OLVG	Amsterdam	1%	0%	1%	1%
OLVG West	*Amsterdam*	*1%*	*0%*	*1%*	*0%*
MC Slotervaart	Amsterdam	0%	1%	3%	3%
VUmc	Amsterdam	1%	1%	5%	8%
Rijnstate	Arnhem	0%	0%	9%	3%
HagaZiekenhuis	Den Haag	0%	0%	0%	0%
HMC	Den Haag	0%	0%	6%	6%
Catharina Ziekenhuis	Eindhoven	1%	0%	5%	7%
MST	Enschede	0%	0%	0%	0%
ADRZ	Goes	0%	0%	6%	4%
UMCG	Groningen	0%	0%	9%	14%
Spaarne Gasthuis	Haarlem	1%	0%	11%	14%
MCL	Leeuwarden	0%	0%	6%	8%
LUMC	Leiden	0%	0%	5%	10%
MC Zuiderzee	Lelystad	0%	0%	7%	7%
MUMC+	Maastricht	0%	0%	8%	7%
Radboudumc	Nijmegen	0%	0%	12%	1%
Erasmus MC	Rotterdam	3%	2%	8%	8%
Maasstad Ziekenhuis	Rotterdam	0%	0%	1%	1%
ETZ	Tilburg	1%	0%	1%	0%
UMC Utrecht	Utrecht	1%	0%	12%	11%
Isala	Zwolle	0%	1%	1%	0%
Mean		**0%**	**0%**	**5%**	**5%**

Quality control

In the 15 years since its foundation, SHM has developed extensive and valuable expertise for monitoring and maintaining data quality. In particular, as the number of patients being followed over a prolonged period of time has grown, data quality control efforts have become more demanding and complex. Moreover, quality control of digital data (obtained

through LabLink) requires a different approach. The quality of manually collected data is checked and improved by means of both manual and automated checks.

Manual quality control

SHM's data quality staff carry out manual quality checks by taking a number of random samples of data from the database that are subsequently compared with the source data in the electronic or paper medical records. Since manual checks are very time-consuming, these random selections are carried out on a risk-driven basis. This means that manual checks are carried out primarily on data that are considered to have a high impact on the outcome of data analyses and on data that are more complex and therefore carry a higher risk of data entry errors.

Table 2 shows the results of the manual quality checks performed by the SHM data quality staff in 2016. These manual checks focussed on collected data that are essential for SHM's output and on complex data that can be used as training material for personal coaching of data collectors.

Data related to cause of death and comorbidity, defined as 'endpoints', continued to be checked in 100% of cases in 2016. Additional data were also collected and classified for data analysis. Moreover, to detect potentially missed cases of myocardial infarction, data from 41 patients were checked in 2016.

As part of the personal coaching programme for those data collectors who required support, a total of 20 patient files were selected in 2016. The results of the quality checks were discussed with the responsible data collector and item-specific training was provided.

In the course of 2016, data from 1,154 patients were checked manually by SHM data quality staff. In addition, for all patients for whom data collectors reported cardiovascular disease or other endpoints in the national SHM database in 2016 (n=1,093), data collected from these patients' 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 12.5 times by the SHM data quality staff member responsible for that centre.

The number of patients whose files were quality-controlled dropped by 60% in 2016 compared with 2015. This decrease is due to an increase in project-based activities within SHM's Data & QC unit as part of the major improvement project, LISA. During the course of the LISA project, and after careful consideration, the scope of manual data collection has been limited to a minimum number of random selections, but in such a way as to guarantee the quality of data as far as possible. It is expected that the backlog in quality checks will be efficiently resolved once LISA has been implemented.

Table 2: Number of patient files checked by data quality staff, according to data selection criterion.

Selection criteria for quality checks	2016	2015
Random selection		
Random selection of adverse event data	0	0
Random selection of antiretroviral medication data	0	0
Random selection of baseline data	0	671
Random selection of CDC event data	0	0
Random selection of co-medication data	0	0
Random selection of data on pregnancies	0	0
Random selection of data on viral hepatitis B infection	0	8
Random selection of data on viral hepatitis C infection	0	2
Random selection of all patient data	0	0
Random selection of data from last year of follow up	0	0
Subtotal random selection	**0**	**681**
Consistency checks		
Inconsistencies in adverse event data	0	0
Inconsistencies in antiretroviral medication data	0	0
Inconsistencies in baseline data	0	0
Priority analysis of baseline data	0	0
Inconsistencies in CDC event data	0	0
Inconsistencies in co-medication data	0	0
Inconsistencies in laboratory data	0	4
Subtotal consistency checks	**0**	**4**
Detection of missed comorbidities, defined as endpoints		
Cardiovascular disease	41	951
Diabetes mellitus	0	0
Chronic liver disease	0	0
Renal disease	0	0
Non-AIDS-defining malignancies	0	0
Subtotal of detected missed comorbidities	**41**	**951**
Comorbidity and cause of death checks		
Total cardiovascular disease	493	707
Myocardial infarction	*(90)*	*(186)*
Invasive cardiovascular procedures	*(101)*	*(135)*
Diabetes mellitus	*(227)*	*(310)*
Stroke	*(75)*	*(76)*
Chronic liver disease	22	43
End-stage kidney disease	41	45
Non-AIDS-defining malignancies	364	254
Cause of death in 100% of cases	173	173
Subtotal of comorbidity and cause of death	**1,093**	**1,222**
Subtotal personal coaching of data collectors	**20**	**38**
Total number of quality checks	**1,154**	**2,896**
Change (%) per year	**60%**	**61%**

2014	2013	2012	2011	2010
0	0	0	0	0
0	3	0	1	0
0	0	56	81	0
0	0	0	0	0
0	0	0	0	0
229	88			
135	169			
138	0			
0	0	0	0	1
0	0	0	0	0
502	**260**	**56**	**82**	**1**
0	0	32	237	1,147
0	0	0	2	2
0	0	0	11	0
160	0	0	0	0
0	0	0	1	2
0	0	0	0	0
156	0	0	1	4
316	**0**	**32**	**252**	**1,155**
	184			
	280			
	219			
	84			
	36			
	803			
357	652	186	223	219
(77)	*(106)*	*(51)*	*(38)*	*(46)*
(98)	*(131)*	*(49)*	*(49)*	*(49)*
(168)	*(312)*	*(54)*	*(76)*	*(101)*
(14)	*(103)*	*(32)*	*(60)*	*(23)*
32	41	12	23	10
25	85	16	34	12
173	332	294	137	177
211	247	227	185	152
798	**1,357**	**735**	**602**	**570**
184	**309**	**168**	**154**	**124**
1,800	**2,729**	**991**	**1,090**	**1,850**
-30%	**175%**	**-9%**	**-41%**	**96%**

Automated quality control

In 2016, automated quality checks were carried out to support the manual quality checks by data quality staff and to further improve efficiency. *Table 3* presents the results of the automated quality checks in 2016. In total, 169 validation rules were defined and 5,797 records with discrepancies were selected for checking by the data collectors. Checking was facilitated by presenting the selected records to the data collectors in user-friendly online reports. The number of records with discrepancies dropped by 53% in 2016, highlighting the effectiveness of automated quality checks and the resulting improvements in data quality compared to the previous year.

LabLink quality control

Both automated and manual checks, developed in 2013, were carried out on the LabLink data in 2016. 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 the 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 expected;
- 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 medical records (carried out by the data collectors).

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

Selection criteria for quality checks	2016		2015		2014		2013		2012	
	Validation rules (n)	Records (n)	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	168	24	198	24	881	26	1,698	25	2,759
Missing and/or inconsistent demographic data	11	85	11	167	11	245	12	247	7	431
Missing and/or inconsistent adverse events data	8	85	8	99	8	93	8	178	6	522
Missing and/or inconsistent antiretroviral medication data	18	1,117	17	4,277	18	2,549	16	3,626	15	20,697
Missing and/or inconsistent CDC event data	5	6	5	53	5	64	5	126	6	161
Missing and/or inconsistent data on viral hepatitis infection	6	17	5	34	6	137	7	291		
Missing and/or inconsistent co-medication data	4	119	4	116	4	144	4	202	4	337
Missing and/or inconsistent laboratory data	31	1,449	31	4,027	32	5,522	26	2,986		
Missing and/or inconsistent end of follow-up data	10	659	10	696	10	359	10	610	10	1,297
Cross comparisons based on HICDEP[a]	52	2,092	51	2,749	52	7,526	48	11,565		
Total number quality checks	**169**	**5,797**	**166**	**12,416**	**170**	**17,520**	**162**	**21,529**	**73**	**26,204**

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

Helpdesk and protocol management

This activity, carried out by a number of SHM's data quality staff, is designed to ensure the data collection protocols are kept up to date and to provide content-based input for staff training, with the aim of further improving the quality of SHM's database.

During 2016, the helpdesk received 199 queries from data collectors, 113 of which could be resolved immediately by the responsible data quality staff member. The helpdesk queries led to 29 code changes in protocols during 2016. These helpdesk-driven protocol changes were included in the overall revision of medically-based protocols, which was carried out in 2016 for the LISA project.

Data management and reporting

Data warehousing 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 2016, the data warehouse produced 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 took place twice in 2016, after which the raw data tables from the data warehouse were processed to yield tables suitable for data analysis. This involved cleaning, clustering, and coding the data according to the standard protocols of various national and international collaborations and the Anatomical Therapeutic Chemical (ATC) classification.

In 2016, these data processing steps resulted in data sets for use by SHM's researchers, centre-specific reports, and the Co-morbidity and Ageing with HIV (AGE_hIV) study. In addition, data processing and data set generation was carried out for four international collaborations, D:A:D, EuroSIDA, EPPICC and BEEHIVE.

Patient-specific reports, graphs and 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 raw data from their own patients. In 2016, these reports, graphs and other standard data queries were maintained, further developed where needed, and improved.

Centre-specific reports

Standard reports for each centre are presented twice a year on a password-protected area of the SHM website. These centre-specific reports are intended to provide treatment teams in the treatment centres with an overview of developments, trends and issues within their own patient populations compared to the national average. These centre-specific reports were updated and made available to the HIV treatment centres twice during the course of 2016.

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

This chapter provides a summary of the patient population registered in Stichting HIV Monitoring's database as of 31 December 2016.

General

Up to and including 31 December 2016, a cumulative total of 25,564 persons with HIV infection were registered through the Dutch HIV treatment centres by Stichting HIV Monitoring (SHM) (*Table 4*), of whom 1,014 were newly-registered in 2016 (*Table 5*). Of the 25,564 registered persons, 20,497 (80%) were men, and 5,067 (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 25,036 of the cumulative total of registered individuals. The remaining 528 (2.1%) persons objected to the collection of their data.

In 2016, data were collected from 19,426 (76%) individuals. Of the 6,138 (24%) individuals with no data collected in 2016, 2,697 had died before 2016, 1,414 had moved abroad and 2,027 had disappeared from care for an unknown reason or had objected to the collection of their data. Taking into account those persons who objected to data collection and those who died in 2016, as of 31 December 2016, there remained 19,226 HIV-positive individuals in care for whom data were collected in 2016.

Adults

Of the 25,036 individuals registered up to and including 2016 and for whom further clinical data were collected, 24,592 were adults at the time of registration, comprising 19,917 (81%) men and 4,675 (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] 30.1-45.3) years for men and 31.5 (IQR 26.1-39.1) years for women. At the end of 2016, 3% of the entire group had tested positive for HIV less than a year earlier, 15% had tested HIV-positive 1 to 5 years ago, 24% had tested HIV-positive 5 to 10 years ago, and 47% had tested HIV-positive more than 10 years ago. For 0.4% of the group, the HIV diagnosis date had not, or not yet, been registered. The remaining 11% of the 24,592 adults had died. The median follow-up duration was 9.0 (IQR 4.4-15.0) years: 8.8 years for men and 10.3 years for women. The total follow up in the adult group was 252,517 person years.

Of the 958 HIV-positive adults registered in 2016 for whom further clinical data were collected, the main transmission route remained sexual contact with other men (74%) in men and heterosexual contact (91%) in women. The median age at diagnosis was 36.5 (IQR 27.7-49.5) years in men and 35.2 (IQR 29.7-47.5) years in women.

Children

Of the 25,036 persons registered as of 31 December 2016, 444 (2%) were children or adolescents. This group consisted of 208 (47%) boys and 236 (53%) girls. The median age at HIV diagnosis was 2.7 (IQR 0.4-9.8) years for boys and 3.1 (IQR 0.4-15.3) years for girls. In the majority of cases, the route of infection was vertical mother-to-child transmission (71%); in 20% of cases, the route of infection was recorded as sexual transmission. In total, 29% of the HIV-positive children were born in the Netherlands, and 58% were born in sub-Saharan Africa. The median duration of follow up was 9.9 (IQR 5.3-14.7) years: 10.2 years for boys and 9.4 years for girls. The total follow up for the group of children and adolescents was 4,628 person years.

In 2016, 19 children and adolescents (11 children aged between 0 and 12 years and 8 adolescents aged 13-17 years) were newly registered, comprising 7 boys and 12 girls. Ten of the 19 newly-registered children and adolescents came from sub-Saharan Africa. Eight of the newly-registered HIV-positive children lived with adoption parents. Seven children and one adolescent had become infected through vertical transmission, while six adolescents had contracted HIV through sexual contact; the route of transmission in the remaining four children and adolescents was unknown. In the case of one child, the parents objected to further registration of clinical data.

Pregnant women

The total number of cumulatively registered pregnancies in HIV-positive women increased from 2,996 in 2015 to 3,180 in 2016. These pregnancies occurred in 1,787 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 pregnant women was mainly through heterosexual contact (93%); in 1.5% of the pregnant women, transmission occurred through injecting drug use. In 37% of the pregnant women, combination antiretroviral therapy (cART) was started before the first pregnancy was diagnosed, and in 50% of the pregnant women, cART was started during the pregnancy. The remaining 13% of the pregnant women did not start cART before or during pregnancy, and 44% of these pregnancies terminated prematurely through either miscarriage or abortion.

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, it was unknown whether the mothers were known to be HIV-positive or had undergone pregnancy screening.

Table 4: Cumulative numbers and percentages of HIV-positive individuals registered by SHM and monitored in one of the HIV treatment centres in the Netherlands and in Curaçao on 31 December 2016.

