HIV Monitoring

Annual report 2018

Annual report 2018, approved by the Stichting HIV Monitoring Governing Board on 23 May 2019

We would like to thank Inge Bartels, Daniela Bezemer, Arianne van der Doelen, Catriona Ester, Mireille Koenen, Amy Matser, Henk van Noort, Maria Prins, Ard van Sighem, Colette Smit, Brenda Tuk, Yunka de Waart, Ferdinand Wit and Sima Zaheri for their contributions.

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

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Foreword

2018 was an exciting and busy year for Stichting HIV Monitoring (SHM), marked by highlights such as the launch of our new data entry system and the 22nd International AIDS Conference, AIDS 2018, that was hosted on our doorstep in Amsterdam.

At the same time, we also continued our important task of monitoring the HIV epidemic in the Netherlands. Drawing on our well-established collaboration with the appointed HIV treatment centres in the Netherlands, we are able to collect and analyse data on relevant health outcomes, including non-communicable co-morbidities and viral hepatitis co-infections, from people living with HIV in clinical care. Through these analyses, we can provide a truly representative picture of the outcome of care for those living with HIV in the Netherlands, thereby providing essential information relevant to both public health and quality of care. The outcomes of these analyses are described in detail in the 2018 HIV Monitoring Report, the key findings of which are included in this annual report.

Preparing for the future

After a great deal of hard work by various teams within the organisation, our new data entry system, called DataCapTree, went live in February 2018. DataCapTree provides our data collectors with a more streamlined, decision-supported system by which to collect information from electronic patient records. As a result, we anticipate that the data collection process will not only become more efficient, but will also ensure that SHM is ready for future technological advances.

SHM also remains committed to safeguarding privacy and data security. I am proud to say that we were well-prepared when the EU General Data Protection Regulation (EU-GDPR) came into force in May 2018, and we will continue to build on this solid foundation to safeguard data privacy.

Foreword

Word of thanks

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 like to extend my sincerest thanks and appreciation to all those living with HIV and 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, 23 May 2019

Message from the governing board chair

In my first year as chair of Stichting HIV Monitoring's governing board, I have been privileged to experience first-hand the commitment with which all those working at the organisation apply themselves to improving the care for people living with HIV. From the collection of data through to the extensive reporting on trends in the HIV epidemic in the Netherlands, each step of the process is carried out with care and dedication. The end product of these concerted efforts is the annual HIV Monitoring Report. This report continues to provide in-depth insight into the HIV epidemic in the Netherlands, pinpointing both the successes, such as an ongoing reduction in the number of newly-acquired HIV infections in the Netherlands, and challenges, such as a persistently high rate of late diagnosis.

In many ways, 2018 was a year that shone a spotlight on the excellent work carried out by Stichting HIV Monitoring. The year marked the 20th anniversary of the ATHENA cohort of people living with HIV and in care in the Netherlands. The ATHENA cohort, managed by Stitching HIV Monitoring since 2001, is unique in its breadth and scope and, over the past 20 years, has played a very important role in furthering the understanding of the HIV epidemic and improving care of people living with HIV.

As part of an ambitious digitalisation programme, SHM's new data entry system, DataCapTree, went live at the beginning of 2018. The culmination of a great deal of hard work and innovation, expertly led by SHM's deputy director, Sima Zaheri, DataCapTree will not only improve the efficiency of data collection at the treatment centres, but also prepares SHM for future technological advancements.

I am sure many of you will remember 2018 as being the year in which the International AIDS conference, AIDS 2018, returned to the Netherlands. The success of this world-class event was, in part, due to the tireless efforts by SHM's director, Peter Reiss, who was co-chair of the conference. On the eve of the conference, Peter Reiss was awarded a royal honour in recognition of his many years of work in the HIV field and his commitment to improving the lives of the people living with HIV in his care and beyond.

Finally, my thanks go to all those involved all the staff at SHM, the HIV healthcare professionals and, of course, the people living with HIV who are in clinical care. I would also like to express my appreciation to my fellow board members for their work on behalf of SHM.

Marc van der Valk, MD, PhD
Chair of the governing board
Amsterdam, 23 May 2019

In this year's report

Stichting HIV Monitoring in 2018

About

STICHTING HIV MONITORING

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.

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, 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 the designated HIV treatment centres in the Netherlands by either treatment centre staff or by SHM data collectors in cooperation with the responsible HIV physician. Patient data are collected and entered into the registration database in a pseudonymised form for storage and analysis.

ABOUT STICHTING HIV MONITORING

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

ABOUT STICHTING HIV MONITORING

HIV TREATMENT CENTRES IN 2018

The monitoring of HIV-positive adults is a collaborative effort involving SHM and, in 2018, 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.

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.

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).

26 HIV treatment centres in the Netherlands in 2018

4 paediatric HIV treatment centres

ABOUT STICHTING HIV MONITORING

HIV treatment centres and subcentres in 2018

1	Noordwest Ziekenhuisgroep	Alkmaar
2	Flevoziekenhuis	Almere
3	Amsterdam UMC, AMC site	Amsterdam
4	Amsterdam UMC, VUmc site	Amsterdam
5	DC Klinieken Lairesse - Hiv Focus Centrum	Amsterdam
6	OLVG	Amsterdam
7	MC Slotervaart*	Amsterdam
8	Medisch Centrum Jan van Goyen (MC Jan van Goyen)	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	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

* MC Slotervaart and MC Zuiderzee were declared bankrupt on 25 October 2018. Data collection continued in both hospitals until final closure early 2019. Patient care for people living with HIV has since been transferred to other nearby HIV treatment centres, where data collection will continue.

Centres for the treatment and monitoring of paediatric HIV:

A	Emma Kinderziekenhuis (EKZ), Amsterdam UMC	Amsterdam
B	Beatrix Kinderziekenhuis (BKZ), UMCG	Groningen
C	Erasmus MC-Sophia Kinderziekenhuis	Rotterdam
D	Wilhelmina Kinderziekenhuis (WKZ), UMC Utrecht	Utrecht

[Click on the hospital name to visit the hospital's website]

ABOUT STICHTING HIV MONITORING

OUR ORGANISATION

Governance and management

Governing board

Our governing board members 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 AMC site of Amsterdam UMC. The governing board convenes twice a year and its duties include approving SHM's budget and the content of the annual report; board members receive no remuneration for this work.

Governing board members in 2018

Name	Position	Representing	Affiliation
Dr M. van der Valk	Chair	NVHB	Amsterdam UMC, AMC site, Amsterdam
Dr Y.T.H.P. van Duijnhoven	Secretary	GGD GHOR Nederland	GGD, Amsterdam
P.W.D. Venhoeven	Treasurer		Alexander Monro Ziekenhuis, Bilthoven
P. Brokx	Member	Hiv Vereniging	Hiv Vereniging, Amsterdam
J. Crasborn	Member	Zorgverzekeraars Nederland	Achmea, Zeist
Prof. K.J. Jager	Member	Amsterdam UMC, AMC site	Amsterdam UMC, AMC site, Amsterdam
P.E. van der Meer	Member	Nederlandse Vereniging van Ziekenhuizen (NVZ)	Albert Schweizer Ziekenhuis, Dordrecht
Prof. M.M.E. Schneider	Member	Nederlandse Federatie Universitair Medische Centra (NFU)	UMC Utrecht, Utrecht

ABOUT STICHTING HIV MONITORING

Advisory board

A scientific advisory board has been established by the governing board to provide the governing board members and SHM's director with strategic advice regarding the registration and monitoring of data from HIV-positive individuals in care in the Netherlands and 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.

Advisory board members in 2018

Name	Affiliation
Prof. D.R. Kuritzkes (Chair)	Brigham and Women's Hospital, MA, USA
Dr J. Arends	UMC Utrecht, Utrecht, the Netherlands
Prof. M. Egger	University of Bern, Bern, Switzerland
Prof. T.B.H. Geijtenbeek	Amsterdam UMC, AMC site, Amsterdam, the Netherlands
Prof. B. Ledergerber	University Hospital Zurich, Zurich, Switzerland
Prof. C. Sabin	University College, London, UK
P.J. Smit	Hiv Vereniging, Amsterdam, the Netherlands

ABOUT STICHTING HIV MONITORING

Working groups

SHM has two working groups that advise the director on executive matters regarding research proposals involving data stored in our national HIV database:

- The SHM working group reviews general scientific research proposals.
- The hepatitis working group works together with the NVHB and assesses scientific research proposals that relate specifically to HIV/hepatitis co-infection.

SHM working group members in 2018

Name	Affiliation
Dr M.E. van der Ende (Chair)	Erasmus MC, Rotterdam
Prof. C.A.B. Boucher	Erasmus MC, Rotterdam
Dr F.C.M. van Leth	KNCV Tuberculosis Foundation, The Hague; AIGHD Amsterdam

SHM working group reviewers in 2018

Name	Affiliation
Dr N.K.T. Back	Amsterdam UMC, AMC site, Amsterdam
Prof. K. Brinkman	OLVG, Amsterdam
Dr D.M. Burger	Radboudumc, Nijmegen
Dr E.C.J. Claas	LUMC, Leiden
Prof. Emer. G.J.J. Doornum	Erasmus MC, Rotterdam
Dr S.P.M. Geelen	UMC Utrecht-WKZ, Utrecht
Prof. A.I.M. Hoepelman	UMC Utrecht, Utrecht
Dr S. Jurriaans	Amsterdam UMC, AMC site, Amsterdam
Prof. T.W. Kuijpers	Amsterdam UMC, AMC site, Amsterdam
Dr W.J.G. Melchers	Radboudumc, Nijmegen
Prof. J.M. Prins	Amsterdam UMC, AMC site, Amsterdam
Prof. P.H.M. Savelkoul	MUMC+, Maastricht
Dr R. Schuurman	UMC Utrecht, Utrecht
Dr H.G. Sprenger	UMCG, Groningen
Dr A.M.J. Wensing	UMC Utrecht, Utrecht

Hepatitis working group in 2018

Name	Affiliation
Dr J. Arends (Chair)	UMC Utrecht, Utrecht
Prof. K. Brinkman	OLVG, Amsterdam
Prof. A.I.M. Hoepelman	UMC Utrecht, Utrecht
Dr J. van der Meer	Amsterdam UMC, AMC site, Amsterdam
Dr. B. Rijnders	Erasmus MC, Rotterdam
Dr J. Schinkel	Amsterdam UMC, AMC site, Amsterdam
Dr E.F. Schippers	HagaZiekenhuis, Den Haag
Dr C. Smit	SHM, Amsterdam
Dr M. van der Valk	Amsterdam UMC, AMC site, Amsterdam
Dr T.E.M.S. de Vries-Sluys	Erasmus MC, Rotterdam

ABOUT STICHTING HIV MONITORING

Management team

Our management team (MT) consists of the director (chair), the deputy director, the communications manager, and a senior researcher representing the data analysis, reporting & research unit. The MT establishes SHM's strategic objectives by common agreement and is responsible for the day-to-day implementation of this strategy. The MT convenes once a week and is advised by the organisation's financial controller and human resources (HR) advisor.

Management team members

Name	Position
P. Reiss	Director
S. Zaheri	Deputy director
A.I. van Sighem	Senior researcher
C.J. Ester	Communications manager

Director

SHM's director is appointed by, and reports to, the governing board. He is responsible for day-to-day operations and is primarily responsible for representing the organisation externally.