		Total		Alive		Deceased		Objection[a]		Data in 2016[b]		No data in 2016			
												Deceased before 2016[c]		Other reasons[d]	
HIV treatment centre	**Location**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adult															
Noordwest Ziekenhuisgroep	Alkmaar	360	1.4	328	91.1	32	8.9	5	1.4	298	82.8	28	7.8	34	9.4
Flevoziekenhuis	Almere	200	0.8	191	95.5	9	4.5	3	1.5	176	88.0	8	4.0	16	8.0
AMC-UvA	Amsterdam	3,025	12.0	2,608	86.2	417	13.8	13	0.4	2.239	74.0	394	13.0	392	13.0
Hiv Focus Centrum	Amsterdam	597	2.4	593	99.3	4	0.7	0	0.0	580	97.2	3	0.5	14	2.3
MC Jan van Goyen	Amsterdam	312	1.2	270	86.5	42	13.5	4	1.3	213	68.3	39	12.5	60	19.2
OLVG	Amsterdam	3,926	15.5	3,459	88.1	467	11.9	158	4.0	2,907	74.0	449	11.4	570	14.5
MC Slotervaart	Amsterdam	860	3.4	701	81.5	159	18.5	12	1.4	599	69.7	155	18.0	106	12.3
VUmc	Amsterdam	659	2.6	569	86.3	90	13.7	12	1.8	467	70.9	89	13.5	103	15.6
Rijnstate	Arnhem	850	3.4	767	90.2	83	9.8	3	0.4	682	80.2	77	9.1	91	10.7
HMC	Den Haag	1,108	4.4	1,018	91.9	90	8.1	45	4.1	830	74.9	85	7.7	193	17.4
HagaZiekenhuis	Den Haag	756	3.0	649	85.8	107	14.2	32	4.2	500	66.1	105	13.9	151	20.0
Catharina Ziekenhuis	Eindhoven	695	2.7	649	93.4	46	6.6	5	0.7	560	80.6	41	5.9	94	13.5
MST	Enschede	619	2.4	505	81.6	114	18.4	4	0.6	387	62.5	109	17.6	123	19.9
ADRZ	Goes	211	0.8	195	92.4	16	7.6	2	0.9	165	78.2	16	7.6	30	14.2
UMCG	Groningen	946	3.7	846	89.4	100	10.6	31	3.3	732	77.4	92	9.7	122	12.9
Spaarne Gasthuis	Haarlem	515	2.0	459	89.1	56	10.9	4	0.8	397	77.1	55	10.7	63	12.2
MCL	Leeuwarden	310	1.2	278	89.7	32	10.3	1	0.3	253	81.6	26	8.4	31	10.0
LUMC	Leiden	729	2.9	661	90.7	68	9.3	41	5.6	556	76.3	64	8.8	109	15.0
MC Zuiderzee	Lelystad	81	0.3	80	98.8	1	1.2	1	1.2	70	86.4	0	0.0	11	13.6
MUMC+	Maastricht	934	3.7	788	84.4	146	15.6	5	0.5	676	72.4	137	14.7	121	13.0
Radboudumc	Nijmegen	765	3.0	675	88.2	90	11.8	19	2.5	606	79.2	88	11.5	71	9.3
Erasmus MC	Rotterdam	2,636	10.4	2,331	88.4	305	11.6	13	0.5	1,963	74.5	288	10.9	385	14.6
Maasstad Ziekenhuis	Rotterdam	780	3.1	724	92.8	56	7.2	8	1.0	656	84.1	52	6.7	72	9.2
ETZ	Tilburg	1,174	4.6	1,093	93.1	81	6.9	19	1.6	939	80.0	73	6.2	162	13.8
UMC Utrecht	Utrecht	1,749	6.9	1,556	89.0	193	11.0	65	3.7	1,354	77.4	187	10.7	208	11.9
Isala	Zwolle	509	2.0	472	92.7	37	7.3	20	3.9	397	78.0	34	6.7	78	15.3
Total		**25,306**	**100.0**	**22,465**	**88.8**	**2,841**	**11.2**	**525**	**2.1**	**19,202**	**75.9**	**2,694**	**10.6**	**3,410**	**13.5**

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HIV treatment centre	Location	Total		Alive		Deceased		Objection[a]		Data in 2016[b]		No data in 2016			
												Deceased before 2016[c]		Other reasons[d]	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Paediatric															
EKZ, AMC–UvA	Amsterdam	71	27.5	71	100.0	0	0.0	1	1.4	64	90.1	0	0.0	7	9.9
BKZ, UMCG	Groningen	28	10.9	28	100.0	0	0.0	0	0.0	26	92.9	0	0.0	2	7.1
Erasmus MC – Sophia	Rotterdam	82	31.8	80	97.6	2	2.4	0	0.0	69	84.1	2	2.4	11	13.4
WKZ, UMC Utrecht	Utrecht	77	29.8	76	98.7	1	1.3	2	2.6	65	84.4	1	1.3	11	14.3
Total		**258**	**100.0**	**255**	**98.8**	**3**	**1.2**	**3**	**1.2**	**224**	**86.8**	**3**	**1.2**	**31**	**12.0**
Curaçao															
SEHOS	Willemstad	1,031	98.6	864	83.8	167	16.2	1	0.1	573	55.6	163	15.8	295	28.6
SEHOS kinderkliniek	Willemstad	15	1.4	5	33.3	10	66.7	0	0.0	0	0.0	10	66.7	5	33.3
Total Curaçao		**1,046**	**100.0**	**869**	**83.1**	**177**	**16.9**	**1**	**0.1**	**573**	**54.8**	**173**	**16.5**	**300**	**28.7**

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

[b] *Data in 2016: registered by SHM in 2016, or deceased during 2016, or last contact with an HIV treatment centre during or after 2016.*

[c] *No data in 2016 – deceased before 2016: patients who are not included in 'data in 2016' and who had died before 2016.*

[d] *No data in 2016 – other reasons: patients who are not included in 'data in 2016' because they moved abroad before 2016 or because they had no contact with their HIV treatment centre in 2016 for an unknown reason.*

Table 5: HIV-positive individuals newly registered in 2016 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									
Noordwest Ziekenhuisgroep	Alkmaar	24	2.4	24	100.0	0	0.0	3	12.5
Flevoziekenhuis	Almere	9	0.9	9	100.0	0	0.0	0	0.0
AMC-UvA	Amsterdam	81	8.1	80	98.8	1	1.2	3	3.7
Hiv Focus Centrum	Amsterdam	23	2.3	23	100.0	0	0.0	0	0.0
MC Jan van Goyen	Amsterdam	17	1.7	17	100.0	0	0.0	0	0.0
OLVG	Amsterdam	120	12.0	120	100.0	0	0.0	4	3.3
MC Slotervaart	Amsterdam	12	1.2	12	100.0	0	0.0	0	0.0
VUmc	Amsterdam	22	2.2	22	100.0	0	0.0	3	13.6
Rijnstate	Arnhem	47	4.7	46	97.9	1	2.1	1	2.1
HMC	Den Haag	44	4.4	44	100.0	0	0.0	1	2.3
HagaZiekenhuis	Den Haag	28	2.8	28	100.0	0	0.0	0	0.0
Catharina Ziekenhuis	Eindhoven	39	3.9	39	100.0	0	0.0	1	2.6
MST	Enschede	38	3.8	37	97.4	1	2.6	1	2.6
ARDZ	Goes	17	1.7	17	100.0	0	0.0	0	0.0
UMCG	Groningen	33	3.3	33	100.0	0	0.0	3	9.1
Spaarne Gasthuis	Haarlem	30	3.0	30	100.0	0	0.0	0	0.0
MCL	Leeuwarden	18	1.8	17	94.4	1	5.6	0	0.0
LUMC	Leiden	26	2.6	26	100.0	0	0.0	5	19.2
MC Zuiderzee	Lelystad	4	0.4	4	100.0	0	0.0	0	0.0
MUMC+	Maastricht	62	6.2	60	96.8	2	3.2	1	1.6
Radboudumc	Nijmegen	26	2.6	26	100.0	0	0.0	0	0.0
Erasmus MC	Rotterdam	106	10.6	105	99.1	1	0.9	2	1.9
Maasstad Ziekenhuis	Rotterdam	39	3.9	39	100.0	0	0.0	0	0.0
ETZ	Tilburg	46	4.6	46	100.0	0	0.0	1	2.2
UMC Utrecht	Utrecht	73	7.3	72	98.6	1	1.4	7	9.6
Isala	Zwolle	17	1.7	16	94.1	1	5.9	1	5.9
Total		**1,001***	**100.0**	**992**	**99.1**	**9**	**0.9**	**37**	**3.7**
Paediatric									
EKZ, AMC-UvA	Amsterdam	3	23.1	3	100.0	0	0.0	0	0.0
BKZ, UMCG	Groningen	3	23.1	3	100.0	0	0.0	0	0.0
Erasmus MC – Sophia	Rotterdam	3	23.1	3	100.0	0	0.0	0	0.0
WKZ, UMC Utrecht	Utrecht	4	30.8	4	100.0	0	0.0	1	25.0
Total		**13**	**100.0**	**13**	**100.0**	**0**	**0.0**	**1**	**7.7**
Curaçao									
SEHOS	Willemstad	54	100.0	54	100.0	0	0.0	0	0.0

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

* *Includes 6 of the 19 children/adolescents newly-registered in 2016.*

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Monitoring of treatment

In 2016, 93% of the 25,036 HIV-positive individuals had ever been treated with cART, whereas 5% had not yet started treatment. No data had yet been registered for 0.5% of patients, and 0.8% were being treated with non-cART regimens. In total, 63% of the first-line cART regimens initiated in 2016 consisted of tenofovir in combination with emtricitabine as the nucleotide/nucleoside reverse transcriptase inhibitor (NRTI) backbone, and 35% consisted of abacavir and lamivudine. The most commonly-used additions to this backbone were dolutegravir (53%) and cobicistat-boosted elvitegravir (29%) *(Table 6)*.

Table 6: *Most frequently-used first-line combination antiretroviral therapy combinations in 2014-2016. (Note: data for 2016 are not yet complete).*

	2014		2015		2016		Total	
	n	%	n	%	n	%	n	%
TDF+FTC+EVG/c	501	34.7	198	17.3	189	28.5	888	27.3
ABC+3TC+DTG	60	4.2	421	36.8	225	34.0	706	21.7
TDF+FTC+EFV	232	16.1	89	7.8	27	4.1	348	10.7
TDF+FTC+RPV	195	13.5	61	5.3	19	2.9	275	8.5
TDF+FTC+DRV/r	160	11.1	77	6.7	23	3.5	260	8.0
TDF+FTC+DTG	34	2.4	139	12.1	71	10.7	244	7.5
TDF+FTC+ATV/r	52	3.6	43	3.8	12	1.8	107	3.3
TDF+FTC+DRV/r+DTG	4	0.3	19	1.7	30	4.5	53	1.6
Other	206	14.3	98	8.6	66	10.0	370	11.4
Total	**1,444**	**100.0**	**1,145**	**100.0**	**662**	**100.0**	**3,251**	**100.0**

Legend: *TDF=tenofovir, FTC=emtricitabine, EVG/c=elvitegravir/cobicistat, ABC=abacavir, 3TC=lamivudine, DTG=dolutegravir, EFV=efavirenz, RPV=rilpivirine, DRV/r=darunavir/ritonavir, ATV/r=atazanavir/ritonavir.*

In 2016, the median CD4 cell count at the start of cART was 410 (IQR 230-580) cells/mm^3. Of those patients who started cART in 2016, 73% started within 6 months of HIV diagnosis.

Collection of HIV sequence data

In 2016, the collection of sequences was expanded and now comprises all HIV treatment centres in the South Holland and Amsterdam regions. In total, to date, 14,058 reverse transcriptase and protease sequences and 91 integrase gene sequences have been collected.

Hepatitis B and hepatitis C co-infection

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-positive 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 2016,

chronic HCV co-infection was found in 6.4% of the monitored HIV-positive individuals. Chronic HBV co-infection was detected in 6.4% of the monitored HIV-positive individuals, and chronic co-infection with both HBV and HCV was found in 0.4% of the monitored HIV-positive individuals. Of the individuals with chronic HBV co-infection, 10.3% had liver fibrosis, 9.7% had liver cirrhosis, and 0.9% had HCC. In individuals with chronic HCV co-infection, these figures were 25%, 14% and 0.6%, respectively. The difference in liver fibrosis and cirrhosis prevalence between individuals with chronic HBV and those with chronic HCV co-infection may be due to the fact that 94% of HBV co-infected individuals received a cART regimen that included one or more agents active against both HIV and HBV. Finally, following the launch of the new direct-acting antiviral agents (DAAs) against HCV, an increasing number of individuals with an HCV/HIV co-infection are now receiving treatment for HCV. In total, 573 individuals with a chronic HVC infection have now been treated with the new DAAs.

Sample collection and storage

Since the start of the AIDS Therapy Evaluation in the Netherlands (ATHENA) project in 1996, an estimated total of 536,410 plasma samples from people 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 epidemiology 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-positive persons being followed in the St. Elisabeth Hospital in Willemstad, Curaçao, was continued during 2016. Results from the monitoring in Curaçao were presented in the Monitoring Report 2016. In total, 1,046 individuals were registered, of whom 54 were newly registered in 2016.

Key outcomes and recommendations in 2016

The HIV epidemic in the Netherlands

HIV-positive individuals registered in the Netherlands as of May 2016

As of May 2016, a total of 18,866 persons living with HIV in the Netherlands (18,657 adults, and 209 children and adolescents) were known to be in care in one of the 26 designated HIV treatment centres. Of these 18,866, 95% (17,909) had started combination antiretroviral therapy (cART), and of these 17,909, 93% (16,739) had suppressed viraemia to below 100 copies/ml 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 2015

In 2015, the majority (64%) of newly diagnosed infections were in men who have sex with men (MSM), 28% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission. Of note, almost one quarter of all newly-diagnosed individuals in 2015 were 50 years or older. Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to approximately 900 new diagnoses in recent years. Although this decreasing trend continued in 2015, the projected number of diagnoses for that year (865) may have been underestimated as registration of HIV diagnoses for this year has not yet been finalised. 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 individuals with a previously negative HIV test has also increased (72% of MSM, 28% of other men and 42% of women diagnosed in 2015 had a known previous negative test). Moreover, fortunately, the proportion of individuals 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 370 and 420 cells/mm^3, respectively, in 2015.

The likelihood of individuals starting cART at higher CD4 counts has also clearly increased. Whilst in 2014, 73% of individuals with a CD4 count of 500 cells/mm^3 had begun cART within 6 months of diagnosis, this proportion rose to 81% in 2015. Nonetheless, far too many individuals continue to present late for care. In 2015, 45% of newly diagnosed individuals presented late for care, i.e., with AIDS or a CD4 count less than 350 cells/mm^3, and 29% 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

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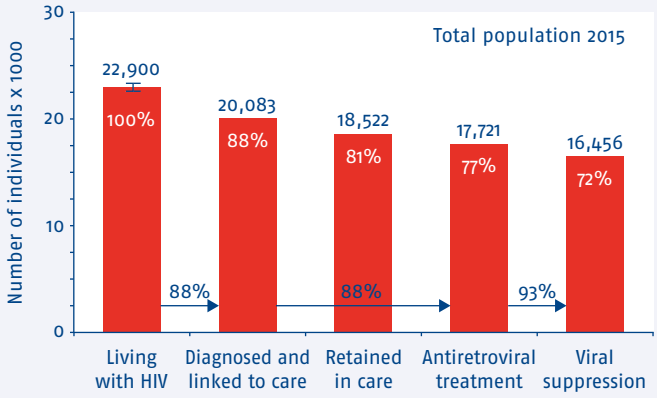
greater for men other than MSM, individuals originating from South and Southeast Asia and sub-Saharan Africa, and individuals aged 45 years or older.

Continuum of HIV care in 2015

By the end of 2015, 22,900 individuals were estimated to be living with HIV in the Netherlands, of whom 2,800 were still undiagnosed. On the basis of this estimated number of 22,900 people living with HIV, a continuum of HIV care has been constructed to depict engagement in HIV care in 2015 across a few key indicators, the last one being the number of individuals with suppressed viral load (See *Figure 3*). By the end of 2015, 20,083 individuals, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM. In total, 18,522 individuals were considered to still be in care. The majority of these individuals, 17,721 in total, had started cART, and 16,456 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 72% of the total estimated population living with HIV and 82% 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 2015.



A re-assessment of the continuum of HIV care for 2014 showed that there was a significant increase in the number of people on cART by the end of that year compared to what was reported in last year's report. Moreover, there was an even more pronounced increase in the number who achieved viral suppression. To better monitor progress towards achieving UNAIDS' 90-90-90 goals, a more timely registration of start of treatment and viral load measurements would be needed. The latter could be markedly improved by extending the automated import of laboratory measurements to all HIV treatment centres in the Netherlands.

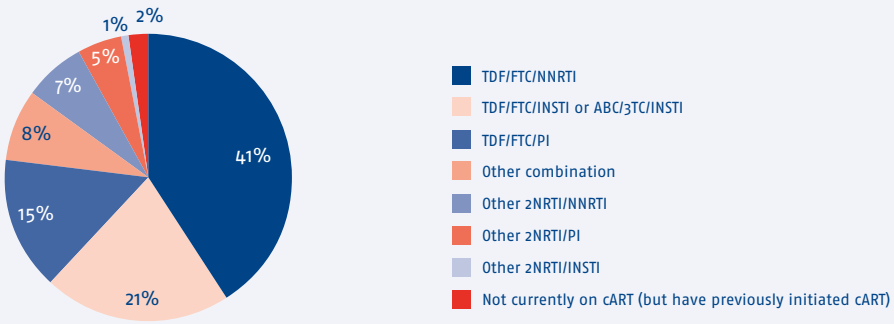
To achieve a significant decline in the rate of new infections, we continue to need improved transdisciplinary strategies for all factors sustaining the epidemic. These strategies should aim to simultaneously reduce the likelihood of HIV infection in key populations at risk, identify infected individuals early, rapidly link all infected persons to care, and immediately offer them the possibility of starting combination antiretroviral therapy.

Combination antiretroviral therapy in adults and quality of treatment and care

In care and on cART in 2015

Initiation of cART following a diagnosis of HIV infection is taking place increasingly earlier in the Netherlands. In 2015, the majority of individuals who entered care and started cART in the Netherlands did so within a month after diagnosis. Concurrently, the median CD4 count at cART initiation has increased to 420 cells/mm^3. Among all HIV-positive individuals in care in 2015 who had ever started cART, the majority received a tenofovir-emtricitabine-based cART regimen combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI; 41%), a protease inhibitor (PI; 16%), or an integrase inhibitor (15%). Overall, integrase inhibitor-based cART was used by 27% of those in care in 2015: 14% received dolutegravir, 7% cobicistat-boosted elvitegravir and 6% raltegravir. cART use in 2015 in the Netherlands among HIV-positive individuals who started treatment is presented in *Figure 4*. Of those on cART with a plasma HIV RNA measurement in 2015, 97% had a suppressed viral load.

***Figure 4:** cART use in 2015 in the Netherlands among HIV-positive individuals who started treatment.*



***Legend:** 3TC=lamivudine; ABC=abacavir; cART=combination antiretroviral therapy; FTC=emtricitabine; INSTI=integrase strand transfer inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; TDF=tenofovir disoproxil fumarate.*

Initial regimen

Three-quarters of all individuals starting cART in 2015 started integrase inhibitor-based cART: 55% received dolutegravir-based cART and 20% cobicistat-boosted elvitegravir-based cART. While the majority (61%) started tenofovir-emtricitabine-based cART, there has been a significant increase in the use of abacavir-lamivudine as the nucleoside reverse transcriptase inhibitor backbone. This trend can be explained by the introduction of the once-daily fixed dose combination of dolutegravir with abacavir-lamivudine (Triumeq®) towards the end of 2014. Of those who started cART in 2015, 40% received abacavir-lamivudine combined with dolutegravir. Although tolerability of cART has continued to improve with time and larger numbers of individuals remain on their initial cART regimen for a longer period of time, drug intolerance or toxicity is still the most common reason for a change of initial treatment.

Virological response

Both short-term and long-term virological suppression rates are high and continue to improve. Among those starting a preferred cART regimen between 2010 and 2015, 92% had a suppressed viral load (HIV RNA <100 copies/ml) after 6 months. These initial suppression rates were significantly higher among participants initiating integrase inhibitor-based cART compared to NNRTI-based or PI-based cART; this effect was strongest among individuals with a high viral load at cART initiation. Among those who initiated cART in or after 2010, 94% had a suppressed viral load after one year and 97% after four years.

Since 2000, the annual proportion of individuals with a viral load >200 copies/ml has decreased to approximately 3%. The risk of viral rebound was higher among individuals under 30 years of age, heterosexual men and women, and those who originated from South America and the Caribbean or sub-Saharan Africa. Those with higher HIV viral load at the start of cART and those starting with CD4 cell counts below 200 cells/mm^3 had an increased risk of viral rebound compared with those starting treatment at higher CD4 cell counts.

HIV drug resistance

Of the HIV-positive individuals who were in clinical care as of May 2016, resistance-associated mutations have been found in 11%, with 8% of these mutations resulting in high-level resistance to at least one antiretroviral drug. Of note, resistance test results were available for only 25% of individuals with viral failure in or after 2000 and for 17% with viral failure in or after 2010. Therefore, the true prevalence of resistance may be different.

Among 10% of individuals with resistance data available within one year of diagnosis, at least one transmitted drug resistance mutation was found; including 4% with nucleoside reverse transcriptase-associated mutations, 5% with non-nucleoside reverse transcriptase-associated mutations, and 2% with mutations in the protease gene. Between 2003 and 2015, there were no significant changes in these proportions, although there was a decreasing trend in most recent calendar years.

Immunological response

The proportion of individuals achieving immunologic recovery on cART continues to improve each year. Based on the last available CD4 and CD8 cell count measurements in 2015, 72% had a CD4 cell count of 500 cells/mm^3 or higher, and 23% had a CD4:CD8 ratio of $\geq$1. Nonetheless, a substantial number of individuals fail to achieve immunological recovery, which increases the risk of both traditionally HIV-associated and non-AIDS-related morbidity. This is particularly true for those who start cART at a more advanced level of immunodeficiency.

Following revised HIV treatment guidelines, prompt treatment initiation of, primarily integrase inhibitor-based, cART has been observed in the Netherlands in 2015. Currently recommended regimens are durable, effective and provide high virological suppression. Nonetheless, the long-term effects of these shifts in antiretroviral drug use should continue to be monitored.

Quality of care

Generally speaking, a number of different quality of care indicators showed limited variability across the 26 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, regardless of size. Across most of the centres an increasing proportion of individuals are starting cART sooner after entering into care, confirming that treatment centres are following new guidelines to offer cART to anyone with newly diagnosed HIV, regardless of their CD4 count. Despite the increasing number of individuals starting cART within 6 months after entering care, some centres could further improve this number among those individuals who enter care with CD4 cell counts above 350 cells/mm^3.

Variation in HCV screening

More substantial variation was observed in repeat HCV screening in MSM. However, this may, to some extent, be explained by centres applying a policy of targeted screening guided by the presence of incident transaminase elevations and/or by differences in the MSM population with respect to known risk-taking behaviour for HCV acquisition. Regular screening for HCV among HCV/HIV co-infected individuals who have been successfully treated for HCV is recommended for early detection of HCV re-infections. Therefore, continued monitoring of repeat HCV screening rates and other reported trends seems warranted.

Morbidity and mortality

Mortality rates remain low in HIV-positive individuals 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 comorbidities, including non-AIDS-defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease, comprise a sizable fraction of those

other causes. Of note, however, the proportion of individuals dying of AIDS (26% of the total number of deaths) remained substantial between 2007 and 2015. This was largely driven by late presentation and late entry into care, and once again stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

Older age and comorbidities

Not surprisingly, older age was an important risk factor for comorbidities 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 2015, 23% were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 45% currently older than 50 years (42% in 2014, 39% in 2013). Of particular concern is the increasing proportion of individuals with multiple comorbidities, the risk of which appears to be increased in those with HIV, as demonstrated, for example, by data from the AGE$_h$IV Cohort Study, in which SHM collaborates with the Academic Medical Center, the Amsterdam Institute for Global Health and Development and the Public Health Service (GGD) in Amsterdam.

Cardiovascular risk

Despite the increasing age of the HIV-positive population, the proportion at high or very high cardiovascular risk only increased slightly over the period 2000-2015. 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 anti-platelet therapy as secondary prevention following a myocardial infarction or ischaemic stroke, and the low 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, screening and treatment for early (pre-malignant) stages of anal cancer, 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 individuals diagnosed with other non-AIDS malignancies increased with increasing age.

Awareness of the role of modifiable, often lifestyle-related risk factors, like smoking, and their management by both physicians and people living with HIV offer important hope of ensuring a lower comorbidity burden and resilient ageing. This is particularly relevant for older individuals or those with another a priori risk of comorbidity, and 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 clearly room for improvement in the use of known effective biomedical interventions for primary and secondary cardiovascular disease prevention according to general guidelines.

Hepatitis B and C co-infections

Screening for hepatitis B (HBV) and C (HCV) co-infection has 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-positive individuals in care in the Netherlands. Approximately 12% of individuals had evidence of ever having been exposed to HCV, 6% were documented as having chronic infection and 2% had acute infection. Seven percent of individuals were shown to have chronic HBV infection.

Overall, individuals with HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. For individuals 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.

An estimated 28% of HIV-positive individuals overall and 20% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. These findings illustrate the importance of continuing our efforts to increase successful HBV vaccination rates in this subgroup, particularly in those who are not receiving a tenofovir-containing antiretroviral regimen.

HCV genotype 1 infection was the most common genotype in individuals with either chronic or acute HCV infection, and most individuals with HCV infection were male and from the Netherlands or other European countries. Importantly, the incidence of acute HCV infection observed in 2015 amongst MSM remains high at a rate of 5.9 diagnoses per 1,000 person years (3.7 per 1,000 person years in 2014). This clearly indicates the need for continued preventive efforts in these men, including the use of the novel highly effective short-course well-tolerated interferon-free combination therapies for HCV, which, by virtue of their high effectiveness, may not only benefit the individual patient, but also importantly reduce the risk of onward transmission.

HCV & direct-acting antiviral agents

Our data clearly show that, with the advent of novel direct-acting antiviral agents (DAAs) in 2014 and 2015, pegylated interferon (PEG-IFN)-containing regimens have largely been replaced in clinical practice by a variety of novel DAAs and more HIV-positive individuals with HCV-co-infection are being treated for HCV infection. More than 500 individuals have received, or are currently receiving, treatment with novel DAAs including one or more of the currently available novel DAAs sofosbuvir, simeprevir, daclatasvir, ledipasvir, ombitasvir, paritaprevir or dasabuvir. Of note, 98% of all individuals with sufficient follow-up data to calculate a sustained virological response were found to have been cured.

Very importantly, these developments have already resulted in a lower total number of HCV-co-infected individuals who remain in need of effective treatment compared to last year's report (499 in 2016, 876 individuals in 2015 vs. 907 in 2014), in spite of an increase in the total number of individuals with HCV co-infection currently retained in care (1,420 in 2016, 1,260 in 2015, and 1,187 in 2014). However, an alarmingly high rate of detectable HCV RNA test results after successful treatment was observed, which strongly suggests HCV re-infection and ongoing transmission of HCV.

The rapidly expanding availability of novel interferon-free regimens for HCV, together with optimised screening for HCV co-infection with time will hopefully limit the impact of HCV co-infection on long-term liver-related morbidity and mortality. To reduce the rate of incident HCV infection among the key affected population of MSM, regular screening for HCV among successfully-treated individuals is recommended for early detection of HCV re-infections, in combination with preventive behavioural interventions aimed at 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. Moreover, approximately 7% of HIV-positive pregnant women do not have fully suppressed viraemia around the time of delivery.

To ensure zero vertical transmissions of HIV, there is a need for continued vigilance for new HIV infections and successful viral suppression at delivery.

Children

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 have started treatment below two years of age.

An increasing number of children living with HIV in the Netherlands are transitioning into adult care. However, almost 35% of the children who transitioned into adult care did not have fully suppressed viraemia at time of transition.

The large number of children who have inadequately-suppressed viraemia at the time of transition to adult care illustrates that optimisation of long-term care for this particularly vulnerable and difficult-to-manage group of young individuals is sorely needed.

HIV in Curaçao

SHM continues to provide assistance to Stichting Rode Kruis Bloedbank with data collection and monitoring of individuals with HIV in care at the St Elisabeth Hospital in Willemstad in Curaçao. In recent years, HIV-positive individuals 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, combination antiretroviral therapy is being started at increasingly higher CD4 cell counts. Although early start of treatment appears to be possible, long-term continuous follow up should be guaranteed to optimise the effect of treatment.

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 drug users. 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 further 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, MC Jan van Goyen, 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). The scientific studies are funded separately by external sources.

Following the Scientific Advisory Committee's positive evaluation of the ACS in 2013 and the absence of new cases of HIV and hepatitis C virus infection among drug users in the preceding years, the ACS started to slim down the follow up of drug users in January 2014. Initially, the visit frequency for some of the cohort was reduced. Finally, in 2016, all drug users who had ever participated in the ACS were invited for an end-of-study interview. A total of 182 end-of-study interviews were held, after which the follow up of drug users was successfully ended. During the 31 years of follow up, a total of 1,680 drug users took part in the study and made a combined total of 28,011 visits to the ACS.

In 2015, expansion of the HIV-negative MSM cohort was initiated. The aim is to have expanded the ACS to a total of 750 HIV-negative MSM in active follow up by the end of 2017. In 2016, 23 new participants were included. The recruitment also includes special efforts to include younger MSM (below 30 years of age) in the ACS.

In addition to the large group of HIV-negative MSM, the ACS also follow a group of HIV-positive MSM. 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 seroconverters who became infected during the ACS follow up and from some of the individuals who were already HIV-positive at inclusion in the ACS.

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In addition, body material from the HIV-negative men is also collected and stored as part of the ACS.

As of 31 December 2016, 2,736 MSM had been included in the ACS. Since the start of the ACS, MSM have visited the GGD Amsterdam 57,466 times. In 2016, 694 MSM, 64 of whom were HIV-positive, were actively followed by the GGD Amsterdam. The preliminary HIV incidence within the ACS in 2016 was 0.53 per 100 person years, with an absolute number of 3 HIV diagnoses in 2016.