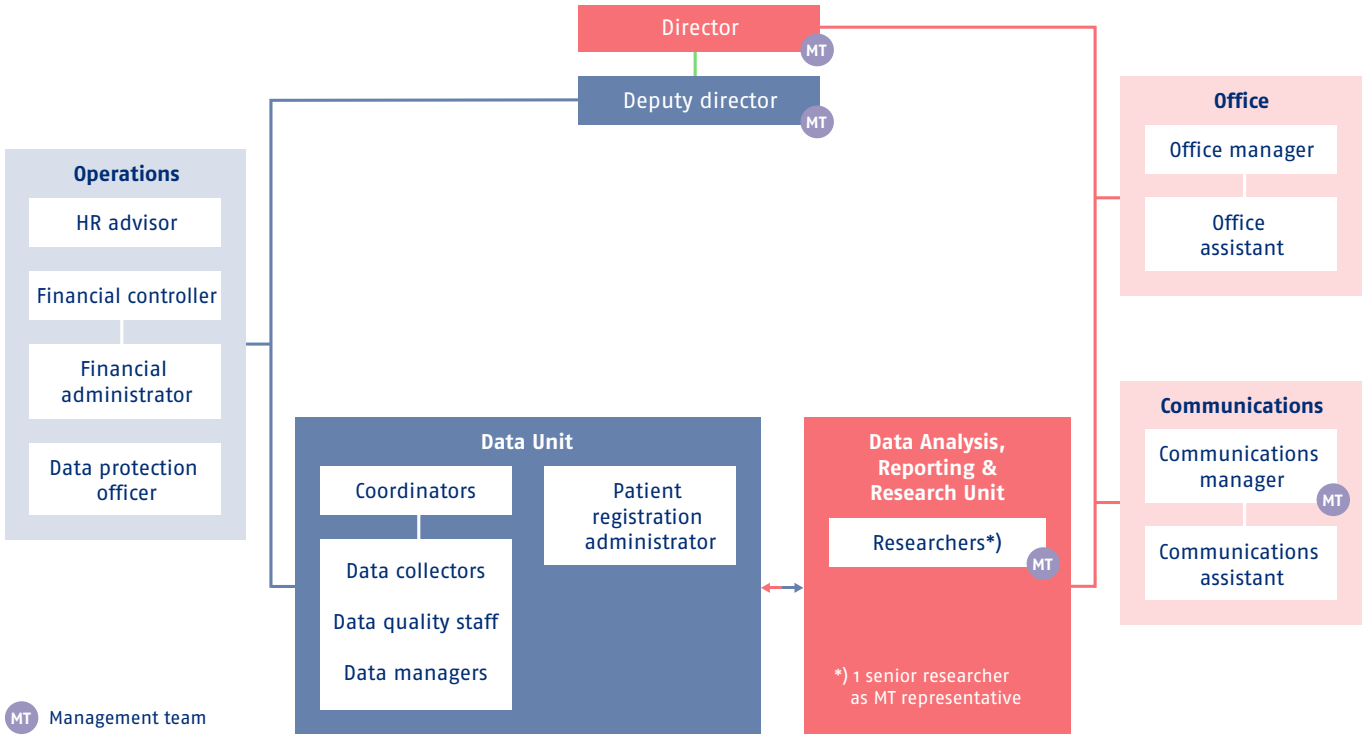
Deputy director

On behalf of the director, the deputy director oversees:

- policy implementation within the data unit, HR and finance,
- organisational and data security,
- various essential processes, such as accommodation and office automation.

ABOUT STICHTING HIV MONITORING

Stichting HIV Monitoring organisational chart.



ABOUT STICHTING HIV MONITORING

Business units and support

We have two main business units that carry out our primary activities:

- data unit,
- data analysis, reporting & research unit.

Data unit

The data unit is led by the deputy director and comprises the following three departments: patient registration & data collection; quality control, helpdesk & protocol management; and data management.

The data unit carries out the following five core activities:

- *Patient registration:* This involves the registration and de-registration of HIV-positive individuals. This administration system is used to assign a pseudonymised code to each registered individual.
- *Data collection and data entry:* This involves the collection of data from all HIV-positive individuals followed in one of the HIV treatment centres in the Netherlands.
- *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:* This core activity is carried out by data managers and involves checking, cleaning, standardising, combining and documenting data.

Data analysis, reporting & research unit

The data analysis, reporting & research unit is led by our director and is staffed by researchers in the fields 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 our annual Monitoring Report. The researchers also contribute to publications involving analyses of SHM's data in peer-reviewed national and international scientific journals.

In addition, the data analysis, reporting & 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. Our researchers contribute to these collaborations by setting up and carrying out scientific research.

ABOUT STICHTING HIV MONITORING

Support

The primary activities of our management team are supported by the communications, HR, office and finance staff. The communications department, led by the communications manager, actively disseminates information about the HIV epidemic in the Netherlands and provides information about our activities through a wide variety of communication channels. The communications manager is also responsible for the annual reporting process, in close collaboration with our director and researchers. The communications manager and office manager report to the director, while the finance and HR staff report to the deputy director.

ABOUT STICHTING HIV MONITORING

Staffing in 2018

Our average staffing level in 2018 comprised 36.76 full-time equivalents (FTEs). In addition, we covered the personnel costs for a total of 7.46 FTEs for data collectors employed by the HIV treatment centres rather than SHM.

SHM personnel in 2018*

Director
Prof. P. Reiss MD, PhD

Deputy director
S. Zaheri MSc

Data analysis, reporting & research unit

Researchers
D.O. Bezemer PhD
T.S. Boender PhD
A.I. van Sighem PhD
C. Smit PhD
F.W.N.M. Wit MD, PhD

Data unit

Data management
M.M.J. Hillebregt MSc
(department coordinator)
A.S. de Jong MSc
T.J. Woudstra

Quality control, helpdesk & protocol management
S. Grivell MSc
(protocol & helpdesk coordinator)

Data quality staff
D. Bergsma MSc
(department coordinator)
R. Meijering MSc
M.S. Raethke MSc
T. Rutkens

Data protection officer
M.M.B. Tuk-Stuster

Patient registration & data collection
L.G.M. de Groot-Berndsen
(department coordinator)
M.M.B. Tuk-Stuster
(patient registration administrator & quality management coordinator)

Data collectors
M. van den Akker
Y.M. Bakker
M. Bezemer-Goedhart
N.M. Brétin
A. El Berkaoui
E.A. Djoechro MSc
J. Geerlinks
R. Regtop
J. Koops MSc
E.I. Kruijne
C.R.E. Lodewijk
E.G.A. Lucas
R. van der Meer MA
L. Munjishvili MA
F. Paling MSc
B.M. Peeck MSc
C.M.J. Ree
Y.M.C. Ruijs-Tiggelman
L. van de Sande MA
P.P. Schnörr MSc
M.J.C. Schoorl MSc
E.M. Tuijn-de Bruin
D.P. Veenenberg-Benschop
S. van der Vliet
S.J. Wisse MSc
E.C.M. Witte

Communications

C.J. Ester PhD
(communications manager)
M.J. Sormani
(communications assistant)
Y. de Waart
(communications and HR assistant)

Human resources, finance & office

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

For the most recent overview of SHM personnel, please visit our website.

Data & quality control in 2018

BACKGROUND

Our data unit carries out five main activities:

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

In addition to the above-mentioned core activities (discussed later in this chapter), the data unit is responsible for various projects designed to further improve both data quality and process efficiency. In 2018, priority was given to the following projects:

- **IT project 'LISA':** This project involved the replacement and concomitant improvement of our data entry system and aimed to:
  - minimise manual input,
  - standardise and optimise data collection, data quality management and data processing,
  - 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 into the SHM database in a pseudonymised form.
- **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.

PROGRESS IN 2018

IT project 'LISA'

As described in previous annual reports, the project to develop a LogicNets-based data entry system as replacement for the Oracle Clinical system was officially launched on 24 May 2016. This project involved a collaboration between LogicNets, ICT automatisering, SHM and ADICT (the general IT service of the Academic Medical Center (AMC) site of Amsterdam UMC).

LISA project: progress and completion in 2018

As planned, data collection in Oracle Clinical terminated on 31 December 2017. The LISA project was subsequently completed on schedule at the beginning of 2018 and the new data entry system, known as DataCapTree, went live in February 2018.

DATA & QUALITY CONTROL IN 2018

Launch of DataCapTree.

In preparation of the launch of DataCapTree, the LogicNets system underwent a chain test at the start of 2018, during which the entire system was tested from start (i.e., data entry) to finish (i.e., data analysis) and any issues that arose during the test were subsequently resolved by the responsible teams. In addition, during January 2018, the data collectors were given training on how to use DataCapTree both centrally at the SHM head office and locally at their own places of work. DataCapTree went live on 5 February 2018 with 36 tested and accepted protocols.

During 2018, the project teams continued converting and programming data collection protocols into decision tree structures within the LogicNets system. In the course of the year, another 52 protocols went into production, following test and acceptance by all test groups. Based on feedback from the data collectors, some of these protocols were further adapted and made more user-friendly at the end of 2018. In total, more than 100 data collection protocols will be programmed within DataCapTree, with the remaining protocols planned to go into production during the course of 2019, following test and acceptance by all test groups.

An evaluation and impact assessment will be carried out once DataCapTree has been completed and in use for one year.

The implementation of DataCapTree should allow us to achieve the following improvements in both efficiency and quality:

1. Protocol management: Data collection protocols are now integrated within the system, allowing more efficient protocol management.

2. Manual data collection: DataCapTree is a decision-support system and allows information to be structured in protocols that have been programmed within the system. This should allow data collectors to carry out the data collection process more efficiently.

3. Quality control: Within DataCapTree, quality checks are now carried out during the primary data collection phase. This supports the data collectors in achieving even higher data quality. Data validation has now also become a fixed component of the data collection process for the entire patient population.

4. Data warehouse: As part of the development of DataCapTree, a new and more modern structure has been set up within the data warehouse, which will allow data to be imported from external sources in the future. This approach enables us to prepare for anticipated developments where, for example, more data may be imported directly from the clinical data warehouses in HIV treatment centres.

DATA & QUALITY CONTROL IN 2018

Lablink delivers lab results from **72%** of people followed by SHM

5. Functional management: Functional management of DataCapTree is now carried out by our department of data management. As a result, we are no longer dependent on third-party support.

LabLink

The interface implemented at an HIV treatment centre that allows laboratory data to be collected electronically wherever possible and entered directly into our data warehouse is known as LabLink. LabLink forms part of our innovation programme to automate data collection as much as possible and, as such, minimise manual data collection.

Using LabLink, HIV-related laboratory data are selected from hospital information systems and sent to SHM in a pseudonymised form. These data are then transferred to SHM's data warehouse by the AMC's IT service (ADICT). In 2012, in collaboration with the AMC's Clinical Research Unit (CRU) and ADICT, a standard LabLink protocol was developed 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.

Expansion of LabLink in 2018

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. In 2018, LabLink was expanded with a new link at Rijnstate hospital and DC Klinieken Lairesse-HIV Focus Centrum. The existing LabLinks at the Elisabeth-TweeSteden Ziekenhuis, Noordwest Ziekenhuisgroep, Leids Universitair Medisch Centrum, Maasstad Ziekenhuis and UMC Utrecht underwent adjustments and further optimisation. In addition, preparatory steps were taken to facilitate implementation of LabLink at HagaZiekenhuis, Leyweg site,

DATA & QUALITY CONTROL IN 2018

LabLink status in HIV treatment centres.

- *Hospitals that transmit laboratory data through LabLink or other automated link.*
- *Hospitals that are in the process of implementing LabLink.*
- *Hospitals that are awaiting decision on whether to implement LabLink or that have postponed LabLink due to other ongoing projects.*

Numbers on map correspond to treatment centre list on page 11.

which is expected to go live in 2019. Finally, adjustments were made to the link with SHM's data warehouse, which had undergone changes and renewal as a result of the implementation of DataCapTree.

In total, 17 HIV treatment centres and sub-centres now use LabLink and, together, deliver electronic laboratory results from 72% of the individuals followed by SHM, which is a 3% increase compared with 2017. Finally, in 2018, the AMC site of Amsterdam UMC continued to transfer results directly to SHM from its laboratory computer system using an internal LabLink connection made possible because SHM uses 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 2018, due to adjustments to the LabLink connections and associated migration of historical data, all combinations of laboratory terms and accompanying samples from previous years were once again harmonised using this tool. In total, this amounted to 6,391,929 unique records.

DATA & QUALITY CONTROL IN 2018

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, all of whom are trained and coached by SHM. Most data collectors are centrally employed by SHM, while a smaller number remain locally employed by the HIV treatment centre. Our experience has shown that centralisation of data collection, which involves the mobile deployment of specially trained staff employed by SHM (central data collectors), is more effective in terms of achieving efficient, timely, and high-quality data collection. We therefore encourage centralisation wherever possible. Although no further opportunities for centralisation arose in 2018, our central data collectors did provide assistance to local data collectors in 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. In addition, our 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 2018, three new data collectors joined SHM and were given specific training on relevant medical information relating to HIV, data collection protocols, and the data entry system. In addition, two central training days were organised for all data collectors in January 2018, in preparation for the implementation of the new data entry system, DataCapTree, on 5 February 2018. Data collectors were also given personal training locally at their own place of work. A third central training day was held on 20 March 2018 to support the implementation of additional protocols within DataCapTree. Finally, a review day was held on 11 October 2018 to refresh knowledge on specific diseases that form part of the data collection process.

Since further development of DataCapTree is to be managed internally within SHM, in 2018 a number of staff members followed a training on the Agile Scrum framework to facilitate effective and flexible software development by the SHM team.