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 and Division of Infectious Diseases at the AMC, and director of SHM), the *Co-morbidity and Ageing with HIV* (AGE_hIV) 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-positive individuals compared with HIV-negative individuals.

Another collaboration closely associated with the AGE_hIV 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 co-morbidity 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-positive individuals. COBRA's EU funding formally ends March 1, 2017, but scientific productivity based on collected data and biomaterial is expected to continue in the coming years.

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/Department of Global Health at the AMC. The project is a multidisciplinary and interdisciplinary collaboration that aims to reduce the number of new HIV infections in Amsterdam and involves 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*), the Dutch Association of HIV-Treating Physicians (NVHB), Amsterdam hospitals, Maasstad Ziekenhuis in Rotterdam, Erasmus MC, and the National Institute for Public Health and the Environment).

RIVM–CIb

The Centre for Infectious Disease Control Netherlands of the National Institute for Public Health and the Environment (*Centrum Infectieziektenbestrijding, Rijksinstituut voor Volksgezondheid en Milieu*; RIVM-CIb) coordinates the control of infectious diseases, including

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 RIVM-CIb 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 RIVM-CIb, and to fulfil RIVM-CIb's reporting requirements to the European Centre for Disease Prevention and Control (ECDC).

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 study aims 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 this epidemic, 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 are primarily funded through the RIVM-CIb and, as of 1 January 2015, the funding is included in the structural institute grant awarded to SHM by the Ministry of Health, Welfare and Sport through the RIVM-CIb.

Harmonic

Harmonic is a collaboration launched in 2014 between SHM and two HIV/hepatitis treatment centres in the Netherlands (UMC Utrecht and Rijnstate hospital in Arnhem) 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 individuals. 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.

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 was to use the scientific strengths of each collaboration to ensure that the best,

most competitive research is performed. EuroCoord is a large, integrated network with a common virtual database, which currently contains data from more than 250,000 HIV-positive individuals from many different settings within and outside Europe. EuroCoord's multidisciplinary approach has allowed HIV research into a number of key areas aimed at improving the management and quality of life of HIV-positive individuals, while 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 outcomes up to 12 to 16 months after initiating combination antiretroviral therapy (cART), according to markers of virus variability (specific mutations, subtypes) and 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 (see below) therefore ceased on 31 December 2015. Some of its associated collaborations have succeeded in continuing parts of their research agendas through alternative funding mechanisms (EPPICC), while others are actively striving to secure alternative funding to enable their work to continue (EuroSIDA and CASCADE).

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-positive 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 was part of EuroCoord, the collaboration that encompassed all EU-funded cohort studies in the field of HIV.

An overview of papers published by COHERE in 2016 can be found under 'Scientific output in 2016'.

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) participate in this study through their HIV seroconverted participants. CASCADE was part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV. With EuroCoord having ended, CASCADE is undergoing reorganisation and is actively engaged in pursuing alternative funding options to continue this longstanding, highly successful collaboration.

An overview of papers published by CASCADE in 2016 can be found under 'Scientific output in 2016'.

EuroSIDA

The EuroSIDA study is a prospective, observational cohort study of more than 16,500 individuals followed in 103 hospitals in 32 European countries, plus Israel and Argentina. The main objective of the study is to assess the outcomes HIV-positive individuals across Europe, with an important focus on assessing regional differences across 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 for EuroSIDA. EuroSIDA was part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV. With EuroCoord having ended, EuroSIDA is undergoing reorganisation and is actively engaged in pursuing alternative funding options to continue this longstanding, highly successful collaboration.

An overview of papers published by EuroSIDA in 2016 can be found under 'Scientific output in 2016'.

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 was part of EuroCoord, the collaboration that encompasses all EU-funded cohort studies in the field of HIV. Within EuroCoord, EPPICC was part of the HIV in children collaboration, *Paediatric European Network for Treatment of AIDS* (PENTA).

An overview of papers published by EPPICC in 2016 can be found under 'Scientific output in 2016'.

ART-CC

The *Antiretroviral Therapy Cohort Collaboration* (ART-CC) coordinated by Prof. Jonathan Sterne, University of Bristol, is a long-standing international collaboration that includes 19 cohort studies in Europe and North America. ART-CC was initiated to carry out prognostic studies to assess the effect of cART in therapy-naive individuals. In 2016, Prof. Peter Reiss and Dr Ard van Sighem represented SHM in the ART-CC steering group. ART-CC's financial support from the Medical Research Council of the United Kingdom has come to an end, but scientific collaboration continues based on the last available joint dataset.

An overview of papers published by ART-CC in 2016 can be found under 'Scientific output in 2016'.

D:A:D study

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. Funding for the D:A:D study ceased as of 1 February 2016. For the time being, scientific productivity continues based on the last available joint dataset.

An overview of papers published by the D:A:D study in 2016 can be found under 'Scientific output in 2016'.

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 2016, SHM continued its leading role in a project to better estimate HIV incidence and prevalence in Europe and within individual European countries. In addition, SHM is partner in a newly commissioned collaborative multi-year project led by Dr Annabelle Gurley and Prof. Kholoud Porter from University College London to improve the monitoring of the HIV continuum of care in Europe.

HIV-CAUSAL

The HIV-CAUSAL collaboration, led by Prof. Miguel Hernan at Harvard University's T.H. Chan School of Public Health, is a multinational collaboration of prospective studies of HIV-

positive individuals from six European countries, Brazil, Canada and the United States. Originally HIV-CAUSAL was an acronym for *HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data*. The collaboration aims to answer three main questions: when to start antiretroviral therapy, what antiretroviral regime to use initially, and when to switch to another regime. These questions are unlikely to be answered by a single study and therefore require a collaborative approach.

The HIV-CAUSAL collaboration pools data collected for clinical purposes within healthcare systems with few barriers to access. The data are analysed using methods specifically designed for causal inference from complex longitudinal data, including inverse probability weighting of marginal structural models, g-estimation of structural nested models, and the parametric g-formula.

The HIV-CAUSAL collaboration is designed to inform evidence-based guidelines and the planning of clinical trials. In addition, the collaboration facilitates understanding 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 2016 can be found under 'Scientific output in 2016'.

Imperial College London and Oxford University

SHM has had a longstanding collaboration since 2002 with the Department of Infectious Disease Epidemiology (DIDE), which is part of the Faculty of Medicine, Imperial College in London. The collaboration focuses on using mathematical modelling and viral phylogenetics to improve our understanding of the HIV epidemic and the potential impact of different interventions, including "treatment as prevention" and pre-exposure prophylaxis (PrEP). Until recently, Prof. Christophe Fraser coordinated the collaboration with SHM as part of the faculty at Imperial College, and currently continues to do so from his new position at the Big Data Institute of Oxford University's Li Ka Shing Centre for Health Information and Discovery.

In the *Bridging the Epidemiology and Evolution of HIV in Europe* (BEEHIVE) project (ERC grant to Prof. Fraser), Oxford University, Imperial College's 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.

SHM also closely collaborates with Imperial College's DIDE (Dr Mikaela Smit and Prof. Tim Hallett) in modelling the future burden of non-communicable comorbidity and the expected impact of various interventions in the ageing population with HIV in care in the Netherlands.

RDI

The HIV Resistance 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 resistance measurements are not available. The developed models power the RDI's HIV Treatment Response Prediction System (HIV-TRePS), a free online tool enabling informed, individualised treatment decision-making.

An overview of papers published by RDI in 2016 can be found under 'Scientific output in 2016'.

Communication activities

Stichting HIV Monitoring actively disseminates information about its activities through a wide variety of communication channels. In doing so, we aim to provide relevant information to people living with HIV, their health care providers, researchers, other health care professionals, the media and other interested parties. This chapter provides an overview of the main communication activities undertaken in 2016.

External communication activities

Monitoring Report 2016, HIV Infection in the Netherlands

Each year, we publish our HIV Monitoring Report just before 1 December, World AIDS Day. The 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 describes trends in HIV-related and non-AIDS-related morbidity and mortality, and includes a chapter dedicated to viral hepatitis. In 2016, the latter provided an update on the use of novel combinations of direct-acting antiviral agents in the treatment of hepatitis C co-infection in HIV-positive individuals. Finally, the 2016 Monitoring Report included a chapter on quality of care in the HIV treatment centres in the Netherlands. This chapter, first introduced in 2015, examines a number of quality of care indicators and was expanded in 2016 to present the findings according to hospital size. Each centre will be sent their centre-specific results of this analysis in the first half of 2017.

The main findings from the 2016 Monitoring Report are described in an earlier section of this annual report (*Key Outcomes and Recommendations*) and were also presented at the 10th Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV) by SHM director, Peter Reiss.

In 2016, in keeping with SHM's policy to reduce paper use, the Monitoring Report was distributed online through the SHM website, as a searchable and downloadable PDF. In addition, all figures and tables were made available in the form of a downloadable PowerPoint presentation on SHM's website. The report's Summary and Recommendations section was, however, printed in both Dutch and English and distributed to stakeholders together with an updated infographics factsheet. 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*).

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/co-morbidities through research projects and scientific publications. In 2016, SHM cohort data were included in 57 publications in peer-reviewed national and international scientific journals and 79 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.

Annual report 2015

The 2015 annual report was published online in May 2016. In addition to an overview of the organizational structure, the annual report provided a detailed overview of the data collection and quality control activities undertaken in 2015 and a summary of the population registered in SHM's database as of 31 December 2015. The annual report also comprised a list of SHM's national and international collaborations, progress reports on research involving SHM's data, and a comprehensive overview of the resulting scientific output. Finally, the annual report included the financial report on SHM's activities in 2015.

eNewsletter

The eNewsletter was sent out on a quarterly basis in 2016 and was well read, with average open rates of 43% and 35% for the Dutch and English-language newsletters, respectively. In 2016, 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. The 2016 newsletters also contained the Spotlight on SHM research item, showcasing a recent publication involving SHM data and based on an interview with the first author. Finally, in November 2016, the English-language newsletter was also published in print format and distributed at NCHIV 2016.

All newsletters are archived on the website and can be accessed via a direct link on the homepage.

Patient leaflet and factsheet

SHM's patient leaflet provides a simple explanation of SHM's activities and data collection process. Produced in both Dutch and English, this leaflet illustrates how coded data provided by people living with HIV in the Netherlands help to drive further improvements in HIV care through national and international research. The leaflet is accompanied by a factsheet insert that uses infographics to summarise the key figures from the latest Monitoring Report. Both the leaflet and the factsheet are intended for distribution to new patients by HIV treating physicians and HIV nurse consultants, and are well-received by the HIV treatment centres.

As well as being distributed with the printed Monitoring Report Summary and Recommendations to SHM's stakeholders, the updated infographics factsheet was also included in conference bags at NCHIV 2016 and at the Soa*Hiv*Seks conference. In addition, copies of the updated factsheet and revised patient leaflet were sent to all treatment centres for distribution to new patients. The leaflets and insert are also available for download on the SHM website.

SHM website

During the course of 2016, 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, along with updates about the latest research projects, presentations and publications involving SHM data.

The website also provides an up-to-date list of treatment centres and data collectors and data quality staff responsible for these centres.

Social media

In 2016, efforts were increased to disseminate SHM news, in particular regarding recent publications, using LinkedIn. This will be continued in 2017.

Events

During the course of 2016, SHM researchers and collaborators presented their work with SHM data at various international and national conferences and meetings. While further information on these presentations can be found later in the report, two Netherlands-based events are described in more detail below.

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

In 2016, SHM organised the 10th 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 (RIVM-CIb), the Aidsfonds, the Amsterdam Institute for Global Health and Development (AIGHD)/ Department of Global Health of the Academic Medical Center of the University of Amsterdam (AMC-UvA) and the Dutch Association of HIV-Treating Physicians (NVHB).

NCHIV 2016 was well-attended, with almost 300 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 HIV prevention, HIV-associated stigma, HIV treatment guidelines and HIV cure. The remaining 16 talks comprised oral abstract presentations on the pathogenesis, epidemiology, prevention and treatment of HIV and HIV/HCV co-infection. During the lunchtime poster session, 46 posters were presented for viewing. Finally, recipients of a new Aidsfonds grant,

the 'high-risk high-gain' grants, presented their research plans to the audience in the form of short elevator pitches.

World AIDS Day

On World AIDS Day, 1 December 2016, 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 during a plenary session.

Internal communication activities

Intranet

This externally-accessible, password-protected site was launched in 2015 and provides a central point of information for employees, with up-to-date contact details, HR documents, standard templates, and internal news and meetings. In 2016, the SHM intranet site was further expanded to include support documents for data collectors, as well as providing regular updates on the progress of the replacement data entry database (LISA project).

Internal newsletter

In 2016, the internal Dutch-language newsletter, entitled *SHM Positive: a collection of all the internal news*, was published four times and remains well-read, with an average open rate of almost 80%. 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, relevant issues such as privacy legislation, 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 2016 include the long-term effects of antiretroviral therapy in Africa, comorbidity research using SHM data, and regional cascades of care. During 2016, the internal meetings also included information on SHM's privacy policy and regular updates on the progress of the ongoing project to replace the current Oracle Clinical data entry database (LISA).

Financial report

Income

In 2016, Stichting HIV Monitoring's (SHM) total income was €4,264,728. The majority of this income came from the structural institute grant for HIV monitoring in the Netherlands that SHM receives each year from the Centre for Infectious Disease Control of the National Institute for Public Health and Environment (*Centrum Infectieziektenbestrijding, Rijksinstituut voor Volksgezondheid en Milieu* (RIVM-CIb)), 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.

Structural institute grant for HIV monitoring in the Netherlands

SHM is a Ministry of VWS-recognised healthcare institute with a structural institute grant (RIVM-CIb grants framework). SHM's governing board established that, in 2016, SHM required a structural institute grant of €3,428,898 for HIV monitoring in the Netherlands. The RIVM/Ministry of VWS awarded an institute grant of €3,120,109. During the course of 2016, the wage-sensitive part of the institute grant was increased by 1.74%, equivalent to €44,093. As such, in the fiscal year of 2016, the Ministry of VWS allocated SHM a total institute grant of €3,164,202 for monitoring HIV in the Netherlands.

HIV monitoring-related collaborations: grants and financial contributions

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 2016, SHM received €1,069,190 as income from HIV monitoring-related collaborations. This income is €149,375 (-12.26%) less than that earned through collaborations in 2015.

During the course of 2016, SHM contributed to the following scientific collaborations:

1. Amsterdam Cohort Studies (ACS)

Since 1984, the ACS have 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 collaborating institutes, including the Academic Medical Centre of the University of Amsterdam (AMC-UvA), the Public Health Service of Amsterdam (*GGD Amsterdam*), and SHM, make use of data and body samples provided by HIV-1 positive 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.

SHM has been responsible for the administration of the ACS since 2005. The RIVM provides the ACS with an annual structural institute grant of €500,000. In addition, the collaborating institutes make a contribution to the coordination, management and financial management costs. 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 on adverse effects of treatment and non-AIDS comorbidities in registered patients collected in part for the benefit of the D:A:D study. Source data verification ensures that key endpoint validity 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.