DATA & QUALITY CONTROL IN 2018

STRUCTURAL 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 provides a clear separation between privacy-sensitive data stored in the registration database and the pseudonymised data stored in the national database.

In 2018, 1,795 individuals were registered and 994 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 individuals followed in the HIV treatment centres in the Netherlands is carried out by data collectors. They collect data straight from either paper or electronic medical records and, based on data collection protocols, standardise, code, and enter the data into SHM's data entry system.

Data collection progress

Table 1 presents the percentage of individuals in treatment centres with a possible backlog in data collection of more than 365 days. The difference between the date of the last visit registered in the database and the date of reporting (5 January 2019) represents the potential data collection backlog in number of days. Data are corrected for individuals who have been lost to follow up or who have died.

The average backlog in data collection in 2018 remained 0%, with just 7 HIV treatment centres with a backlog of 1% or more. This is a good result given that, in 2018, data collectors focused strongly on improving the quality of existing data and were closely involved in testing protocols for DataCapTree. 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. The backlog in the centres with ≥1% backlog in 2018 is expected to improve further now that DataCapTree is in use.

< Back to page 20

DATA & QUALITY CONTROL IN 2018

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

HIV treatment centre	Location	2018
Adult		
Noordwest Ziekenhuisgroep	Alkmaar	1%
Flevoziekenhuis	Almere	1%
Amsterdam UMC, AMC site	Amsterdam	0%
Amsterdam UMC, VUmc site	Amsterdam	0%
DC Klinieken Lairesse – Hiv Focus Centrum	Amsterdam	0%
MC Jan van Goyen	Amsterdam	0%
OLVG	Amsterdam	0%
MC Slotervaart	Amsterdam	0%
Rijnstate	Arnhem	0%
HagaZiekenhuis, Leyweg site	Den Haag	0%
HMC	Den Haag	1%
Catharina Ziekenhuis	Eindhoven	0%
Medisch Spectrum Twente	Enschede	0%
Admiraal De Ruyter Ziekenhuis	Goes	1%
Universitair Medisch Centrum Groningen (UMCG)	Groningen	0%
Spaarne Gasthuis	Haarlem	0%
Medisch Centrum Leeuwarden	Leeuwarden	0%
Leids Universitair Medisch Centrum	Leiden	0%
MC Zuiderzee	Lelystad	0%
Maastricht UMC+	Maastricht	0%
Radboudumc	Nijmegen	1%
Erasmus MC	Rotterdam	0%
Maasstad Ziekenhuis	Rotterdam	0%
ETZ	Tilburg	0%
Universitair Medisch Centrum Utrecht (UMC Utrecht)	Utrecht	1%
Isala	Zwolle	0%

HIV treatment centre	Location	2018
Paediatric		
Emma Kinderziekenhuis, Amsterdam UMC	Amsterdam	0%
Beatrix Kinderziekenhuis, UMCG	Groningen	0%
Erasmus MC-Sophia Kinderziekenhuis	Rotterdam	4%
Wilhelmina Kinderziekenhuis, UMC Utrecht	Utrecht	0%
Average		**0%**

< Back to page 25

DATA & QUALITY CONTROL IN 2018

Quality control

In the 17 years since our foundation, we have developed extensive and valuable expertise for monitoring and maintaining data quality. In particular, as the number of people being followed over a prolonged period of time has grown, data quality requirements have become more demanding and complex. For example, data obtained electronically (i.e., through LabLink) require a different quality control approach to those collected manually, which are checked and improved by means of both manual and automated checks.

Manual quality control

Manual quality checks were carried out as usual in 2018 by our data quality staff, albeit to a lesser extent than in previous years due to additional duties such as testing protocols for DataCapTree and providing support to data collectors following implementation of this new data entry system. As a result, quality checks in 2018 focussed on the data of deceased patients. For 236 individuals, the cause of death was classified and validated based on the CoDe (Coding Causes of Death in HIV) classification. In addition, checks were carried out on 45 endpoint-defined comorbidities. The data on these comorbidities were also entered into research forms as part of an international collaboration, the RESPOND study.

Finally, in 2018, structural assistance was provided to the data collector in Curaçao. Remote training was provided throughout the year and tailored training was provided during a 5-day visit by one of our data quality staff to the data collection site in Curaçao.

LabLink quality control

Both automated and manual checks, developed in 2013, were carried out on the LabLink data in 2018. One-off checks for acceptance of new LabLink connections with a laboratory were carried out on data in an acceptance test 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 message 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 a comparison with laboratory results in the electronic medical records (carried out by the data collectors).

DATA & QUALITY CONTROL IN 2018

536
queries resolved by the helpdesk in 2018

Helpdesk and protocol management

This activity, carried out by a number of our 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 2018, the helpdesk received 713 queries from data collectors, 536 of which could be resolved in 2018 by the responsible data quality staff member. The number of submitted queries rose by 568 compared with 2017. This increase reflected a greater need for assistance among data collectors due to the implementation of DataCapTree and the associated changes to the data collection and data entry process. In some cases, the queries resulted in protocol changes. These helpdesk-driven protocol changes were included in the overall revision of medically-based protocols in DataCapTree.

In 2018, our helpdesk staff also developed training material to train the data collectors in how to enter data into DataCapTree.

Data management and reporting

Data warehousing and data processing

The data warehouse is a relational database (located on an SQL server at the AMC site of Amsterdam UMC) and extracts data from all SHM source systems. The data warehouse is structured on the basis of the protocols integrated within DataCapTree. To facilitate storage in the data warehouse, each answer option used in the protocols has been assigned a unique identification number. DataCapTree now includes a total of 3,162 protocol-specific options. These answer options are formulated clearly and in a user-friendly way to minimise data entry errors. Finally, the Anatomical Therapeutic Chemical (ATC) classification has also been included in the data warehouse so that drugs can immediately be coupled to the correct ACT code.

The protocols in the DataCapTree database make it possible for records in the data warehouse tables to be created, changed or updated in real time. As soon as a data collector submits a protocol, the manually collected data are entered into the data warehouse. Data received via LabLink are updated on a daily basis within the data warehouse. To facilitate further development of the data warehouse and the data entry system, separate environments have been created, including the acceptance test environment and the production environment.

DATA & QUALITY CONTROL IN 2018

In 2018 an account management tool was developed to allow functional management and, in particular, to manage the assignment of roles and permissions to users of the three SHM applications, namely the registration database, DataCapTree, and Report Builder. The account management tool allows an account to be created for a user of these applications. Subsequently one or more roles, as well as the HIV treatment centre for which access is required, can be coupled to the account. This ensures that a user can only view those data for which they have been assigned permission. The applications are all stored on the network of the AMC site of Amsterdam UMC. To log onto one of these SHM applications from an HIV treatment centre outside the AMC, a two-step verification process has been created. This entails logging in with a user name and password, combined with an additional access code sent by SMS to a mobile phone number that is trusted and known to SHM. These mobile phone numbers are registered in the account management tool and managed by SHM.

No further data from those people who object to collection of their data following inclusion can be collected in DataCapTree. Any existing data are immediately removed from reports and data sets intended for analysis. This is achieved through the use of a filter within the data warehouse to ensure people who have objected to data collection are excluded.

All the information in the data warehouse, except LabLink data, is real-time. A data freeze is carried out twice a year, after which the raw data tables from the data warehouse are processed to yield tables suitable for data analysis. This involves cleaning, clustering, and coding the information according to the standard protocols of various national and international collaborations and the ATC classification. In 2018, these data processing steps resulted in data sets for use by our researchers, for centre-specific reports, and for two international collaborations, EuroSIDA and RESPOND.

Patient-specific reports, graphs and queries

Each centre has access to Microsoft Report Builder, in which treatment teams can view and download reports, graphs and queries relating to raw data from their own patients. Following revision of the data warehouse structure, these reports are now being restructured and are expected to be available to the HIV treatment centres in 2019.

Privacy

AT STICHTING HIV MONITORING

On 25 May 2018, the Dutch Personal Data Protection Act (*Wet bescherming persoonsgegevens*) was replaced with a new Europe-wide framework for data privacy, the General Data Protection Regulation (GDPR). The GDPR is designed to harmonise laws on personal data processing by both private companies and governments in the European Union (EU). The aim is not only to protect personal data within the EU, but also to facilitate free movement of data within Europe. The GDPR requires each member state to provide at least one independent authority responsible for monitoring adherence to the regulation. In the Netherlands, this task has been assigned to the Dutch Data Protection Authority.

In the Netherlands it has been mandatory to report data breaches since 1 January 2016. Organisations that process personal data must report data breaches to the Data Protection Authority. In some cases, those involved (i.e., the people whose data may have been compromised) must be informed. This mandatory notification remains largely unchanged under the GDPR. One important difference, however, is that as of 25 May 2018, organisations are required to document all data breaches, even those that do not have to be reported to the Data Protection Authority or the people involved.

SHM's policy for dealing with privacy-sensitive information has previously been revised to meet the ISO 27001 standards. This included technical and organisational measures to prevent data breaches and, in 2016, the creation of a central point of notification for incidents relating to quality and/or information security. All members of staff have access to an incident notification form. Incident notifications that involve a possible data breach are assessed as soon as possible, but no later than two working days after receipt, to establish whether they involve a data breach that should be reported to the Data Protection Authority. In addition, appropriate action is taken to prevent the reported situation recurring in the future. In this way, we strives to minimise risks.

In preparation for the EU GDPR that came into effect on 25 May 2018 and more stringent privacy regulations, we took a number of additional measures in 2018 to ensure that we meet all the requirements and to further raise awareness among our staff. As such, we have appointed a data protection officer and updated our privacy policy. Our revised privacy policy ensures that the GDPR requirements are largely incorporated in our work processes and protocols, including a privacy document entitled 'How to deal with privacy-sensitive information', our staff handbook, a risk management system, data processing contracts with external partners, and a protocol for reporting data privacy incidents and data breaches.

PRIVACY AT STICHTING HIV MONITORING

In the run-up to the launch of the GDPR, our staff attended regular presentations on the topic of privacy and information was distributed in internal newsletters and on our intranet site. More recently, SHM staff have been required to follow an obligatory e-learning module developed by the AMC site of the Amsterdam UMC to raise awareness about privacy and information security.

Privacy will remain a priority in 2019 and during coming years. We will continue to review and revise processes where necessary to guarantee that our data are optimally protected.

Registration

OF HIV-POSITIVE INDIVIDUALS IN 2018

GENERAL

Up to and including 31 December 2018, a cumulative total of 27,559 people living with HIV were registered by Stichting HIV Monitoring (SHM) (*Table 2*), of whom 969 were newly-registered in 2018 (*Table 3*). In total, 255 individuals were registered at an HIV treatment centre specialised in HIV care for children and adolescents.

Further clinical data were collected for 26,910 (97.6%) of the registered individuals. The remaining 649 (2.4%) persons objected to the collection of their data. Of the 969 people who were newly registered in 2018, 60 (6.2%) were registered as objecting to data collection.

In 2018, data were collected from 20,393 (76%) individuals. Of the 6,517 (24%) individuals with no data collected in 2018, 2,998 had died before 2018, 1,710 had moved abroad and 1,809 had disappeared from care for an unknown reason. Of the individuals who had ever been registered as objecting to data collection, 79 were known to have died prior to 2018 and 4 had moved abroad.

Box 1: Definitions of infection, diagnosis, entry into care, and registration.

Infection	The moment an individual acquires an HIV infection. The time of infection is often unknown.
Diagnosis	The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or years after infection.
Entry into care	The moment an HIV-positive individual is first seen for care in an HIV treatment centre, which usually is within a few weeks of HIV diagnosis.
Registration	The moment an HIV-positive individual in care is notified to SHM by their treating HIV physician or nurse and registered in the SHM database. Registration is usually within a few months of entering care, but can take longer. Collection of demographic and clinical data from the time of HIV diagnosis can only be done after an HIV-positive individual is registered with SHM.

REGISTRATION OF HIV-POSITIVE INDIVIDUALS IN 2018

ADULTS

Of the 26,910 individuals registered up to and including 2018 and for whom further clinical data were collected, 26,441 were adults at the time of registration: 21,506 (81%) men and 4,935 (19%) women.

In 2018, there were 901 adults who were newly-registered and for whom clinical data were collected. These comprised 771 (86%) men and 130 (14%) women.

CHILDREN

Of the 26,910 persons registered up to and including 2018, 469 (2%) were children or adolescents at the time of registration. This group consisted of 221 (47%) boys and 248 (53%) girls. In 2018, 8 children and adolescents (6 children aged between 0 and 12 years and 2 adolescents aged 13-17 years) were newly registered, comprising 5 boys and 3 girls.