D:A:D was made financially possible by the Oversight Committee for the Evaluation of Metabolic Complications of HAART, to which, on request by the European Medicines Agency, various pharmaceutical manufacturers of antiretroviral compounds contribute. The Oversight Committee decided to terminate its contribution to the D:A:D study as of 1 February 2016. Consequently, the annual contribution received by SHM for participation in the collaboration will come to an end.

In 2016, SHM contributed to the D:A:D study data merge for the 17th, and final, time. For this contribution, SHM received a sum of €479,932 from the Rigshospitalet, University of Copenhagen, which coordinates the D:A:D study. This amount is based on the number of person years added by SHM.

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

In 2016, ECDC awarded SHM a grant of €15,000 for the project entitled 'Further development and upgrade of the ECDC HIV modelling tool'. This 8-month project ended on 31 March 2016. A tool had previously been developed to improve the reliability of estimates of HIV prevalence and incidence in different European countries. This project further developed the existing tool, both methodologically and technically, to improve its functionality and user-friendliness.

4. EuroCoord

SHM's participation in EuroCoord from 2011 through to 2015 has contributed to the harmonisation of data collection by HIV cohorts in Europe, including SHM's ATHENA cohort in the Netherlands. This, in turn, has improved 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). In July 2016 the project closed financially

and it transpired that SHM had declared an excess of €38,106 during previous years. This excess was corrected in 2016.

5. Comorbidity and Ageing with HIV (AGE_hIV)

In 2016 SHM received a sum of €38,314 from the AGE_hIV study. This study aims to describe the incidence and prevalence of a wide range of comorbidities and known associated risk factors in HIV-positive individuals compared with HIV-negative individuals. SHM plays an important role in this study, which is coordinated by the Amsterdam Institute for Global Health and Development (AIGHD) at the AMC.

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

In 2016, SHM received a payment of €15,842 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 a wide range of ageing-related comorbidities are more common and possibly occur at a younger age in HIV-positive persons compared to HIV-negative 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.

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

As part of the scientific research collaboration, SHM received a sum of €23,208. 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 data within a single network to efficiently address questions arising within this specific population.

8. European Social Fund: sustainable employment

In 2016, as part of a project entitled 'SHM: a sustainable future' and set up to investigate sustainable employability of staff, SHM received a grant of €10,000 from the Ministry of Social Affairs and Employment.

9. Other income

In total, SHM received €31,336 from other sources of income. SHM staff are involved in organising the Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV) and the associated salary expenses (€23,582) are charged to Stichting NCHIV. In addition, data management work carried out on behalf of the H-TEAM project resulted in an income of €3,936.

Expenditure

In 2016, the total expenses of SHM were €4,082,699. Three main expense categories for 2016 are outlined below:

1. **Personnel costs**
   A large portion of SHM's expenses comprises personnel costs. At €2,432,077 in 2016, personnel costs once again represented the largest expense for SHM, namely 59.6% of the total expenditure. As per 31 December 2016, SHM had a total of 44 employees (an average of 37.3 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 2016, SHM also incurred material costs such as license and maintenance costs of the national HIV monitoring database, housing costs, administration and consultancy costs, depreciation of automation equipment, and other operational costs. In 2016, material costs amounted to €694,948.

3. **Payments**

   Amsterdam Cohort Studies payment
   In line with the budget, SHM transfers the RIVM funding (€500,000) earmarked for the ACS to GGD Amsterdam and the AMC. SHM is responsible for ACS's financial administration, but does not charge the ACS any management costs for this service. In addition, a sum of €25,000 dating from 2015 was paid to the AMC and GGD Amsterdam through UMC Utrecht.

   Payments to HIV treatment centres
   In 2016, HIV treatment centres received a payment of €53.07 per patient, based on the number of patients in active follow up on 31 December 2015. In 2016, 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, the HIV treatment centres received a sum as a contribution towards the costs of collecting and storing patients' plasma. Seventeen treatment centres have transferred the role of data collection to SHM.

   In total, in 2016 SHM paid the HIV treatment centres €473,955 for patient data collection and entry and storage of patients' samples. For the assistance in data collection by SHM employees, an amount of €61,069 was deducted from the above-mentioned payments.

   D:A:D event payments
   As part of the D:A:D study, physicians are required to complete Cause of Death (CoDe) forms. SHM will pay the relevant HIV treatment centres €17,788 for this work carried out in 2016.

Operating result

The operating result (€189,482) indicates that the total costs in 2016 remained well within SHM's income. A large portion of this positive result, which will be added in full to the reserves, stems from payments from the D:A:D study.

Reserves

SHM's total financial reserves (including the deferred grant revenue, general reserve and earmarked reserves for investment) amounted to €4,134,997 on 31 December 2016.

1. **Deferred grant reserve**
   The deferred grant reserve amounted to a positive balance of €53,013 on 31 December 2016. This amount includes the negative 2016 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. **Designated reserves**
   As per 31 December 2015, a total of €3,699,778 has been reserved for HIV-related projects and the IT project LISA , of which € 1,280,301 has been reserved for the the latter.

Contingency reserves as of 31 December 2016

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

SHM strives to foster a culture of respectful and honest conduct; such a culture forms the foundation for preventing any form of fraudulent conduct. 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 by management setting the example, but also by means of various current 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, other 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.

2017

Board resolutions

As of May 2016, 19,496 individuals were registered with SHM. Here, the term registered refers to all patients for whom data were collected during the past two years. These included 234 children, 337 pregnant women and 267 individuals who had died. Excluding those who had died, as of May 2016, a total of 19,229 registered individuals were still in care. This represents an increase of 564 compared to May 2015.

In 2017, the number of registered individuals is predicted to increase by 2.1% compared to 2016. This increase is based on the average increase in the number of HIV-positive individuals over time since 2004. Since 2004, this rate has been decreasing and it is expected to become negative for the first time in 2020. As a result, the number of individuals in care is expected to decline from 2020 onwards.

The gradual increase in the proportion of older individuals in SHM's database and the associated increase in age-related comorbidity makes it increasingly important to adequately collect clinical information about age-related comorbidity and associated risk factors. Furthermore, even when an HIV infection is well suppressed with antiretroviral therapy, HIV-positive individuals remain at increased risk of age-related comorbidity. In addition to collecting information on non-infectious comorbidity (including cardiovascular disease, diabetes mellitus, renal function and malignancies), it is also necessary to collect information on chronic liver disease, which is frequently but not exclusively associated with hepatitis B (HBV) and hepatitis C (HCV) co-infection. Moreover, with the advent of the rapidly growing arsenal of direct-acting antiviral agents (DAAs) against HCV, registration and monitoring of the use of these agents have become extremely important. Equally, of increasing importance is the registration of the short and longer-term impact of these agents on the incidence of new HCV infections and on that of long-term liver complications.

In 2009, the Hepatitis Working Group, set up by SHM together with the Dutch Association of HIV-Treating Physicians (NVHB), developed a protocol for the standardised collection of an extensive set of relevant data on HBV and HCV co-infection and related morbidity and mortality. As a result, SHM invested in expanding the data collection capacity, with priority initially assigned to collecting more extensive data on HCV, followed by more extensive collection of HBV data from 2014 onwards; the latter has now been completed. This investment has allowed efficient and effective registration of the use of DAAs in HCV treatment and of the impact of this treatment. In the future, this development will also make it possible

to register the effect of interventions to "cure" HBV, which, similar to HIV, is a persistent viral infection. Research into such interventions is currently making rapid progress.

As of 1 January 2018, SHM's present data entry system, Oracle Clinical, will no longer be supported by the AMC, which hosts and manages SHM's data entry system. SHM therefore had to purchase a new data entry system to replace Oracle Clinical. A key requirement in selecting a new system was that it should be better tailored to SHM's core activities and sit well within SHM's innovation strategy. The selected replacement system, currently being built under the project named 'LISA', is expected to be implemented at the start of 2018. The anticipated improvement in efficiency, which should become visible from 2018 onwards, is based on various aspects of the new system, such as a modern structure that facilitates data import from external sources, the ability to collect information according to a protocol-based structure, the obviation of a number of manual quality control procedures, the integration of data collection protocols, independent functional management of the system by SHM without requiring services of the supplier, and the possibility of expanding the system with additional modules. The total investment in LISA from 2015 through to 2017 is estimated to be €1,291,000.

Grants/other financial contributions

The structural institute grant provided to SHM by the Ministry of VWS through the RIVM-CIb for HIV monitoring in the Netherlands represents the largest portion of SHM's income; in 2016, the RIVM awarded SHM a sum of €3,120,109. In addition, on 22 September 2016, the wage-sensitive part of the 2016 grant was indexed by 1.74%, providing an additional sum of €44,093. This brings the total 2016 institute grant for HIV Monitoring in the Netherlands to €3,164,202. The 2017 budget will be based on this sum.

The institute grant for the Amsterdam Cohort Studies (ACS) from the RIVM-CIb on behalf of the Ministry of VWS is also paid out to SHM on an annual basis. SHM pays this structural institute grant of €500,000 in full to the two organisations that carry out the research, namely the AMC and GGD Amsterdam. SHM has an administrative role, and as such is solely responsible for the financial administration for the ACS.

In addition to these structural institute grants, SHM's income consists of project-related grants and contributions, including both national and international grants.

Contributions totalling €55,800 have been budgeted for the following projects to which SHM contributes: ECDC, AGE$_h$IV, and COBRA.

In 2017, SHM will participate in a project coordinated by the Swiss HIV Cohort that aims to obtain insight into the optimal strategy by which to screen for hepatocellular carcinoma in patients with an HIV/HBV co-infection and who are being treated with antiretroviral therapy containing tenofovir. This project has received funding from NEAT-ID (The European treatment network for HIV, hepatitis and global infectious diseases), and the budgeted allocation for SHM is €6,200.

A sum of €20,500 has been budgeted for other income in 2017, €20,000 of which has been budgeted as reimbursement of the hours invested by SHM staff in organising the Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV).

Number of staff

The budgeted number of SHM staff for 2017 is equivalent to 37.4 FTEs. Compared with the 2016 financial statement, this represents an increase of 0.1 FTEs.

The budget for 2017 has taken into account the salary increases approved as part of the 2015-2017 collective labour agreement (CAO) for university medical centres. Consequently, an indexation of 1% was applied to salaries. SHM also followed the CAO by increasing salaries by one periodic step on the salary scale for employees with good performance and who have not yet reached the maximum on their salary scale.

In total, the 2017 budget includes €124,077 less for personnel costs than the actual personnel costs in 2016 (€2,308,000 versus €2,432,077). The costs incurred in 2016 for externally contracted staff and the contribution to the sick leave and work disability provision do not form part of the 2017 budget.

Expenses

The estimated costs for 2017 for the patient database, services provided by third parties, IT equipment, housing, office supplies and conferences are slightly higher than the 2016 costs (€643,467). This represents a total increase of €31,533 over a budget of €675,000 (4.7%).

The IT depreciation costs have risen markedly in the 2017 budget, from €18,466 in 2016 to €122,500 in 2017, due to the IT project, LISA. The total investment in this project is expected to be €1,291,000 and these costs will be written off over a 5-year period. This depreciation will be covered by the designated reserves.

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

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 to €412,886, after deduction of the costs of data collection assistance. For 2016, the projected balance payment is €425,000.

Balance sheet (after appropriation of profits)

Assets	31 Dec 2016 (€)	31 Dec 2015 (€)
Fixed assets		
Intangible fixed assets	422,509	0
Tangible fixed assets	9,947	9,096
Total fixed assets	**432,456**	**9,096**
Current assets		
Accounts receivable	3,287	46,327
Receivables and accrued assets	185,707	183,309
Liquid assets	4,634,489	4,695,234
Total current assets	**4,823,483**	**4,924,870**
Total assets	**5,255,939**	**4,933,966**

Liabilities	31 Dec 2016 (€)	31 Dec 2015 (€)
Capital reserves		
Deferred grant revenue	53,013	170,690
General reserve	382,206	382,206
Earmarked reserves	3,699,778	3,392,619
Total capital reserves	**4,134,997**	**3,945,515**
Provisions		
Sick leave and work disability provision	0	127,400
Short-term liabilities		
Accounts payable	131,949	60,014
Short-term liabilities and accrued expenses	988,993	801,037
Total short-term liabilities	**1,120,942**	**861,051**
Total liabilities	**5,255,939**	**4,933,966**

Profit and loss account

Revenue

	2016 budget (€)	2016 (€)	2015 (€)
Structural institute grants	3,621,987	3,664,202	3,606,930
Other grants and financial contributions	438,160	569,190	718,564
Other revenue	22,500	31,336	35,410
Total revenue	**4,082,647**	**4,264,728**	**4,360,904**

Operating costs

Personnel costs	2,601,070	2,432,077	2,280,173
Depreciation of fixed assets	42,981	18,466	10,082
Other operating costs	824,162	643,467	655,220
Project-related costs	0	33,015	65,731
Payments	985,000	955,674	981,500
Total operating costs	**4,453,213**	**4,082,699**	**3,992,706**
Year result	**-370,566**	**182,029**	**368,198**

Financial profit and loss

Interest and similar revenue	25,000	8,614	33,362
Interest and similar expenses	-1,200	-1,161	-1,088
Total financial profit and loss	**23,800**	**7,453**	**32,274**
Year result	**-346,766**	**189,482**	**400,472**

Appropriation of year result

	2016 (€)	2015 (€)
The year result was distributed as follows:		
Deferred grant revenue	-117,677	101,442
General reserve	0	0
Earmarked reserves	307,159	299,030
	189,482	**400,472**

2017 budget

Revenue	2017 budget (€)
VWS/RIVM grant for HIV monitoring in the Netherlands	3,164,200
VWS/RIVM grant for ACS	500,000
Project-based grants and financial contributions	62,000
Other revenue	20,500
Total revenue	**3,746,700**
Operating costs	
Personnel costs	2,195,000
Other personnel costs	113,000
Subtotal personnel costs	*2,308,000*
Depreciation of fixed assets	122,500
Costs of licence and use of external database for patient data	220,000
Development of database for patient data	50,000
Third party services	85,000
Subtotal third party costs	*355,000*
Office IT and website	110,000
Housing expenses	92,500
Office expenses	62,500
Travel and conference expenses	55,000
Subtotal other operating costs	*320,000*
Payments Amsterdam Cohort Studies	500,000
Payments HIV treatment centres	425,000
Subtotal payments	*925,000*
Total operating costs	**4,030,500**
Year result	**-283,800**
Financial profit and loss	
Interest and similar revenue	10,000
Interest and similar expenses	-1,200
Total financial profit and loss	**8,800**
Year result	**-275,000**

The 2017 financial results will be influenced by incidental depreciation and other costs related to an IT project.

Scientific output 2016

In 2016, Stichting HIV Monitoring (SHM) received 6 new requests to make use of SHM's cohort data. During the year, 57 articles were published in international peer-reviewed journals. In addition, 79 abstracts were accepted for presentation at 14 meetings and conferences (51 posters and 28 oral presentations). An overview of research projects, publications and presentations can be found on our website, *www.hiv-monitoring.nl*.