8
children & adolescents with HIV newly registered in 2018

PREGNANT WOMEN

Up to and including 31 December 2018, 3,383 pregnancies had been registered in a total of 1,853 women living with HIV. In 58% of these women, the HIV diagnosis was known prior to conception of their first pregnancy since registration; in 42% of the pregnancies, the HIV diagnosis was established during the first pregnancy since registration.

During 2016 and 2017, 228 pregnancies were registered, 91 of which were first pregnancies since registration in SHM's database. In 30% of these first pregnancies since registration, HIV was diagnosed during the pregnancy. Due to the transition to SHM's new data entry system in 2018, no data on pregnancies were collected in that year. The data on pregnancies will be updated in 2019.

REGISTRATION OF HIV-POSITIVE INDIVIDUALS IN 2018

Table 2: Total number of HIV-positive individuals registered by SHM as of 31 December 2018, according to most recent HIV treatment centres.

		Total		Alive		Deceased		Objection[a]		Data in 2018[b]		No data in 2018			
												Deceased before 2018[c]		Other reasons[d]	
HIV treatment centre	**Location**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adult															
Noordwest Ziekenhuisgroep	Alkmaar	406	1.5	364	89.7	42	10.3	7	1.7	317	78.1	38	9.4	44	10.8
Flevoziekenhuis	Almere	251	0.9	237	94.4	14	5.6	5	2.0	211	84.1	14	5.6	21	8.4
Amsterdam UMC, AMC site	Amsterdam	2,888	10.6	2,449	84.8	439	15.2	11	0.4	2,003	69.4	426	14.8	448	15.5
Amsterdam UMC, VUmc site	Amsterdam	730	2.7	629	86.2	101	13.8	18	2.5	494	67.7	96	13.2	122	16.7
DC Klinieken Lairesse - Hiv Focus Centrum	Amsterdam	968	3.5	956	98.8	12	1.2	4	0.4	931	96.2	9	0.9	24	2.5
Medisch Centrum Jan van Goyen	Amsterdam	348	1.3	304	87.4	44	12.6	3	0.9	235	67.5	42	12.1	68	19.5
OLVG	Amsterdam	4,169	15.3	3,643	87.4	526	12.6	168	4.0	3,049	73.1	492	11.8	460	11.0
MC Slotervaart	Amsterdam	798	2.9	619	77.6	179	22.4	12	1.5	508	63.7	167	20.9	111	13.9
Rijnstate	Arnhem	943	3.5	844	89.5	99	10.5	5	0.5	756	80.2	92	9.8	90	9.5
HMC	Den Haag	1,162	4.3	1,059	91.1	103	8.9	43	3.7	857	73.8	91	7.8	171	14.7
HagaZiekenhuis, Leyweg site	Den Haag	815	3.0	700	85.9	115	14.1	35	4.3	536	65.8	100	12.3	144	17.7
Catharina Ziekenhuis	Eindhoven	781	2.9	731	93.6	50	6.4	7	0.9	620	79.4	49	6.3	105	13.4
Medisch Spectrum Twente	Enschede	663	2.4	544	82.1	119	17.9	6	0.9	415	62.6	116	17.5	126	19.0
Admiraal De Ruyter Ziekenhuis	Goes	235	0.9	219	93.2	16	6.8	5	2.1	175	74.5	15	6.4	40	17.0
Universitair Medisch Centrum Groningen	Groningen	1,052	3.9	924	87.8	128	12.2	62	5.9	753	71.6	104	9.9	133	12.6
Spaarne Gasthuis	Haarlem	542	2.0	478	88.2	64	11.8	5	0.9	409	75.5	60	11.1	68	12.5
Medisch Centrum Leeuwarden	Leeuwarden	341	1.2	305	89.4	36	10.6	3	0.9	270	79.2	35	10.3	33	9.7
Leids Universitair Medisch Centrum	Leiden	775	2.8	694	89.5	81	10.5	45	5.8	558	72.0	77	9.9	95	12.3
MC Zuiderzee	Lelystad	103	0.4	102	99.0	1	1.0	1	1.0	86	83.5	1	1.0	15	14.6
Maastricht UMC+	Maastricht	1,042	3.8	878	84.3	164	15.7	5	0.5	719	69.0	159	15.3	159	15.3
Radboudumc	Nijmegen	852	3.1	741	87.0	111	13.0	35	4.1	662	77.7	92	10.8	63	7.4

[a] *Objection: consent not given for collection of clinical data.*
[b] *Data in 2018: registered by SHM in 2018, or deceased during 2018, or last contact with an HIV treatment centre during 2018.*
[c] *No data in 2018 – deceased before 2018: individuals who are not included in 'data in 2018' and who had died before 2018.*
[d] *No data in 2018 – other reasons: individuals who are not included in 'data in 2018' because they moved abroad before 2018 or because they had no contact with their HIV treatment centre in 2018 for an unknown reason.*

< Back to page 32

[Continued on page 36]

REGISTRATION OF HIV-POSITIVE INDIVIDUALS IN 2018

Table 2: Continued.

HIV treatment centre	Location	Total n	Total %	Alive n	Alive %	Deceased n	Deceased %	Objection[a] n	Objection[a] %	Data in 2018[b] n	Data in 2018[b] %	No data in 2018: Deceased before 2018[c] n	No data in 2018: Deceased before 2018[c] %	No data in 2018: Other reasons[d] n	No data in 2018: Other reasons[d] %
Adult (continued)															
Erasmus MC	Rotterdam	2,802	10.3	2,452	87.5	350	12.5	19	0.7	2,015	71.9	337	12.0	431	15.4
Maasstad Ziekenhuis	Rotterdam	899	3.3	837	93.1	62	6.9	12	1.3	747	83.1	57	6.3	83	9.2
ETZ	Tilburg	1,296	4.7	1,203	92.8	93	7.2	23	1.8	1,023	78.9	85	6.6	165	12.7
UMC Utrecht	Utrecht	1,851	6.8	1,646	88.9	205	11.1	69	3.7	1,390	75.1	201	10.9	191	10.3
Isala	Zwolle	592	2.2	545	92.1	47	7.9	39	6.6	442	74.7	40	6.8	71	12.0
Total		**27,304**	**100.0**	**24,103**	**88.3**	**3,201**	**11.7**	**647**	**2.4**	**20,181**	**73.9**	**2,995**	**11.0**	**3,481**	**12.8**
Pediatric															
Emma Kinderziekenhuis, Amsterdam UMC	Amsterdam	70	27.5	70	100.0	0	0.0	0	0.0	61	87.1	0	0.0	9	12.9
Beatrix Kinderziekenhuis, UMCG	Groningen	29	11.4	29	100.0	0	0.0	0	0.0	26	89.7	0	0.0	3	10.3
Erasmus MC-Sophia Kinderziekenhuis	Rotterdam	84	32.9	82	97.6	2	2.4	0	0.0	71	84.5	2	2.4	11	13.1
Wilhelmina Kinderziekenhuis, UMC Utrecht	Utrecht	72	28.2	71	98.6	1	1.4	2	2.8	54	75.0	1	1.4	15	20.8
Total		**255**	**100.0**	**252**	**98.8**	**3**	**1.2**	**2**	**0.8**	**212**	**83.1**	**3**	**1.2**	**38**	**14.9**
Curaçao															
SEHOS	Willemstad	1,129	98.7	958	84.9	171	15.1	0	0.0	670	59.3	167	14.8	292	25.9
SEHOS kinderkliniek	Willemstad	15	1.3	5	33.3	10	66.7	0	0.0	0	0.0	10	66.7	5	33.3
Total Curaçao		**1,144**	**100.0**	**963**	**84.2**	**181**	**15.8**	**0**	**0.0**	**670**	**58.6**	**177**	**15.5**	**297**	**26.0**

Download Table 2

[a] *Objection: consent not given for collection of clinical data.*
[b] *Data in 2018: registered by SHM in 2018, or deceased during 2018, or last contact with an HIV treatment centre during 2018.*
[c] *No data in 2018 – deceased before 2018: individuals who are not included in 'data in 2018' and who had died before 2018.*
[d] *No data in 2018 – other reasons: individuals who are not included in 'data in 2018' because they moved abroad before 2018 or because they had no contact with their HIV treatment centre in 2018 for an unknown reason.*

REGISTRATION OF HIV-POSITIVE INDIVIDUALS IN 2018

Table 3: Total number of people who were first registered by SHM in 2018, according to most recent HIV treatment centre.

HIV treatment centre	Location	Total n	Total %	Alive n	Alive %	Deceased n	Deceased %	Objection[a] n	Objection[a] %
Adults									
Noordwest Ziekenhuisgroep	Alkmaar	18	1.9	18	100.0	0	0.0	0	0.0
Flevoziekenhuis	Almere	10	1.0	10	100.0	0	0.0	0	0.0
Amsterdam UMC, AMC site	Amsterdam	67	7.0	66	98.5	1	1.5	0	0.0
Amsterdam UMC, VUmc site	Amsterdam	30	3.1	30	100.0	0	0.0	1	3.3
DC Klinieken Lairesse-Hiv Focus Centrum	Amsterdam	39	4.0	39	100.0	0	0.0	0	0.0
Medisch Centrum Jan van Goyen	Amsterdam	9	0.9	9	100.0	0	0.0	0	0.0
OLVG	Amsterdam	136	14.1	132	97.1	4	2.9	5	3.7
MC Slotervaart	Amsterdam	8	0.8	8	100.0	0	0.0	0	0.0
Rijnstate	Arnhem	49	5.1	49	100.0	0	0.0	1	2.0
HMC	Den Haag	17	1.8	17	100.0	0	0.0	1	5.9
HagaZiekenhuis, Leyweg site	Den Haag	31	3.2	31	100.0	0	0.0	3	9.7
Catharina Ziekenhuis	Eindhoven	34	3.5	34	100.0	0	0.0	0	0.0
Medisch Spectrum Twente	Enschede	29	3.0	29	100.0	0	0.0	1	3.4
Admiraal De Ruyter Ziekenhuis	Goes	10	1.0	10	100.0	0	0.0	2	20.0
Universitair Medisch Centrum Groningen (UMCG)	Groningen	34	3.5	33	97.1	1	2.9	15	44.1
Spaarne Gasthuis	Haarlem	16	1.7	16	100.0	0	0.0	0	0.0
Medisch Centrum Leeuwarden	Leeuwarden	12	1.2	12	100.0	0	0.0	3	25.0
Leids Universitair Medisch Centrum	Leiden	29	3.0	29	100.0	0	0.0	5	17.2
MC Zuiderzee	Lelystad	5	0.5	5	100.0	0	0.0	0	0.0
Maastricht UMC+	Maastricht	47	4.9	46	97.9	1	2.1	0	0.0
Radboudumc	Nijmegen	37	3.8	37	100.0	0	0.0	3	8.1
Erasmus MC	Rotterdam	71	7.4	71	100.0	0	0.0	4	5.6
Maasstad Ziekenhuis	Rotterdam	63	6.5	62	98.4	1	1.6	0	0.0
ETZ	Tilburg	68	7.1	68	100.0	0	0.0	1	1.5
UMC Utrecht	Utrecht	54	5.6	54	100.0	0	0.0	2	3.7
Isala	Zwolle	40	4.2	40	100.0	0	0.0	13	32.5
Total		***963**	**100.0**	**955**	**99.2**	**8**	**0.8**	**60**	**6.2**

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

* *Includes 2 of the 8 children/adolescents newly-registered in 2018.*

< Back to page 32

[Continued on page 37]

REGISTRATION OF HIV-POSITIVE INDIVIDUALS IN 2018

Table 3: Continued.

HIV treatment centre	Location	Total n	Total %	Alive n	Alive %	Deceased n	Deceased %	Objection[a] n	Objection[a] %
Paediatric									
Emma Kinderziekenhuis, Amsterdam UMC	Amsterdam	4	66.7	4	100.0	0	0.0	0	0.0
Beatrix Kinderziekenhuis, UMCG	Groningen	2	33.3	2	100.0	0	0.0	0	0.0
Total		**6**	**100.0**	**6**	**100.0**	**0**	**0.0**	**0**	**0.0**
Curaçao									
SEHOS	Willemstad	57	100.0	56	98.2	1	1.8	0	0.0

Download Table 3

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

* *Includes 2 of the 8 children/adolescents newly-registered in 2018.*

REGISTRATION OF HIV-POSITIVE INDIVIDUALS IN 2018

Of the HIV-positive people monitored by SHM:

6% had a chronic HCV co-infection

2% had an acute HCV co-infection

6% had a chronic HBV co-infection

HIV SEQUENCE DATA

Up until 31 December 2018, 15,334 reverse transcriptase and/or protease sequences and 228 integrase gene sequences had been included in the SHM database. To date, three laboratories have submitted sequences for 2018. These sequences are used to examine resistance to treatment regimens and to investigate possible HIV transmission networks.