Completed research projects

I08044 Prima SHM R5x4 HAART
Grijsen M, Welkers M.

I12001 The rate of mother-to-child-transmission of hepatitis C virus in HIV-1 infected mothers
Van der Ende I, Snijdewind I, Smit C, Schutten M, Hartwig N, de Wolf F.

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.

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.

I14201 Failure of donor selection: what can the virus of the donor tell us?
Van de Laar T, Bezemer D, van Laethem K, Vanderwalle G, de Smet A, van Wijngaerden E, Claas E, van Sighem A, Vandamme A, Compernolle V, Zaaijer H.

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 started in 2000. Until its formal closure in February 2016, D:A:D successfully followed close to 24,000 patients from 11 cohorts in Europe, Australia and the United States.

Methods: The study has been highly successful in meeting 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 (including CROI 2017), 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/DAD.

Conclusions: In spite of the study having been highly productive and having generated influential and important findings, it had to be formally stopped February 1, 2016, given that the Study Group and the DAD Oversight Committee have not been successful in securing continued funding. In the summer of 2016, the final data merger was executed on data and validated clinical events accrued up to February 1st 2016. For the time being, scientific productivity continues, based on the last available joint dataset.

I05513 HIV resistance response database initiative (RDI)

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

Date of approval: 1 October 2005

Ongoing.

I08115 Proposal for collaboration and data exchange between SHM and RIVM for national 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.

Date of approval: 2008

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) increased 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. Using in depth records from the ATHENA cohort, we previously identified and characterised 617 transmission events to MSM with evidence for recent infection (12 months) at time of diagnosis. We quantified the sources of transmission by age and diagnosis status of the probable transmitters.

Methods: Through phylogenetic analysis of available partial HIV-1 pol sequences from the Netherlands, we identified probable transmission events to MSM with recent infection at time of diagnosis. Types of evidence for recent infection in the year before diagnosis were a previous negative test (76%), laboratory diagnosis (7%) or clinical diagnosis of acute infection (17%). Phylogenetically probable transmissions were then characterised through data from the ATHENA cohort. The proportion of transmissions by age/diagnosis status was calculated by averaging individual-level viral phylogenetic transmission probabilities across recipients as described previously.

Results: 729 MSM out of 4,206 newly diagnosed MSM in 2004-2010 were in recent infection at time of diagnosis and had a sequence sampled by 2013; we sought to characterise sources of transmissions to this group. 509 probable transmission events between 2004 and 2010 could be characterised through phylogenetic analysis. The estimated proportion of transmissions from young men aged <28 years increased substantially from 2004-2007 to 2008-2010, with most of these transmissions originating from undiagnosed young MSM. Transmissions were not concentrated within age groups. Further, transmission dynamics appear to have shifted substantially over calendar time. Men aged <28 years transmitted increasingly amongst peers as well as older men. Approximately half of the increase in transmissions from young men between 2004-2007 and 2008-2010 was attributable to the expected number of young men for whom a sequence was not available by 2013.

Conclusions: The retrospective transmission analysis up to December 2010 suggests that young men are increasingly linked within the MSM epidemic in the Netherlands, and appear to infect relatively more, older men than previously. Analyses of sequences up to 2015 are ongoing and will clarify this trend and help explain the rise in age at diagnosis in recent years.

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

Cornelissen M, Gall A, Vink M, Zorgdrager F, Binters S, Edwards S, Jurriaans S, On SH, Bakker M, Gras L, de Wolf F, Reiss P, Kellam P, Berkhout B, Fracer C, van der Kuyl AC.

Date of approval: 19 September 2012

Background: The first phase of the *Bridging the Epidemiology and Evolution of HIV in Europe* (BEEHIVE) collaboration, which included 1) collecting stored serum/plasma samples from selected patients and 2) testing the efficacy of HIV RNA isolation procedures for whole genome sequencing, finished in 2016 and the results have been published. In 2016 we continued to include samples from other European cohorts [Germany (n=361), Finland (n=31)] and from the HIV-1 treatment centres in the Netherlands (OLVG n=28, Groningen n=13 and AMC n=44; after obtaining patient's informed consent). At the end of 2016, a total of 2,909 isolated RNA samples had been sent to Sanger; sequencing has been completed.

Results: The results of the first phase have been published. In brief, we reported that manual isolation with the QIAamp Viral RNA mini kit (Qiagen) provides superior results over robotically extracted RNA. In addition, a detail protocol based on these findings is currently being written as a chapter for a book entitled "Viral Metagenomics" in the Springer lab protocol series "Methods in Molecular Biology", to be published in 2017/2018. We have also initiated a minor project on the HIV-1 Tat protein, the essential regulator of viral gene expression. We have noticed considerable variation in the length of the C-terminal domain of Tat in Dutch HIV-1, ranging from 77 to 124 amino acids. We have subsequently set up functional assays to analyse whether this polymorphism correlates with a change in activity.

Conclusions: First BEEHIVE publication appeared in 2016 and new studies using the BEEHIVE data have been initiated.

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. 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 Amo 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 of 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-positive 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 clinic survey, data about clinical indicators of HIV disease was collected (data source: SHM). The clinical survey is a multisite 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-positive 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 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 NGOs and the community. Throughout Europe, 1,782 participants were recruited, of which 134 in the Netherlands.

Data are currently being analysed for final publications, and abstracts have been sent for presentation at various conferences.

Likely country of HIV acquisition: Preliminary results from the European clinical survey show an estimated proportion of overall post-migration HIV acquisition of 66% (95% CI: 64%-68%); 75% among men having sex with men (MSM), 60% and 51% in heterosexual men and women, respectively. The probability of post-migration HIV acquisition was 75% for migrants from Latin America & Caribbean and 46% for people from sub-Saharan Africa. Factors associated with post-migration HIV acquisition among heterosexual women and MSM were age at migration, length of stay in host country,

employment and HIV diagnosis year. Among heterosexual men, geographical origin, length of stay in host country, employment and HIV diagnosis year were associated with post-migration HIV acquisition.

HIV testing and access to primary care: Preliminary results from the European clinic survey show there were high rates (82.0%) of previous negative testing among migrant gay/bisexual men, but less than half of women and heterosexual men (46.7% and 43.4% respectively) reported ever having had a negative test. Previous negative testing was associated with migration related factors among three gender-related groups: women (post-migration antenatal care); heterosexual men (immigration status) and gay/bisexual men (current country of residence and number of partners post-migration). Access to primary care was found to be high in all groups and was most strongly associated with current country of residence.

Preliminary results from the European community survey show that between 60-90% of migrants within this sample had previously tested for HIV. HIV testing was strongly associated with sexual behaviour (all groups); experience of forced sex or post-migration antenatal care (women); and access to primary care and health status (heterosexual men). Between 60-73% migrants had access to primary care. For women and heterosexual men access to primary care was associated with current residence and immigration status; among gay/bisexual men it was associated with current residence and HIV status.

I3120 SPREAD Program 3.0 – Surveillance of transmission of HIV-1 drug resistance

Hofstra LM, van Sighem AI, van Litsenburg M, Bierman W, Brinkman K, van der Ende ME, Hoepelman AIM, van Kasteren M, Op de Coul E, Richter C, Boucher CAB, Wensing AMJ.

Date of approval: 19 May 2014

Background & methods: The SPREAD cohort collects data from 28 European countries. Data collection and verification for 2011-2013 have been completed for all countries, including data from the six Dutch participating centres via the SHM. Over 4,000 patients have been included for 2011-2013. The data analysis team included participants from various European countries. In addition to the European analysis, we have started a specific analysis on the Dutch dataset.

Results: Results show that transmitted drug resistance mutations (TDRM) in the Netherlands have been stable for many years. Despite the long-term use of NNRTI-based regimens with a low genetic barrier to resistance, transmitted NNRTI resistance did not increase. Based on these results, we have additionally investigated the rate of virological failure (VF) in Dutch patients on treatment over time.

Conclusion: The very low rate of VF in patients treated with NNRTIs, reflecting careful use of NNRTIs in the Netherlands, indicates the limited time to transmit potentially acquired NNRTI resistance. The higher VF rate in patients using PIs likely reflects the use of PIs in a selected patient population rather than the potency

of the regimen. These data suggest that the prevalence of TDRM is nowadays predominantly driven by circulation of strains carrying drug resistance mutations in the therapy-naive population.
Preliminary results based on the Dutch data were presented at the NCHIV Conference in November 2016, during the poster session. A paper describing these data is in preparation. The analysis of the European data has been finalised and a paper is in preparation.

I14065 Incidence of hepatocellular carcinoma in HIV/HBV co-infected 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) co-infected patients. Current screening recommendations are based on incidence estimates in untreated HBV-infected patients and might be inadequate for HIV/HBV co-infected 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-co-infected 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 co-infected. 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 individuals with liver cirrhosis compared with those without liver cirrhosis. Further analyses are underway and a paper is in preparation.

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 people living with HIV (PLWH) than in HIV-negative individuals. The pathophysiological mechanism is thought to be multifactorial. The current Dutch cardiovascular risk management guidelines recommend risk assessment based on the SCORE risk equation adjusted for national data (SCORE-NL risk equation). However, it is unknown whether the SCORE-NL risk equation also accurately identifies PLWH 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 PLHIV in the Netherlands, and (2) to compare the predictive value of various CVD risk equations in PLWH.

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 (to) has been defined for all study participants, and all variables have been labelled. The risk equations evaluated within this project have been coded in STATA syntax: SCORE-NL equation, D:A:D risk equation 2010, D:A:D risk equation 2015 (reduced and full), Framingham risk equation, and Pooled Cohort Risk Equation. In addition, 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, and we are planning to impute the missing data using multiple imputation by chained equation in R. Methodological issues are currently being addressed.

Results: No results available, analysis ongoing.

l14087 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 trials and was therefore chosen as a comparison drug for efficacy, toxicity and potential decrease in eGFR in this study.

Methods: The primary goal of this nationwide 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: Data analysis on original data is complete. Additional data have been requested and will be analysed as soon as available.

Conclusions: In progress.

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

Borjas-Howard J, Rokx C, Bierman WFW, Tichelaar YIGV, Pieterman E, Smit C, Wit FWNM, Verbon A, Meijer K, Rijnders BJA.

Date of approval: 21 August 2014

Introduction: HIV patients are at increased risk for first venous thrombotic events (VTE) compared to the general population. What determines this increased risk in HIV and whether HIV patients remain at increased risk for recurrent VTE is unclear. An assessment of VTE risk factors and a reliable recurrence estimate are essential to determine the optimal duration of anticoagulant therapy (AC). We assessed the risk factors for a first VTE and evaluated VTE recurrence in HIV patients.

Methods: Observational study using data of the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. To identify VTE, we systematically reviewed charts of patients who initiated AC in 2003-2014 in 12 participating centres, covering 70% of ATHENA. The sensitivity of this case-finding strategy was confirmed by full chart review of all patients in 2 centres. We analysed risk factors for first VTE (regardless of location) by time-updated Cox regression models. VTE recurrence after AC withdrawal was analysed only in patients with a first VTE in proximal leg veins or pulmonary arteries. VTE associated with oestrogen use, pregnancy, surgery, cancer or trauma were considered provoked.

Results: 229 first VTE occurred in 14,386 HIV patients (80% males) during 97,556 person years (PY) of follow up (2.3 VTE/1000 PY). The time spent at lower CD4 T-cell counts was independently associated with higher first VTE risk and remained significant after correction for the increased hospitalisation risk in HIV patients with low CD4 T-cell counts. HIV patients with CD4 T-cell counts >500 cells/mm^3 had 1.3 VTE/1000 PY while HIV patients with CD4 T-cell counts <200 cells/mm^3 had 7.1 VTE/1000 PY. 153 of 202 HIV patients with first VTE localised in

proximal leg veins or pulmonary arteries had withdrawn AC, including 108 with unprovoked VTE. 32 recurrent VTE occurred (59 VTE/1000 PY; 95%CI: 41-83). Kaplan-Meier recurrence estimates at 1, 2 and 5 years of follow up were 17%, 20%, and 29% for unprovoked first VTE and 5%, 9%, and 15% for provoked first VTE.

Conclusions: The increased risk for a first VTE in HIV patients was strongly driven by lower CD4 T-cell counts. VTE incidence in those with high CD4 T-cell counts approached that in non-HIV patients. The VTE recurrence rate was high in patients with unprovoked first VTE and clustered in the first year after AC withdrawal. These results suggest that AC withdrawal in HIV patients with unprovoked VTE and low CD4 T-cell counts should be cautiously considered.

Abstract presented as poster at CROI 2017. Final publication in preparation.

I14144 GIS-hiv: Geographical information system to determine high prevalence areas of targeted screening and early case-finding

Op de Coul E, Joore I, van Sighem A, Bom B, Hillebregt M, Prins J, Geerlings S, van Bergen J.

Date of approval: 8 February 2015

Background: Mapping of areas with high HIV prevalence in the Netherlands for surveillance and prevention purposes.

Methods: Geographic Information System (GIS) techniques were used to display HIV diagnoses at the municipal level (the Netherlands) and at the district level (three largest cities).

Results: The maps show that ten municipalities in the Netherlands have an HIV prevalence of 2 or more per 1000 population (15-60 years), including Amsterdam (8.1) and suburbs, Rotterdam (3.4), The Hague (2.7) and Arnhem (2.5). Within the three largest cities, differences between districts are observed; especially in Amsterdam, where HIV was highly concentrated within two districts: central Amsterdam (9-28) and South-East Amsterdam (5-20). In Rotterdam and The Hague, HIV prevalence rates are lower and differences between districts are smaller.

Conclusions: Geographical analyses show differences in HIV prevalence for Dutch municipalities and districts in large cities. These data can be used for new, more targeted, HIV interventions.

I14145 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

Background: Many people living with HIV (PLWH) suffer from depressive symptoms. In previous research, it was found that self-help (in booklet format) cognitive behavioural therapy (CBT) is effective in treating depression in PLWH. We are currently developing an online self-help programme (based on the booklet) for PLWH and depressive symptoms. The main objective of this study is to investigate the effectiveness of the self-help programme compared to a waiting-list control group in reducing depressive symptoms. Secondary objectives include the investigation of moderators and mediators

of treatment outcome. Furthermore, we will investigate the change in medical parameters.

Methods: The self-help programme consists of four components: activation, relaxation, changing irrational cognitions, and goal attainment. The intervention group will work on the self-help programme for six weeks, 2-4 hours a week. They will receive weekly motivational support from a coach by telephone. The waiting-list control group will receive minimal support from a coach, through a weekly telephone call. We will examine the change in depressive symptoms from baseline to post tests in both groups as measured by the Patient Health Questionnaire 9 (PHQ-9) and the Center for Epidemiologic Studies Depression Scale (CES-D scale). Secondary study parameters include activation, cognitive coping, self-efficacy, symptoms of anxiety, and medical data.