HEPATITIS B AND HEPATITIS C CO-INFECTION

Up to and including 31 December 2018, 1,433 (6%) of the monitored HIV-positive individuals were found to have a chronic hepatitis C virus (HCV) co-infection, while 598 (2%) were found to have a primary HCV co-infection. Of these 598 individuals, 30 were first diagnosed with HCV in 2018, none of whom were newly registered with SHM in 2018.

In 2018, chronic hepatitis B virus (HBV) co-infection was detected in 1,665 (6%) of the monitored HIV-positive individuals. HBV was first diagnosed in 2018 in 25 of these individuals, 17 of whom were newly registered with SHM in 2018.

In 2018, SHM registered 6 cases of liver fibrosis and 5 liver cirrhosis events. Due to the transition to SHM's new data entry system in 2018, no data were collected on hepatocellular carcinoma in that year; these data will be updated in 2019.

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 viral phylogenetic research into evolution of the epidemic and HIV transmission networks. 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, continued in 2018. In total, 1,144 HIV-positive individuals were registered, of whom 57 were newly registered in 2018.

HIV in the Netherlands

KEY FINDINGS FROM OUR 2018 HIV MONITORING REPORT

This chapter provides a summary of the key findings from the latest HIV Monitoring Report that was published on 22 November 2018. The full report is available on our website.

Download 2018 HIV Monitoring Report

THE HIV EPIDEMIC IN THE NETHERLANDS IN 2017

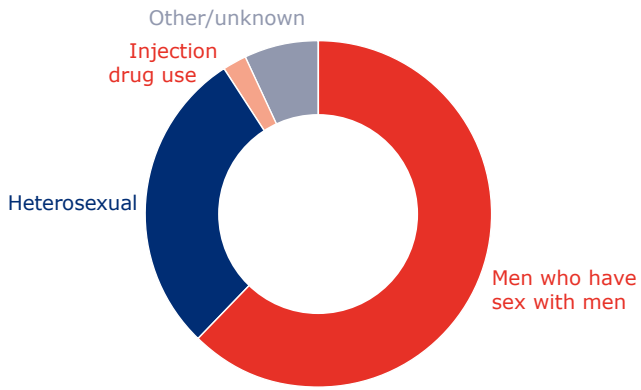
Trend of fewer new HIV diagnoses continues in 2017

Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to below 900 new diagnoses in recent years. This decreasing trend continued in 2017. The projected number of new diagnoses for 2017 is 749, although this may change as registration of HIV diagnoses for 2017 has not yet been finalised.

Majority of new diagnoses continue to be in men who have sex with men

In 2017, the majority (69%) of newly-diagnosed infections were in men who have sex with men (MSM), while 23% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission.

***Figure 1:** Most likely route of HIV transmission in people in HIV care in the Netherlands in 2017.*



< Back to Foreword

HIV IN THE NETHERLANDS KEY FINDINGS

People newly-diagnosed with HIV rapidly receive specialised care

Over 95% of people newly-diagnosed with HIV entered specialised HIV care within 6 weeks after diagnosis. This rate was more or less the same regardless of where the diagnosis was made (i.e., hospital, general practice, sexually transmitted infections clinic, or other test location).

HIV testing is becoming more common

The rates of testing for HIV appear to be increasing in the Netherlands. This conclusion is based on the following observations. Firstly, our data show that the proportion of individuals with a previously negative HIV test has increased (73% of MSM, 33% of other men and 49% of women diagnosed in 2017 had a reported previous negative test). In addition, the proportion of individuals who are diagnosed with HIV relatively early in their infection (including during primary HIV infection) continues to increase, particularly among MSM. This is reflected in the CD4 count at diagnosis gradually having risen over time to a median of 380 cells/mm^3 in 2017.

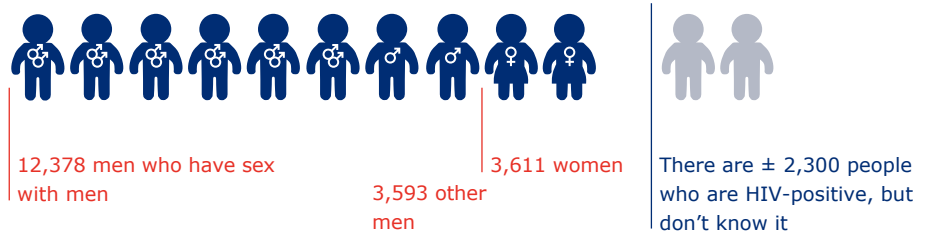
Late presentation for care remains a problem that needs attention

Despite the observed earlier diagnosis among certain groups, too many people still present late for care, i.e., with an already markedly impaired immune system (CD4 count below 350 cells/mm^3) or even AIDS; in 2017, this was the case for 37% of MSM, 63% of other men and 52% of women.

How many people were in HIV care in 2017?

As of 31 December 2017, a total of 19,582 people living with HIV in the Netherlands (19,390 adults and 192 children and adolescents) were known to be in care in one of the 26 adult or 4 paediatric HIV treatment centres.

Figure 2: *Number of people living with HIV and in care in the Netherlands in 2017.*



HIV IN THE NETHERLANDS KEY FINDINGS

CONTINUUM OF HIV CARE IN 2017: 90-93-95

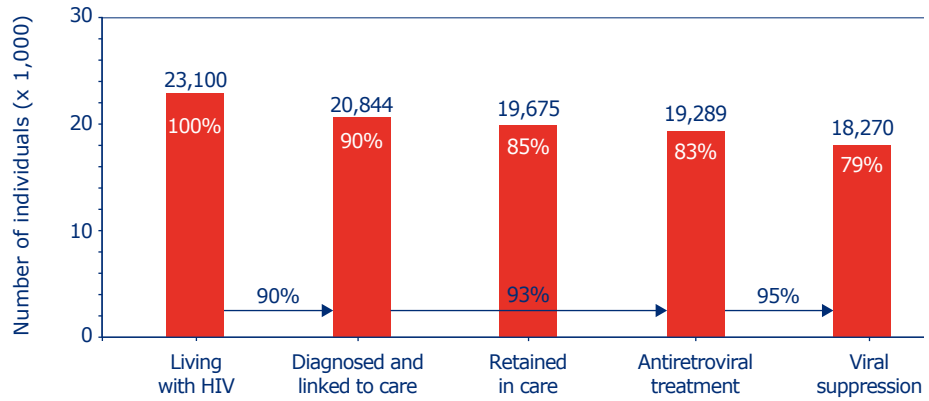
One of the goals of HIV treatment is to achieve viral suppression. The key steps that need to be achieved to reach viral suppression are illustrated in a continuum of HIV care. A continuum of care also gives a measure of progress towards achieving the UNAIDS 90-90-90 goals for HIV care by 2020.

The continuum of care for the Netherlands shows we have now reached these goals (90-93-95 in 2017, see *Figure 3*):

- By the end of 2017, 23,100 individuals were estimated to be living with HIV, of whom an estimated 2,300 were still undiagnosed.
- In total, 20,844 individuals (**90%** of the total number estimated to be living with HIV) had been diagnosed, linked to care, and registered by SHM.
- Of the individuals who had been diagnosed, linked to care, and registered by SHM, the majority (19,289; **93%**), had started antiretroviral treatment, and 18,270 of those (**95%**) had achieved viral suppression.

This means that overall, 79% of the total estimated population living with HIV and 88% of those diagnosed and linked to care had a suppressed viral load by the end of 2017.

Figure 3: Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2017, based on UNAIDS 90-90-90 goals for 2020: 90-93-95.



HIV IN THE NETHERLANDS KEY FINDINGS

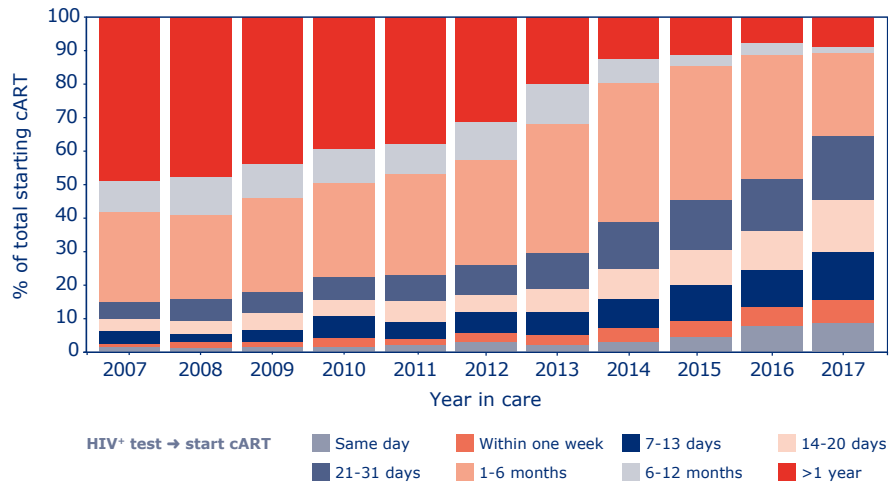
The figures for the Netherlands are impressive compared with other parts of the world. Nonetheless, in 2017 there were around 750 new diagnoses and an estimated 2,300 people who remained undiagnosed. To achieve a significant decline in these numbers, novel transdisciplinary strategies are needed to simultaneously reduce the likelihood of HIV transmission in key populations at risk, identify individuals with HIV infection early, rapidly link all people living with HIV to care, and immediately offer them the possibility of starting combination antiretroviral therapy.

COMBINATION ANTIRETROVIRAL THERAPY IN ADULTS

In 2017, most people started HIV treatment within a month of diagnosis

People are increasingly starting cART sooner after being diagnosed with HIV. Of those starting cART in 2017 more than half did so within one month, and 90 percent within 6 months after diagnosis. Importantly, this was the case irrespective of the CD4 cell count at diagnosis.

Figure 4: *Time between HIV diagnosis and starting combination antiretroviral therapy (cART) for those starting cART between 2007–2017.*



Legend: *cART=combination antiretroviral therapy.*

HIV IN THE NETHERLANDS KEY FINDINGS

People are increasingly starting treatment with a less impaired immune system

People are increasingly starting cART at higher CD4 counts. The proportion of people who had a CD4 count of 500 cells/mm^3 or above at diagnosis and who had begun cART within 6 months of diagnosis rose from 87% in 2015 to 91% in 2017.

Most common cART regimens in 2017

Initial regimen

More than 80% of people started on an integrase inhibitor-containing regimen in 2017, with abacavir/lamivudine/dolutegravir and tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir being the most frequently prescribed initial regimens in 2017.

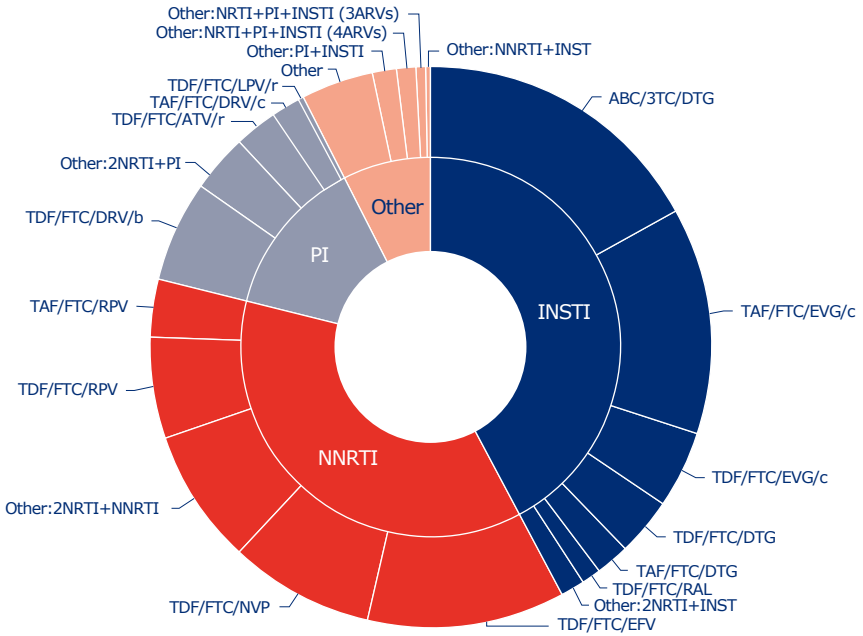
The likelihood of discontinuing or switching the initial regimens has been decreasing since 1996. As in previous years, toxicity continued to be a main reason for discontinuing or switching the initial regimen during the first year of treatment. Toxicity-related discontinuations were often due to neuropsychiatric, gastrointestinal, or renal problems, or medication-related skin rash. Other, more recent, important reasons for discontinuation or regimen switch during the first year of treatment include regimen simplification or the availability of new drugs.

Integrase inhibitor–based cART used increasingly frequently

Since its introduction a few years ago, integrase inhibitor-based cART has been implemented on a large scale in the Netherlands: in 2017, 42% of all adults in care and on cART received an integrase inhibitor, compared to 27% in 2015. Half of the population on cART in 2017 received a backbone consisting of tenofovir disoproxil fumarate/emtricitabine, although the availability of new fixed-dose combinations has led to an increase in the use of abacavir/lamivudine and tenofovir alafenamide/emtricitabine. Among all HIV-positive individuals in care and on treatment in 2017, the majority received a cART regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (42%), a non-NRTI (NNRTI, 36%), or a protease inhibitor (14%) (*Figure 5*). The most commonly-prescribed regimens in 2017 were abacavir/lamivudine/dolutegravir (17%), tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir (13%), and tenofovir disoproxil /emtricitabine combined with efavirenz (11%) or nevirapine (8%).

HIV IN THE NETHERLANDS KEY FINDINGS

Figure 5: Combination antiretroviral therapy (cART) use in 2017 by all HIV-positive individuals in care.



Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NVP=nevirapine; PI=protease inhibitor; RAL=raltegravir; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

Excellent virological response, including in long-term survivors

Both short-term and long-term viral suppression rates remain high and continue to improve. Of all adults in care and on cART in 2017, 97% had an undetectable viral load (<200 copies/ml). Individuals who had been diagnosed with HIV before 1996 and who remained in care and on cART in 2017 (i.e., long-term survivors) had equally high levels of viral suppression.

Changing cART landscape

Following revised HIV treatment guidelines, prompt cART initiation has continued to become more common in 2017. In recent years, the introduction of new integrase inhibitor-based once-daily fixed-dose combinations has changed the landscape of cART use in the Netherlands. All currently-recommended regimens are durable.

HIV IN THE NETHERLANDS KEY FINDINGS

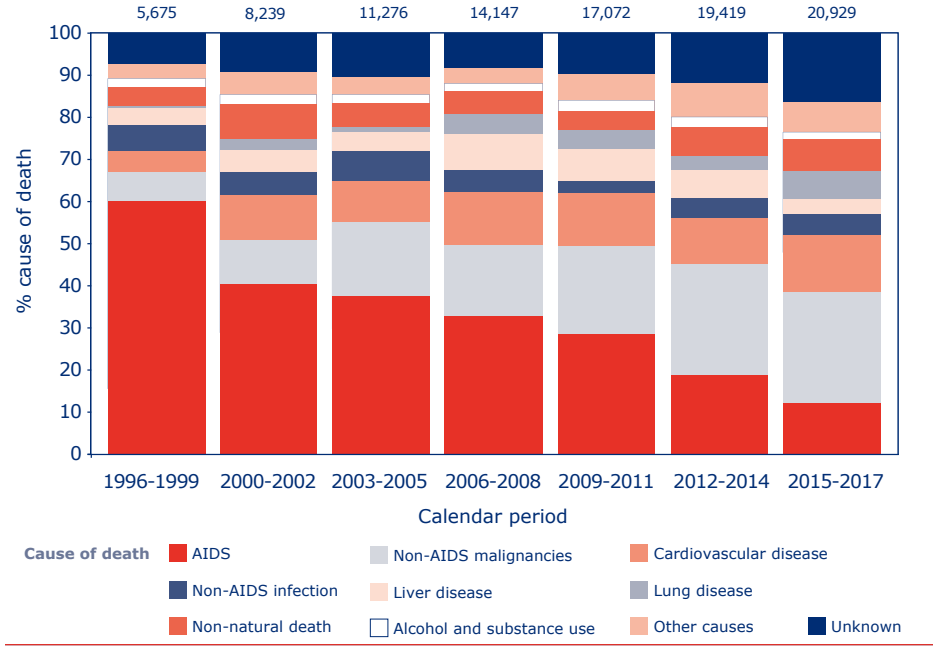
MORBIDITY AND MORTALITY

Sustained decline in AIDS-related death

Mortality remains low in HIV-positive individuals in care in the Netherlands. There has been a sustained decline in the risk of death from AIDS, with a shift towards death from non-AIDS comorbidities, including non-AIDS-defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease (*Figure 6*).

Those cases of AIDS-related death that do occur are largely driven by late entry into care, which once again stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

Figure 6: Relative changes in cause of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. Numbers above each bar represent the number of people at risk during that calendar period.

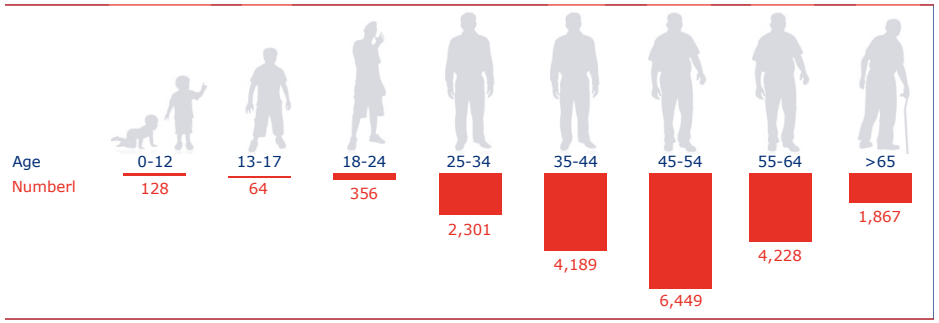


HIV IN THE NETHERLANDS KEY FINDINGS

Ageing and comorbidities

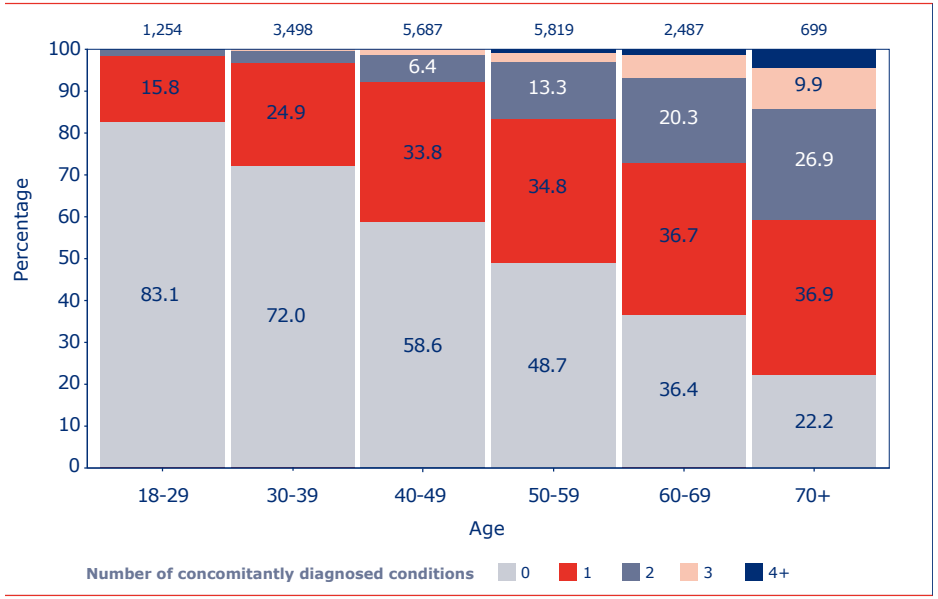
A substantial proportion of those people who were newly-diagnosed with HIV and entered HIV care in 2017 were older individuals; 27% were 50 years or older. At the same time, the overall population of people with HIV in care in the Netherlands also continues to age, with 48% currently older than 50 years compared with 39% in 2013 (*Figure 7*).

***Figure 7:** : Age distribution of people living with HIV and in care in the Netherlands in 2017.*



As in the general population, older age was an important risk factor for comorbidities such as cardiovascular disease and non-AIDS malignancies. Of particular concern is the increasing proportion of individuals with multiple comorbidities, the risk of which appears to be increased in those with HIV (*Figure 8*).

Figure 8:** Prevalence of non-HIV/AIDS multimorbidity in adults in HIV care in 2017. **Numbers on top of the bars represent the number of individuals contributing data to that age category.



HIV IN NEDERLAND BELANGRIJKSTE BEVINDINGEN REPORT

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 2000-2017. 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 antiplatelet 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 in high-risk individuals.

Non-AIDS malignancies

The most common non-AIDS malignancies are lung cancer, Hodgkin's lymphoma, anal, gastrointestinal, prostate, and head and neck cancers. Although the incidence rate of non-AIDS malignancies in the Netherlands has remained stable over time, the number of deaths due to these malignancies has increased. However, when taking the increasing age of the HIV-positive population into account, we did observe a decline in the risk of new non-AIDS malignancies in men, including anal cancer. This may be the result of a reduction in risk factors such as smoking, as well as expanded screening and treatment for early stages of anal cancer, together with a higher proportion of individuals living with higher CD4 cell counts in more recent years.

Improved awareness of risk factors may reduce comorbidity

Resilient ageing in people living with HIV and a lower comorbidity burden can be achieved by increasing awareness of the role of modifiable and often lifestyle-related risk factors among both physicians and the people living with HIV themselves. This is particularly relevant for older individuals and those at increased risk of comorbidity, and applies not only to conditions such as cardiovascular disease and diabetes mellitus, but also to cancer, chronic kidney disease and loss of bone mineral density.

HEPATITIS B AND C VIRUS CO-INFECTIONS

Hepatitis B and C virus screening is now universal

Hepatitis C (HCV) and hepatitis B (HBV) co-infections are far more prevalent in HIV-positive individuals than in the general population due to shared routes of transmission. Screening for HCV and HBV co-infection is part of the standard of HIV care in the Netherlands, and the presence or absence of these co-infections is now documented for almost all HIV-positive individuals.

HIV IN THE NETHERLANDS KEY FINDINGS

Hepatitis C virus co-infection

Approximately 12% of all individuals monitored by SHM had evidence of ever having been exposed to HCV, with 6% having documented evidence of chronic infection and 2% having evidence of acute HCV infection at the time of the first diagnosis. Most individuals with HCV infection were male and from the Netherlands or other European countries.

Hepatitis B virus co-infection

The prevalence of chronic HBV infection has decreased over time as a result of increased HBV vaccination rates, together with the HBV-prophylactic effect of tenofovir for treatment of HIV. Six percent of individuals ever in care were found to have chronic HBV infection.

HBV vaccination remains a priority

An estimated 29% of HIV-positive individuals overall and 21% of MSM had not been exposed to HBV and had not been successfully vaccinated and therefore 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.

Risk of dying from HCV or HBV co-infection is decreasing

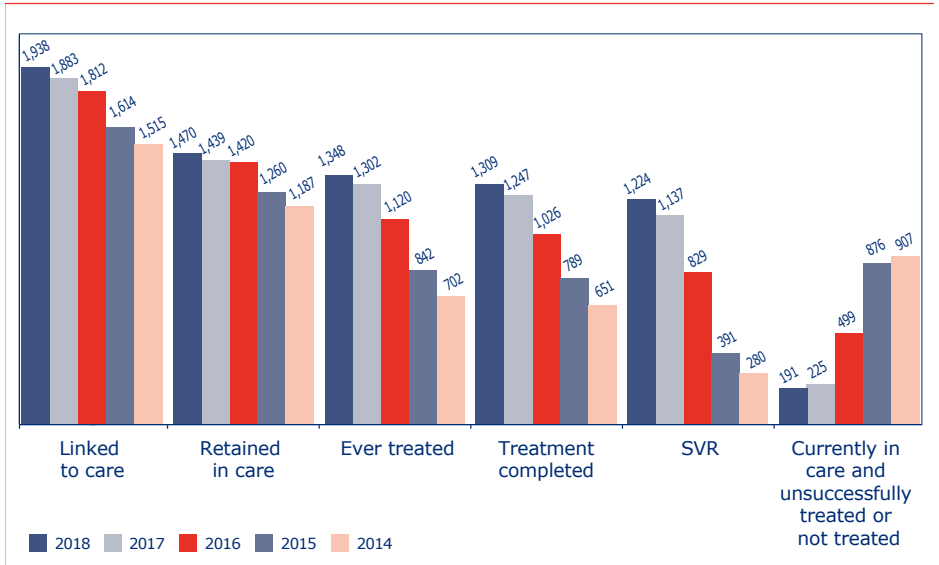
Overall, HIV-positive individuals with a chronic HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. However, people diagnosed with chronic HCV or HBV after 2000 (i.e., after tenofovir was introduced) have a lower risk of liver-related death. For those with chronic HBV infection, this is likely a result of increasingly effective HBV treatment through the use of tenofovir-containing cART that became available in 2002.