Results: Participants have been included in the study and data collection has started. Medical data will be obtained from SHM in 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) practising 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-positive 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 ≥1HCV 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-positive MSM with elevated risk of HCV infection nor of high risk HIV/HCV co-infected MSM driving the HIV epidemic.

Manuscript has been submitted.

l15004 The impact of combinations of strategies for HIV prevention among men who have sex with men

Reitsema M, Mangen MJ, van Benthem B, op de Coul E, Wallinga J, van Sighem A, Schim van der Loeff M, Xiridou M.

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 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 and the Network Study among MSM in Amsterdam. Frequency of HIV/STI testing was estimated from data of the national database of STI clinics in the Netherlands. The model was calibrated to data on HIV diagnoses from Stichting HIV Monitoring.

Results: Analyses of behavioural and testing data reveal that HIV-diagnosed MSM were more likely to engage in condomless anal intercourse with any of their partners, compared to HIV-negative MSM and MSM with unknown serostatus. Known HIV-positive MSM were also more likely to consistently test for STIs at least every half year. The percentage of MSM reporting to test consistently at least every six months increased with the number of reported partners. The frequency of sexual activity between steady partners decreased with the duration of the partnership. Results from the model indicate that characteristics of steady sexual partnerships (number of new partners, duration, sex frequency, condom use) are less important for HIV transmission than the respective characteristics of casual sexual partnerships.

Conclusions: These findings suggest that MSM in the Netherlands continue to engage in risky sexual behaviours, but they also seem to be aware of their risk to acquire HIV and/or other STIs. This, in combination with our finding that HIV transmission is very sensitive to changes in risk behaviour with casual partners, could explain the persistence of HIV among MSM in the Netherlands. Moreover, it implies that the current interventions employed nationally and regionally substantially help in preventing rises in HIV transmission, but they are not able to induce further considerable reductions.

I15021 Global resistance following virological 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, Rinke 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 tenofovir (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. Sequence analysis of TDF resistance is ongoing.

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

Bolijn R, Op de Coul E, van Sighem A, Blok WL, Kretzschmar M, Heijne J on behalf of the ATHENA national observational HIV cohort.

Date of approval: 22 April 2015

Background: To investigate the value of in-care viral load (ICVL) and other viral load (VL) metrics for HIV surveillance by comparing time trends and associations with numbers of new HIV diagnoses.

Methods: Data from 20,740 HIV patients registered in the Dutch ATHENA cohort between 2002-2013 were used. We compared: six ICVL metrics (i.e., mean of the mean/first/last/highest log VL (logVL), median of the median logVL, first logVL for newly diagnosed combined with mean logVL for all others), logVL at diagnosis, proportion of patients with transmission risk (>400 copies/ml) or suppressed VL (≤200 copies/ml). Subgroup differences were assessed using Kruskal-Wallis and chi-square tests. Negative binomial regression was used for associations between VL metrics and numbers of new diagnoses 1-4 years later.

Results: Most ICVL metrics showed similar decreasing trends over time. Differences in covariables were found for all VL metrics. Mean ICVL showed the strongest association with new diagnoses: a decrease of one log unit in mean ICVL was associated with a 21% decrease in new diagnoses two years later.

Conclusions: VL metrics may be of value for enhancing HIV surveillance by identifying subgroup differences in impact of treatment on viral suppression, and by predicting numbers of new diagnoses in subsequent years.

Manuscript in preparation.

I15040 Monitoring recent HIV infection in the Netherlands: implementation of Recent Infection Testing Algorithm (RITA) into routine HIV surveillance

Op de Coul E, de Bree G, van Sighem A, Brinkman K, Prins J, Jurriaans S.

Date of approval: 2015

Background: In January 2014, the RIVM implemented a serological assay in the routine HIV surveillance at all STI centres in the Netherlands to enable estimates of HIV incidence for different populations (phase

1). The assay, an avidity test (Architect-immunoassay) combined with CD4 count, viral load and epidemiological data (abbreviated to RITA: Recent Infections Testing Algorithm), quantifies the avidity of antibodies reflecting the time since HIV seroconversion. The goal of this enhanced surveillance is to monitor trends in recent infections (<6 months) in the Netherlands, and to better characterise the HIV epidemic by identifying (sub)populations at risk to inform local and national HIV intervention programmes.

In phase 2 of the RITA surveillance, we plan to test leftover samples from newly diagnosed HIV patients in HIV treatment centres in the Netherlands to get a broader overview of recent infections among persons diagnosed outside the STI centres. To study the feasibility of implementation in HIV treatment centres, we will start with HIV treatment centres in Amsterdam (AMC, OLVG, and to be approached: Jan van Goyen, Sint Lucas Andreas Ziekenhuis and Slotervaart). The treatment centres will send residual plasma or serum specimens from confirmed newly HIV-diagnosed patients before treatment has started to Sanquin Blood Supply, who will conduct the avidity testing. Data on CD4 counts and viral load at diagnosis or first entry into care, HIV-1 subtype and epidemiological information such as transmission risk group, age, country of birth etc. will be obtained from Stichting HIV Monitoring. The outcomes (percentages of recent HIV infections for various subgroups) will be reported as part of the regular surveillance in the annual HIV/STI report prepared by the RIVM/CIb in collaboration with Stichting HIV Monitoring.

Results: Sample collection is ongoing.

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: The Adherence-Improving self-Management Strategy (AIMS) is effective in increasing adherence and reducing viral load, but its cost-effectiveness remains unclear.

Methods: To develop a Markov model comparing the relative risks of the AIMS intervention (intervention versus control), with longitudinal SHM data on patient trajectories (clinical and costs) in routine clinical care. The model also incorporates productivity losses and HIV transmission risks. A lifetime Markov model was developed to estimate the costs of AIMS per quality adjusted life-years (QALYs) gained from a societal perspective.

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: HIV/hepatitis B virus (HBV) co-infected subjects are thought to have faster progression to end-stage liver disease (ESLD) than HBV mono-infected subjects. We assessed whether this remains in the current cART era.

Methods: Data from subjects with follow-up completion post-2003 were compared between HIV/HBV co-infected subjects in the Dutch HIV Monitoring database and HBV mono-infected subjects from two centres. The primary outcome of composite ESLD included portal hypertension, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related mortality. Outcomes were analysed using time-dependent Cox regression models adjusted for follow-up time and relevant covariates. Subset analyses were done in subjects with follow up pre-2003.
Results: Incidence of ESLD, all-cause and liver-related mortality was 7% vs. 15%, 13% vs. 6%, and 2% vs. 3% respectively, in 1,336 co-infected versus 742 mono-infected subjects. After adjustment, co-infected subjects had no increased probability for ESLD compared to mono-infected subjects (HR 0.5 [95% CI 0.3–0.9]), contrary to co-infected subjects monitored pre-2003 in the sub-analyses (HR 8.6 [1.2–64.2]). While the probabilities for all-cause (HR 10.8 [6.4–18.0]) and liver-mortality (HR 5.9 [2.1–16.8]) were increased in co-infected subjects, these rates decreased compared to pre-2003. In the current combined cohort, treatment with tenofovir or entecavir was inversely associated with all outcomes. Other predictors for ESLD were older age, being of sub-Saharan African descent, advanced fibrosis, elevated alanine aminotransferases, and higher HBV DNA levels.

Conclusions: HIV/HBV co-infected patients no longer seem to be at increased risk for progression to ESLD compared to HBV mono-infected patients, likely due to widespread use of highly effective cART with dual HBV and HIV activity.

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

Background: In the Netherlands, 15,000 HIV-positive individuals are in care and receive antiretroviral therapy. The total costs for HIV care are substantial, with annual medication costs alone accounting for €125 million. The total direct and indirect costs for care in general and for different cART regimens in particular in relation to their effectiveness has not been evaluated. The aim of our study is to evaluate cost-effectiveness of different aspects of HIV care for the individual patient, public health, and society. In the first phase of our project we will define and map all relevant cost components in HIV care.

Methods: The outcome of the first phase will enable us to identify those parameters that will become an integral part of standardised data collection by SHM. This way we will build an infrastructure allowing continued use of the SHM database for health-economic analyses in the future. Finally, we will perform a retrospective study over the past 10 years to analyse the trends in costs and cost-effectiveness of different cART regimens. Results of this project will enable stakeholders (policymakers, health care professionals, HIV-infected individuals and payers) to make rational decisions for future treatment and care scenarios in the Netherlands.

Results: 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: HIV co-infection may accelerate the progression to liver fibrosis and cirrhosis in chronic HCV. Recently, a study among HCV mono-infected 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. Data on the rate of liver fibrosis progression and its determinants soon after HCV seroconversion in those with underlying HIV infection are lacking. We will retrospectively study liver fibrosis progression, assessed by FIB-4 scores, in HIV-positive individuals in the Netherlands who acquired acute HCV.

Methods: Any HIV-positive individual with an acute HCV infection on or after 1 January 1999, identified in the SHM database, were included. In addition, cases identified in the MOSAIC study were included. Follow-up duration less than 2 years after the estimated date of infection is an exclusion criterion. Descriptive analyses, multilevel modelling and Cox regression analysis will be carried out.

Results: Data collected until 31/01/2016 have been used. In total, 526 cases have been identified from the SHM and the MOSAIC database; 75 were excluded due to a follow up of less than 2 years). Datasets have been prepared for analysis and statistical analysis is in progress.

Conclusions: None yet.

I15142 Use of regular outpatient medication in HIV/HCV co-infected patients in the Netherlands

Smolders EJ, Smit C, De Kanter CTMM, Dofferhoff ASM, Arends JE, Brinkman K, Rijnders B, van der Valk M, Reiss P, Burger DM, on behalf of the ATHENA national HIV observational cohort.

Date of approval: 2 March 2016

1) High need to switch cART or co-medication with the initiation of DAAs in HIV/HCV co-infected patients

Objective: To describe the use of non-antiretroviral co-medication and combination antiretroviral therapy (cART) in HIV/hepatitis C virus (HCV) co-infected patients, and to predict the potential for drug-drug interactions (DDIs) with direct-acting antivirals (DAAs) against HCV.

Methods: Retrospective, cross-sectional study, using the Dutch nationwide ATHENA observational HIV cohort database. All patients with a known HIV/HCV co-infection on 1 January 2015 were included. Co-medication and cART registered in the database on 1 January 2015 were listed. The potential for DDIs between DAAs and co-medication/cART were predicted using the Hep Drug Interaction Checker. DDIs were categorised as: (1) no clinically relevant DDI; (2) possible DDI; (3) contraindication; or (4) no information available.

Results: We included 777 patients of whom 488 (63%) used non-antiretroviral co-medication. At risk for a category 2/3 DDI with non-antiretroviral co-medications were 299 patients (38%). Most DDIs were predicted with paritaprevir/ritonavir, grazoprevir/elbasvir (11% of the drugs). Concerning cART, daclatasvir/sofosbuvir is the most favourable combination as no cART is contraindicated with this combination. In genotype 1/4 patients, grazoprevir/elbasvir is least favourable as 75% of the patients must alter their cART.

Conclusions: This study showed that co-medication use in the ageing HIV/HCV population is frequent and diverse. There is a high potential for DDIs between DAAs and co-medication/cART.

2) Management of drug interactions with DAAs in Dutch HIV/HCV co-infected patients: adequate but not perfect

Objective: Direct-acting antivirals (DAAs) for treatment of hepatitis C virus (HCV) infection can be involved in drug-drug interactions (DDIs), both with combination antiretroviral therapy (cART) and non-antiretroviral co-medication. In this study, we mapped how physicians manage DDIs between DAAs and co-medication/cART and analysed treatment outcomes.

Methods: Retrospective, follow-up study, using a Dutch cohort of HIV/HCV co-infected patients (ATHENA cohort). HIV/HCV co-infected patients treated with DAAs (January 2015 to May 2016) were included. Co-medication and cART 3 months before DAA initiation were identified. Potential DDIs with the selected DAA regimen were checked using the Hep Drug Interaction Checker. DDIs were categorised as: (1) no clinically relevant DDI; (2) possible DDI; (3) contraindication; or (4) no information available. Subsequently, analysis was performed to determine whether the cART regimen was changed and co-medication discontinued.

Results: 423 patients were treated with DAAs, of whom 421 used cART and 251 used other comedication. Before commencing DAA treatment, 26,199 prescriptions of co-medication causing a category 213 DDI were discontinued before DAA initiation, including 3/6 prescriptions of contraindicated drugs. 198 patients had a category 2/3 DDT between their DAA regimen and their cART. All 48 patients with a category 3 DDI changed their cART before DAA initiation. Currently, of the 341 patients in whom HCV treatment response could be assessed, 334 (98%) had achieved a sustained virological response.

Conclusions: Prescription patterns suggest Dutch physicians are well aware of potential DDIs with DAAs, in particular when it

concerns cART. Improved awareness is needed for co-medication DAA category 3 interactions.

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

Background: A significant part of the HIV-positive population is co-infected with hepatitis C virus (HCV). HIV/HCV co-infection is associated with faster progression to liver fibrosis and less spontaneous HCV clearance compared to the HCV mono-infection population. With the introduction of the direct-acting agents (DAAs) the vast majority of HCV- infected patients will reach a sustained viral response (SVR), improving their overall prognosis. Although the DAAs are very effective, they also involve high costs. For that reason, in some countries healthcare insurance will only cover HCV treatment in patients with high-grade liver fibrosis or cirrhosis. This policy is based on the assumption that these patients will benefit the most by reaching SVR in preventing clinical liver-related morbidity. However, current prediction rules in patients with liver disease – e.g. the Child-Pugh score – focus on mortality in the first upcoming years but do not asses the risk for decompensated liver disease in the long-term.

Objective: In 2015 van der Meer *et al.* published a reliable prediction rule to predict long-term outcomes among HCV-mono-infected patients with advanced liver disease. This prediction rule was validated in other HCV mono-infection cohorts. Considering the high prevalence of HIV/HCV co-infection, we are conducting a study to validate this prediction rule in an HIV/HCV co-infected population.

Methods: Data on all HIV/HCV co-infected patients with 'advanced hepatic fibrosis' (AHF) (advanced fibrosis or cirrhosis) – based on clinical criteria, fibroscan or liver biopsy – were retrieved from the SHM database. Patients with a hepatitis B virus co-infection were excluded from the analysis. The date of diagnosis of AHF was considered as baseline. Laboratory markers of liver disease severity (platelet value, bilirubin, albumin, asparate aminotransferase (AST), alanine aminotransferase (ALT) were registered if available 6 months prior to baseline. Furthermore, all dates of events of hepatic decompensation (the occurrence of ascites, hepatic encephalopathy, hepatocellular carcinoma and oesophageal variceal bleeding), death or SVR after treatment were registered. Additional data related to HIV and antiretroviral treatment were retrieved as well. Patients were censored from analysis from the moment they died, experienced a clinical event of decompensated liver disease or when they reached SVR after HCV-treatment.