Successful HCV treatment with direct-acting antivirals has progressed further

Our data clearly show that the large majority of HIV-positive individuals with HCV co-infection have now received treatment for HCV. By 31 December 2017, over 800 individuals had received or were receiving treatment with novel direct-acting antiviral agents (DAAs). Of all people treated with DAAs, 97% achieved a sustained virological response and no longer had evidence of an active HCV infection. These developments have resulted in fewer HCV co-infected individuals remaining in need of treatment than in previous years (*Figure 9*).

HIV IN THE NETHERLANDS KEY FINDINGS

Figure 9: Hepatitis C virus continuum of care.



Legend: *SVR=sustained virological response.*

Successful HCV treatment prevents HCV transmission

Successful treatment of HCV may also prevent onward HCV transmission, as suggested by the lower number of acute HCV infections observed in the past year, together with the rapid decline in prevalence of active HCV infections. In MSM the prevalence of active HCV infections decreased to less than 1% in 2017. Although there has been a drop in the HCV re-infection rate in most recent years, re-infection following successful treatment continues to be reported, indicating that HCV transmission has not ceased completely.

Regular HCV screening among sexually-active MSM recommended

Over time, the rapidly expanding availability of DAA regimens for HCV, together with optimised screening for HCV co-infection, is expected to limit the impact of HCV co-infection on long-term liver-related morbidity and mortality; however, this effect should be monitored. To reduce new HCV infections among the key affected population of sexually-active MSM, regular screening for HCV among successfully-treated individuals is recommended for early detection of HCV re-infections, in combination with preventive behavioural interventions.

HIV IN THE NETHERLANDS KEY FINDINGS

CHILDREN LIVING WITH HIV

No new cases of perinatal transmission of HIV within the Netherlands since 2015

Of 603 children diagnosed with HIV before the age of 18 and ever registered by SHM, the majority (77%) remain in care.

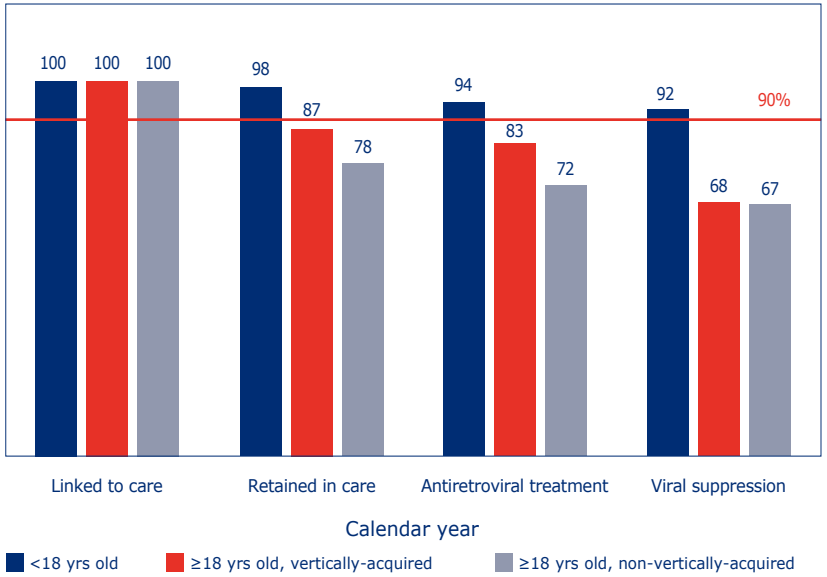
The majority (67%) of children who acquired HIV perinatally were born outside the Netherlands, Perinatal transmission of HIV within the Netherlands has become extremely rare with no new cases reported since 2015.

Of the children who are currently in care, 115 (25%) were born outside the Netherlands and adopted by Dutch parents.

Favourable outcomes for HIV-positive children

There is a high retention-in-care rate among children currently under the age of 18. Outcomes for children who are receiving cART are generally favourable and have resulted in a low mortality rate and good long-term immunological responses (*Figure 10*).

Figure 10: Cascade of care by age and mode of HIV acquisition, as of 31 December 2017. The numbers on top of the bars indicate the proportion of individuals.



HIV IN THE NETHERLANDS KEY FINDINGS

Poorer viral suppression around transition to adult care

Of those individuals who were originally registered as a child, 77% were still in care in 2017, 61% of whom were older than 18 as of 31 December 2017. Of the children who had transitioned from paediatric to adult care, 21% did not have suppressed viraemia at the time of transition, suggesting challenges for these adolescents with respect to adherence to treatment around the time of transition to adult care.

Optimisation of long-term care for young people

The large proportion of adolescents who have inadequately-suppressed viraemia at the time of transitioning to adult care illustrates that long-term care for this particularly vulnerable and difficult-to-manage group of young individuals clearly needs to be further optimised.

QUALITY OF CARE

High overall retention in care

The quality of care provided in Dutch adult HIV treatment centres was explored using indicators based on the national guidelines issued by the Dutch Association of HIV-Treating Physicians. Overall, retention in care was found to be high in most HIV treatment centres in the Netherlands, although it was lower for people not born in the Netherlands.

Earlier start of cART and high rates of viral suppression

In addition, across most centres, people are starting cART sooner after entering into care, confirming that most centres are following the guideline to offer cART to everyone with newly-diagnosed HIV regardless of CD4 count. However, there are some centres in which this policy could be improved further for people who enter care with CD4 cell counts above 350 cells/mm^3. Regardless of time since entering care, a median proportion of 99% of all patients who entered care between 2012 and 2016 and who were retained in care in 2017 had initiated cART.

Viral suppression rates in the first 6 months on cART, as well as during longer term use of treatment, were high across all centres, regardless of the number of people receiving care at a particular centre.

HIV IN THE NETHERLANDS KEY FINDINGS

Heterogeneity in repeat HCV screening

Greater heterogeneity was observed in repeat HCV screening in MSM. This variation is due to a difference in screening policy, with centres screening partly on the basis of elevated liver enzymes. Given that HCV transmission still occurs, continued monitoring of (repeat) HCV screening rates is certainly warranted.

HIV IN CURAÇAO

In recent years, individuals with HIV in care at the St Elisabeth Hospital in Willemstad in Curaçao appear to be diagnosed increasingly earlier in their infection, as shown by a declining proportion of individuals presenting late for care. As a consequence, cART is being started at increasingly higher CD4 cell counts. However, although early start of treatment appears to be possible, data also suggest that long-term retention in care needs to be improved to optimise the sustained effect of treatment.

Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV and AIDS started in 1984 among men who have sex with men (MSM) and were expanded in 1985 to include people who use drugs. 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 in men and women who use drugs. In the past decade, the focus has broadened to include the epidemiology and natural history of blood-borne and sexually transmitted infections (STI) other than HIV. In recent years, this research has been further extended with prospective testing for STI and human papillomavirus infection.

From the outset, research within the ACS has taken a multidisciplinary approach. The collaborating institutes within the ACS framework are the Public Health Service of Amsterdam *(Geneeskundige en Gezondheidsdienst Amsterdam; GGD Amsterdam)*, the Academic Medical Center (AMC) site of Amsterdam UMC, MC Jan van Goyen, Sanquin Blood Supply Foundation, DC Klinieken Lairesse - 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.

In 2018, a special publication entitled 'ACS Magazine' was issued for the occasion of the world AIDS conference in July of that year in Amsterdam. In this publication, junior researchers, leading national and international researchers, nurses, laboratory staff, physicians, and cohort participants shared their thoughts on the importance of the ACS and on the significance of their contributions to the ACS.

Following consultation with the ACS's scientific advisory group in 2015, follow up of people who use drugs ended in 2016 due to the absence of new HIV and hepatitis C infections in preceding years. During the 31 years of follow up, 1,680 people who use drugs took part in the study and made a combined total of 28,011 visits to the ACS.

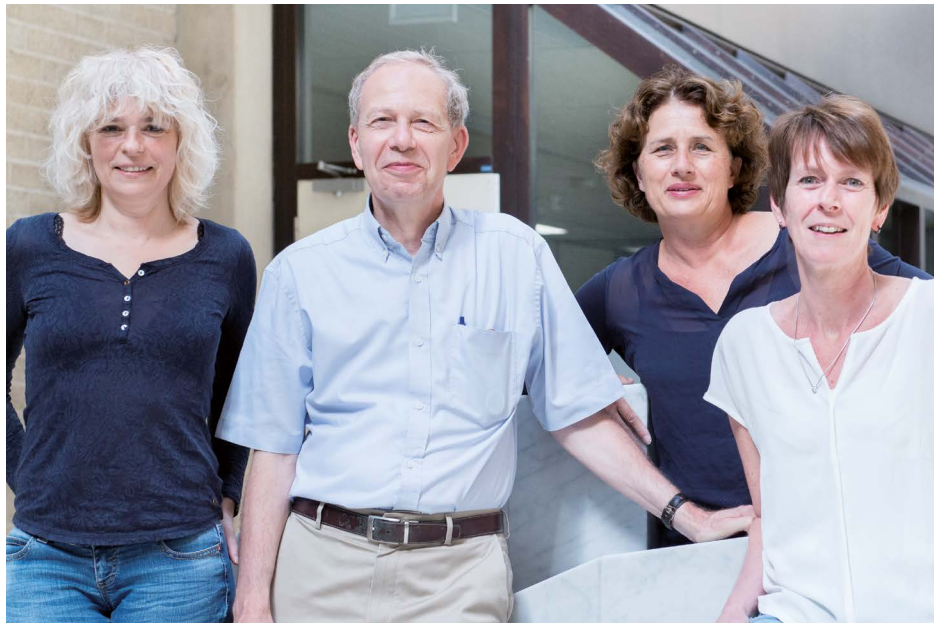
In line with the plan presented to the International Scientific Advisory Committee, which issued a positive evaluation of the ACS in 2013, expansion of the group of HIV-negative participants in the MSM cohort was initiated in 2015, with special efforts made to recruit younger MSM (below 30 years of age). In 2018, 92 new participants were included in the ACS, with a median age of 28 years. On 31 December 2018, there were 748 HIV-negative MSM in active follow up.

As well as following this large group of HIV-negative MSM, the ACS also follow a group of HIV-positive MSM. This follow up takes place primarily

AMSTERDAM COHORT STUDIES

through the standard HIV medical care and through monitoring by SHM. In addition to the standard medical care, samples are collected and stored for specific immunological and virological studies. These samples are collected from HIV seroconverters who acquired HIV during the ACS follow up and from some of the individuals who were already HIV-positive at inclusion in the ACS. In addition, body material from the HIV-negative men is also collected and stored as part of the ACS.

As of 31 December 2018, 2,901 MSM had ever participated in the ACS. Since the start of the ACS, these MSM have made 60,408 study visits. In 2018, 729 MSM, 47 of whom were HIV-positive, made a study visit to the GGD. HIV was diagnosed in 3 of the 682 HIV-negative participants in 2018. The preliminary HIV incidence within the ACS in 2018 was 0.45 per 100 person years.



The ACS steering committe (from left to right): Lia van der Hoek, Peter Reiss, Maria Prins, Neeltje Kootstra.*

**Photo by Roland van den Eijnden, Ministry of MEDIA.*

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 healthcare providers, researchers, other health professionals, policy makers, the media, and other interested parties. This chapter provides an overview of the main communication activities undertaken in 2018.

The HIV Monitoring Report 2018.

EXTERNAL COMMUNICATION ACTIVITIES

HIV Monitoring Report 2018: 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 epidemic. In addition, the Monitoring Report describes trends in HIV-related and non-AIDS-related morbidity and mortality, and includes chapters dedicated to viral hepatitis and to quality of care in Dutch HIV treatment centres.

The main findings from the 2018 Monitoring Report are described in an earlier section of this annual report '(HIV in the Netherlands in 2018: Key findings from our latest HIV Monitoring Report)'.

Distribution of 2018 HIV Monitoring Report

The full 2018 HIV Monitoring Report was made available as an online PDF on our website. As a new feature in 2018 and to facilitate access, each chapter and its accompanying figures could also be downloaded individually from the website. The report's Summary and Recommendations section was 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 the national conference on sexually transmitted diseases and HIV (*Nationaal Congres Soa*Hiv*Seks*) held on 23 November 2018.