Using the clinical and biochemical data, the risk score was assessed using the prediction rules from the study by van der Meer *et al.* Outcomes are divided in three groups with the highest quartile representing the high-risk group, the lowest quartile representing the low-risk group and the remaining 50% representing the intermediate-risk group. Using the C statistic we will assess the predictive accuracy of the model in this HIV/HCV co-infected group. Predicted mortality

and clinical disease progression rates will be compared with those observed.

Results: There are no results available yet.

Conclusions: Pending results.

I16011 Type of cART regimen and the risk for immune reconstitution and inflammatory syndrome in HIV-1 infected patients. Is integrase inhibitor use an independent risk factor?

Wijting IEA, Rokx C, Wit FWNM, Reiss P, Rijnders BJA.

Date of approval: 2 March 2016

Background: Integrase inhibitor (INI)-containing cART is recommended as first choice by HIV-treatment guidelines for cART-naive HIV-1 infected individuals. Use of INI is associated with an accelerated HIV-RNA decline and enhanced CD4 T-cell recovery compared with PI-containing and NNRTI-containing cART. However, in HIV-1 late presenters, patients with CD4 T-lymphocytes <200 cells/mm^3, these factors are associated with IRIS, a pathological immune reaction against antigens of opportunistic infections (OI). Whether the use of INI-containing cART increases the incidence of IRIS is unknown. Phase III trials of licensed INI rarely include late presenters (<10%) and are thus unable to answer this question. We hypothesise that INI-containing cART is an independent risk factor for IRIS.

Methods: Observational multicentre study within the ATHENA cohort. Eligible patients initiated cART from 24 March 2009 (date that raltegravir became available as first INI) or later, had CD4 ≤200 cells/mm^3, and met at least one of the three following criteria: 1) suffered from any of the following OI; PCP, toxoplasmosis, Kaposi, CMV, cryptococcosis, mycobacterial infections, PLM and/or 2) had initiated corticosteroids ≤12 months after cART initiation and/or 3) died ≤12 months after cART initiation. This patient selection was used to limit the population to those at highest IRIS risk, as IRIS is not an entity in the ATHENA cohort which can be collected automatically. IRIS definitions were used to find IRIS cases in patient files manually: IRIS criteria by French *et al.* (French IRIS) and IRIS diagnosed by treating physician (clinical IRIS). Patient files were reviewed for both IRIS definitions using a standardised CRF.

The primary outcome was the incidence of French IRIS as well as the combined clinical or French IRIS. To count every patient only once, patients were considered having a French or a clinical IRIS and not both (when a patient met both definitions, they were considered to have a French IRIS because of higher specificity of this definition). Cox regression was used to compare the risk of IRIS in INI and non-INI users, while controlling for potential confounders; demographic, virological, immunological and clinical parameters (e.g., type of OI prior to cART). The observation window was 12 months after cART initiation. Patients were censored when switching from INI to non-INI and vice versa.

Results: Of approximately 18,000 patients registered in SHM, 780 met the inclusion criteria. Of them, 369 were analysed in 2016. We expect the remaining 411 to be analysed in the first 6 months of 2017. Median CD4 count and median viral load were 39 cells/mm^3 and 275,423 copies/ml at cART initiation.

Most prevalent OI were PCP (n=172), candidiasis (n=143), Kaposi (n=38), mycobacterial infections (n=51) and toxoplasmosis (n=27). The incidence of clinical and French IRIS were 19% and 19% (INI), respectively, versus 9% and 7% (non-INI), respectively. Any form of IRIS was observed in 26 of 69 (38%) of the INI users compared to 47 of 300 (16%) in the non-INI users (odds ratio 3.25, 95%CI 1.83-5.80). Cox regression analysis showed use of INI to be independently associated with French IRIS (hazard ratio 2.62, 95%CI 1.35-5.10, p=0.0045) and all IRIS cases (HR 2.60, 95%CI 1.63-4.44, p=0.0001). Other risk factors for IRIS were cryptococcosis, atypical mycobacterial infection, CMV and female gender.

Conclusions: These preliminary data suggest that INI use in patients diagnosed with an OI and a CD4 count ≤200 cells/mm^3 is an independent risk factor for IRIS. If confirmed after increase of the sample size and in other studies, the use of an INI as part of the initial cART may have to be revisited in HIV-1 late presenters who are initiating cART.

l16038 Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients: a multicentre cohort study

Ward PH, van Bilsen W, van den Berg CHSB, Rijnders BJA, Brinkman K, Mulder JW, Gelinck LBS, Hoepelman AIM, Wit FWNM, van de Beek D, Prins JM.

Date of approval: 20 June 2016

Objectives: To investigate the incidence and risk factors of immune reconstitution inflammatory syndrome (IRIS) associated with toxoplasmic encephalitis (TE) in patients starting cART.

Methods: An historical multicentre cohort study. We included all HIV-positive patients diagnosed with TE in six Dutch hospitals between 1996 and 2016. Diagnosis of TE-IRIS was made using predefined IRIS criteria. We distinguished paradoxical TE-IRIS (worsening of underlying treated infection) from unmasking TE-IRIS (unmasking of subclinical infection after start of cART). We compared CD4 count, plasma viral load and timing of cART initiation between patients with and without paradoxical TE-IRIS.

Results: 211 TE cases were included. Among 143 cases at risk for paradoxical TE-IRIS, we identified five cases of paradoxical TE-IRIS (3.5%). In six other cases we could not differentiate paradoxical TE-IRIS from recurrence of disease due to inadequate secondary *Toxoplasma* prophylaxis. There was no difference in time between start of TE treatment and cART initiation for patients who did or did not develop paradoxical TE-IRIS (p=0.50). Within the group of 2,228 patients who started cART while having a CD4 count below 200 x 10^6/L and receiving adequate primary prophylaxis, we identified eight cases of unmasking TE-IRIS (0.36%). Unmasking TE-IRIS could not be differentiated from a newly occurring TE in six other patients, as they were not receiving adequate primary prophylaxis against *Toxoplasma*.

Conclusion: Unmasking TE-IRIS was rare in this cohort, whereas paradoxical TE-IRIS did occur more often. We found no relationship between the timing of cART initiation and the occurrence of paradoxical TE-IRIS.

I16060 Evaluation dolutegravir and elvitegravir for the treatment of HIV-1 in the Netherlands: a focus on switchers and adverse events

Bollen P, Hakkers CS, Boender S, Brouwer A, Hoepelman IM, Brinkman K, van den Berk GEL, Wit F, van Crevel R, Arends JE, Burger D.

Date of approval: 30 August 2016

Background: In phase III studies dolutegravir showed remarkably low discontinuation rates due to adverse events (2-3%) in naive and treatment-experienced patients after 48 weeks of treatment. However, in clinical practice we have noticed in our out-patient population that adverse events, such as insomnia and abnormal dreams, do occur in patients using dolutegravir. Sometimes even at such a severity that patients have to discontinue the use of the drug. Unfortunately, so far, there are no post-marketing data available on the occurrence of adverse events.

Objectives: In this retrospective cohort study we will therefore analyse treatment-naive and treatment-experienced patients that started on dolutegravir as part of their HIV treatment. We will focus on the incidence, particular reasons and risk factors of treatment discontinuations on dolutegravir in both naive and experienced patients. In addition, we will provide descriptive statistics of the treatment-naive and treatment-experienced populations using dolutegravir.

Methods: Patients that met our inclusion criteria and started treatment with cART based on dolutegravir (n=2,216) or elvitegravir (n=1,200) were extracted from the SHM database (freeze May 2016). An analysis plan was constructed in collaboration with SHM to answer primary and secondary research questions. Descriptive statistics were performed on both dolutegravir and elvitegravir groups. Reasons for discontinuation and adverse events were converted to categorical variables to allow for evaluation.

Results: Currently we are working on the development of a multivariable Cox model to find predicting variables for discontinuations on dolutegravir and elvitegravir. The final analysis is planned for March 2017.

I16072 Comparison of the occurrence of 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 2)

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

Date of approval: 11 August 2016

Background: HARMONIC is a retrospective study (conducted by Rijnstate Hospital and University Medical Center Utrecht in cooperation with the SHM) in which we compare patients with hepatitis B (HBV) mono-infection and HIV/HBV co-infection with regards to the occurrence of liver related outcomes. Clinical, laboratory and serological data from all patients were collected by SHM data collectors. In the first analyses (see I15065), the cohorts were compared on composite end-stage liver disease outcome (ESLD; liver-related mortality, hepatocellular carcinoma, liver decompensation and advanced fibrosis/cirrhosis) and all-cause mortality. HIV-infection status was

not an independent predictor for composite ESLD nor for all-cause mortality in time-updated cox proportional hazard models in 876 HIV/HBV co-infected patients versus 628 HBV mono-infected patients, contrary to results in older studies from the pre-cART era.

Methods: In this study we would like to compare occurrences of HBsAg and HBeAg seroclearance, HBV reactivation, and HBsAg and HBeAg reverse seroconversion in the HIV/HBV coinfection group vs. the HBV mono-infection group. All data are already available.

Results: Analyses are ongoing.

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HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls
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BEEHIVE

From clinical sample to complete genome: comparing methods for the extraction of HIV-1 RNA for high-throughput deep sequencing

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Appendix 1: Composition of Stichting HIV Monitoring

SHM board

Name	Position	Representing	Affiliation
Dr F.P. Kroon	Chair	Nederlandse Vereniging HIV Behandelaren (NVHB)	LUMC
Y.T.H.P. van Duijnhoven (as of May 2016)	Secretary	GGD GHOR Nederland	GGD Amsterdam
Dr P.W.D. Venhoeven	Treasurer		Prinses Maxima Centre for Paediatric Oncology
Prof. K. Stronks	Member	AMC-UvA	AMC-UvA, Amsterdam
L.J.M. Elsenburg (until November 2016)	Member	Hiv Vereniging	Hiv Focus Centrum
P. Brokx (as of November 2016)	Member	Hiv Vereniging	Hiv Vereniging
Dr M.M.E. Schneider (as of May 2016)	Member	Nederlandse Federatie Universitair Medische Centra (NFU)	UMC Utrecht
P.E. van der Meer	Member	Nederlandse Vereniging van 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 (until December 2016)	Imperial College, Faculty of Medicine, Dept. of Infectious Disease Epidemiology, London, UK
Prof. M. Egger	University of Bern, Switzerland
Prof. C. Sabin (as of December 2016)	Research Dept. of Infection & Population Health, University College London, UK
Prof. B. Ledergerber (as of December 2016)	Dept. of Infectious Diseases & Hospital Hygiene, University Hospital Zürich, Switzerland
Prof. T.B.H. Geijtenbeek	AMC-UvA, Dept. Experimental Immunology, Amsterdam
P.J. Smit	Hiv Vereniging, Amsterdam
Dr M. van der Valk	AMC-UvA, Dept. Internal Medicine, Amsterdam

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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

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)	Radboudumc, 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	UMC Utrecht-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. 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 until 1 November 2016)	Rijnstate, Dept. of Internal Medicine, Arnhem
Dr J. Arends (Chair as of 1 November 2016)	UMC Utrecht, Dept. of Internal Medicine, Utrecht
Dr C. Smit	Stichting HIV Monitoring, Amsterdam
Prof. K. Brinkman	OLVG, Dept. of Internal Medicine, Amsterdam
Prof. A.I.M. Hoepelman	UMC Utrecht, Dept. of Virology, 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 A. Vollaard	LUMC, Dept. of Infectious Diseases, Leiden

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SHM personnel

Position	Name
Director	Prof. P. Reiss MD
Data analysis, reporting & research	
Researchers	D.O. Bezemer PhD
	T.S. Boender PhD
	A.I. van Sighem PhD
	C. Smit PhD
	F.W.N.M. Wit PhD
PhD candidates	E. Engelhard MSc (external, until 30 April 2016)
	R. van den Hengel MSc (until 31 May 2016)
Data & QC	
Manager	S. Zaheri MSc
Data management	M.M.J. Hillebregt MSc (coordinator)
	A.S. de Jong MSc
QC & protocol management	S. Grivell MSc (protocol & helpdesk coordinator)
	A.M. Jansen MSc (data quality staff coordinator)
Data quality staff	D. Bergsma MSc
	P.T. Hoekstra-Mevius MSc (until 31 March 2016)
	A. de Lang PhD († 22 November 2016)
	R. Meijering MSc
	M.J.C. Rademaker MSc (until 30 November 2016)
	M.S. Raethke MSc
	S. Schnörr MSc (until 30 November 2016)
Patient registration & data collection	L.G.M. de Groot-Berndsen (coordinator)
	M.M.B. Tuk-Stuster (patient registration & quality management coordinator)
Data collectors	M. van den Akker
	Y.M. Bakker
	M. Bezemer
	M. Broekhoven-van Kruijne (until 31 January 2016)
	E.J. Claessen
	A. El Berkaoui
	R. Henstra-Regtop
	J. Koops
	E.I. Kruijne

C.R.E. Lodewijk
L. Munjishvili
B.M. Peeck
C.M.J. Ree
Y.M.C. Ruijs-Tiggelman
T. Rutkens
L. van de Sande MA
M.J.C. Schoorl MSc
A.G. Timmerman MSc
E.M. Tuijn-de Bruin
D.P. Veenenberg-Benschop
S. van der Vliet
S.J. Wisse MSc
T.J. Woudstra

Communications

C.J. Ester PhD (manager)
M.J. Sormani

Staff

I. Bartels (HR advisor)
D. de Boer
A. J.P. van der Doelen (controller)
M.M.T. Koenen (office manager)
H.J.M. van Noort MSc (financial administrator)
Y de Waart (office assistant)

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.

AIGHD
Amsterdam Institute for Global Health and Development.

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

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

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

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 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 (<200 CD4 cells per mm^3 blood).

CDC
US Centers for Disease Control and Prevention.

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

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)*.

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
Dutch association for people living with HIV.

HKZ
Foundation for Harmonisation of Healthcare Quality Review *(Harmonisatie Kwaliteitsbeoordeling in de Zorgsector)*.

Immune recovery
If treatment is effective and HIV is well-controlled, the immune cells regain their normal function and CD4 cell counts are close to normal. This is defined as immune recovery.

Immunological failure
A type of HIV treatment failure. There is no consensus on the definition of immunological failure. However, some experts define immunological 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 do not 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 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 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 (NtRTI)
A type of antiretroviral HIV drug. Nucleotide reverse transcriptase inhibitors (NtRTIs) interfere with the HIV life cycle in the same way as NRTIs. Both block reverse transcription. NtRTIs are included in the NRTI drug class.

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

Person year
Person years combines the number of persons and their time contribution (e.g., in years) in a study. In the ATHENA cohort, the person years generally refer to the cumulative number of years that individuals were followed by SHM.

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 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
The Netherlands' National Institute for Public Health and the Environment *(Rijksinstituut voor Volksgezondheid en Milieu)*.

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.

Sustained virological response (SVR12 or SVR24)
Undetectable hepatitis C virus in blood 12 or 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection.

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.

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

VWS
Dutch Ministry of Health, Welfare and Sport *(Ministerie van Volksgezondheid, Welzijn en Sport)*.

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