COMMUNICATION ACTIVITIES

Scientific output

SHM also contributes to the 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 2018, SHM's ATHENA cohort data were included in 42 publications in peer-reviewed national and international scientific journals and 47 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.

2017 annual report

Our 2017 annual report was published online in May 2018, in a new, more online-friendly format. In addition to an overview of the organisational structure, the annual report provided a detailed overview of the data collection and quality control activities undertaken in 2017 and a summary of the population registered in SHM's database as of 31 December 2017. 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 our activities in 2017.

eNewsletter

The eNewsletter was sent out three times in 2018: in May, July (in the run-up to AIDS2018) and December. The 2018 newsletters featured interviews with various experts in the field of HIV, along with news about our research and developments within SHM, such as an interview with our new governing board chair, an article on our new data entry system, DataCapTree, and information on how we prepared for the new data protection legislation (GDPR). Finally, in November 2018, the English-language winter edition was also published in print format and distributed at the *Soa*Hiv*Seks* conference. This edition marked the 20th anniversary of Stichting HIV Monitoring's ATHENA cohort, with an article looking back at how the ATHENA cohort was originally set up, and also highlighted the recently-published ATHENA cohort profile in BMJ Open. All newsletters are archived on our new website and can be accessed via a direct link on the homepage.

COMMUNICATION ACTIVITIES

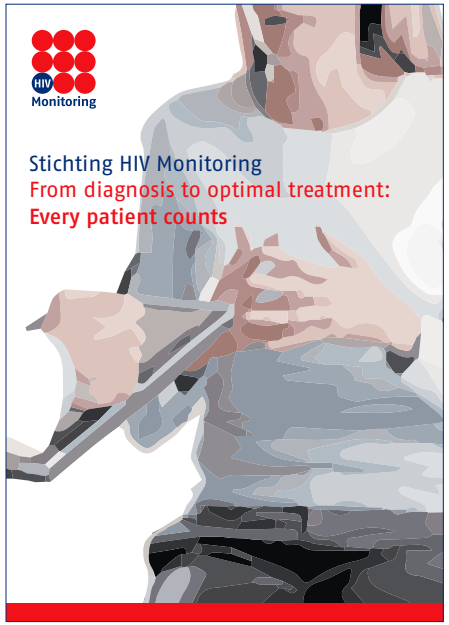
Brochure about SHM and factsheet

Our brochure provides a simple explanation of our activities and data collection process. Produced in both Dutch and English, this brochure 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 brochure is accompanied by a factsheet insert that uses infographics to summarise the key figures from the latest Monitoring Report. Both the brochure 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 to our stakeholders together with the printed Monitoring Report Summary and Recommendations, the infographics factsheet was also included in conference bags at the *Soa*Hiv*Seks* conference. In addition, copies of the updated factsheet were sent to all treatment centres for distribution to new patients. Copies of the brochure are sent to the HIV treatment centres on request. The brochure and insert are also available for download on our website.

SHM's patient brochure.



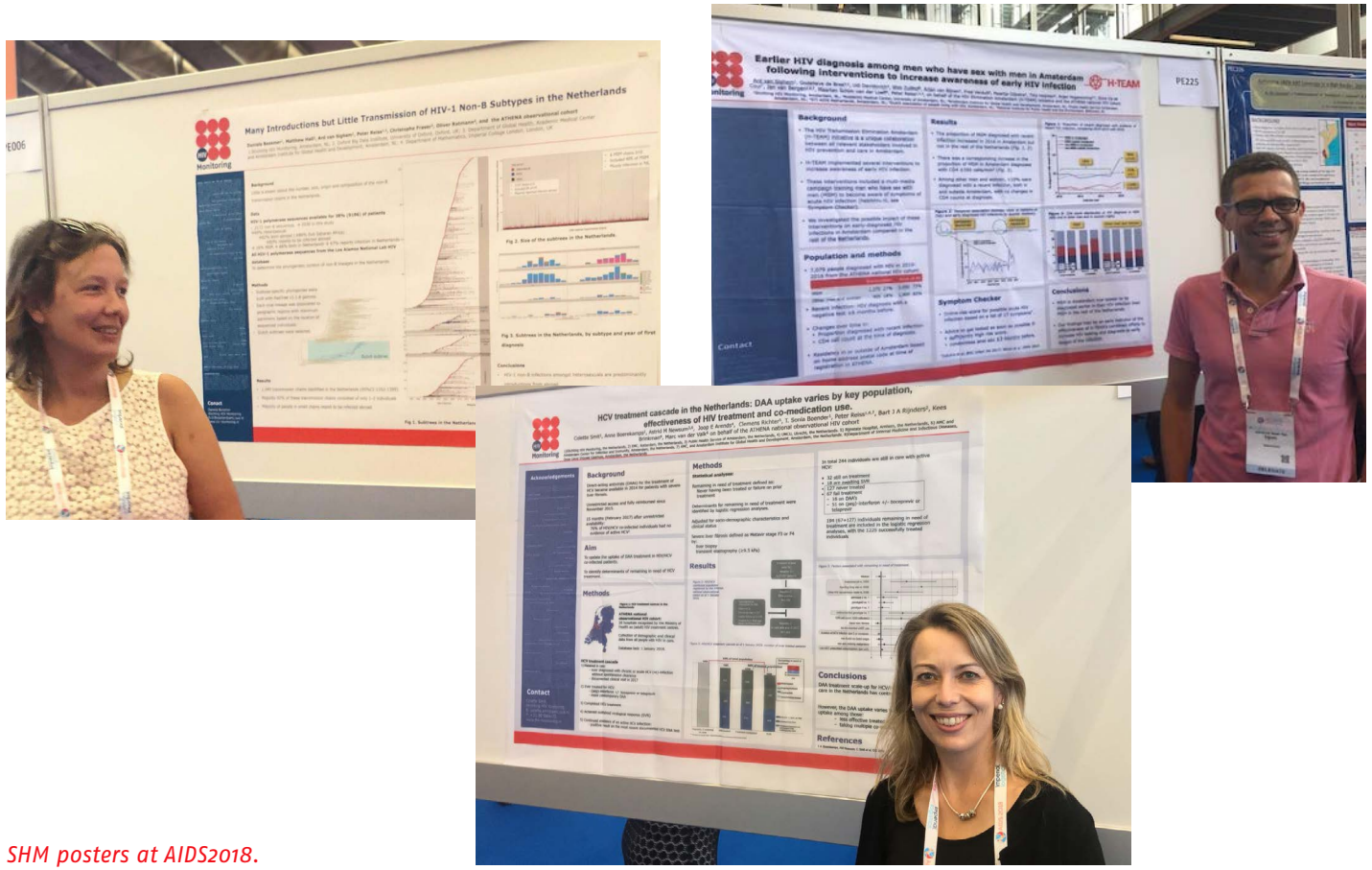
SHM website

In 2018, the SHM website underwent a rigorous update and facelift. As a result, it is now optimised for use on mobile devices and easier to navigate, with important information more readily accessible. During the course of the year we also continued to update our website on an ongoing basis, for example with news about SHM and our latest research and publications.

Events

In 2018, our 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 this report, two Netherlands-based events that took place in 2018 are described in more detail below.

COMMUNICATION ACTIVITIES



SHM posters at AIDS2018.

AIDS2018

One of the highlights of 2018 was the highly successful international AIDS conference, AIDS2018, that took place in Amsterdam in July. SHM's director, Peter Reiss, was the local co-chair of the conference, and many of our staff attended the conference and were actively involved, presenting scientific posters, running workshops or volunteering. In total, SHM contributed data or scientific expertise to at least 11 poster or oral poster presentations, on topics ranging from PrEP and antiretroviral therapy to HCV and ageing-related comorbidities.

Workshop at AIDS2018

SHM co-organised a workshop in collaboration with the Netherlands' National Institute of Health & Environment and Oxford University, entitled 'Theory in practice: Combining new methods and data for HIV prevention'. The workshop was designed to teach participants how to get more out their data by combining the data with different analysis and modelling techniques.

COMMUNICATION ACTIVITIES

Volunteers at AIDS2018, including a number of SHM staff.

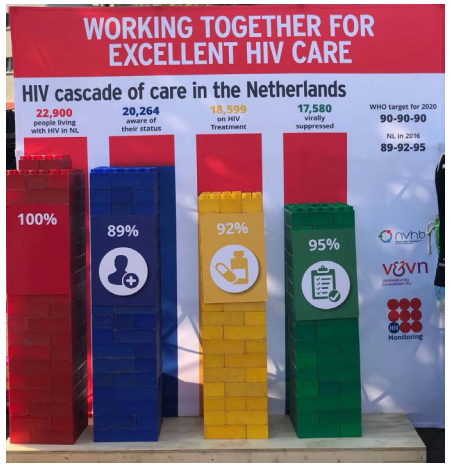
Drop-in session at AIDS2018

Together with Anastasia Pharris of the ECDC, SHM researcher Ard van Sighem hosted a special ECDC drop-in session to answer any questions people may have about the ECDC HIV modelling tool. Ard was instrumental in developing this tool, which uses evidence-based methods to amongst others estimate HIV incidence in a particular population.

SHM engagement tour: The ins and outs of a nationwide HIV monitoring system

In the week of AIDS2018 we organised a conference engagement tour, during which a group of AIDS2018 delegates visited our offices to gain greater insight into our work. The tour explained how we monitor HIV in the Netherlands, highlighting the steps involved in the data collection process using our new, state-of-the-art data entry system, DataCapTree. The visitors were also given the opportunity to work with a model of DataCapTree and enter mock data into the system themselves.

COMMUNICATION ACTIVITIES



Meet & greet organised by SHM, NVHB and HIV nurse consultants.

Positive Flame tour: meet and greet

The Positive Flame tour took place in the week of AIDS2018 and followed a route through the city of Amsterdam, stopping at organisations working in the HIV field along the way.

Together with the Dutch Association of HIV-Treating Physicians (NVHB) and the HIV/AIDS nurse consultants unit of the Dutch Nurses' Association (V&VN), SHM represented the organisations involved in HIV care in the Netherlands at a meet & greet stand located near the Spinoza monument in Amsterdam. Under the slogan 'Working together for excellent HIV care', HIV-treating physicians, HIV nurse consultants and SHM staff joined forces to literally build the HIV cascade of care for the Netherlands. In addition, a representative of each organisation joined part of the Positive Flame walk for a short interview. The three ambassadors, Henrieke Prins (NVHB), Colette Smit (SHM) and Klaas Hoeksema (V&VN hiv consulenten) were also interviewed in our Summer 2018 newsletter.

World AIDS Day

In the run-up to World AIDS Day (1 December 2018), Stichting HIV Monitoring was present at the *Soa*Hiv*Seks* conference on 23 November 2018, with a stand providing information about SHM's activities. We also organised a workshop at the conference, entitled 'HIV in the Netherlands in 2018: what's going well and what could be improved?'. The interactive workshop involved a moderated panel discussion based around presentations of findings from the 2018 Monitoring Report by SHM researchers Ard van Sighem and Ferdinand Wit.

*SHM's workshop at the 2018 Soa*Hiv*Seks conference.*

COMMUNICATION ACTIVITIES

*SHM stand at Soa*Hiv*Seks 2018.*

INTERNAL COMMUNICATION ACTIVITIES

Intranet

This externally-accessible, password-protected platform provides a central point of information for all our employees, with up-to-date contact details, HR documents, standard templates, and internal news and meetings. During 2018, the intranet provided updates on upcoming events, news and the progress of the replacement data entry database (DataCapTree).

Internal newsletter

In 2018, the internal Dutch-language newsletter, entitled *SHM Positive: a collection of all the internal news*, was published four times. It continues to provide a channel through which all employees, including those working outside the SHM offices in Amsterdam, can get to know new colleagues and stay 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 with recent scientific developments relevant to SHM's work, either by an invited speaker or one of our researchers. Scientific topics covered in 2018 included acute HCV infection in people living with HIV, phylogenetic analysis of HIV transmission, and research into pulmonary function in people living with HIV, in addition to highlights of various conferences throughout the year. During 2018, the internal meetings also included information on SHM's privacy policy and HR-related issues.

Our collaborations

IN 2018

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

NATIONAL COLLABORATIONS

Academic Medical Center, Amsterdam

SHM collaborates with the Academic Medical Center (AMC) 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 *Comorbidity and Ageing with HIV* (AGE_hIV) cohort study aims to assess the incidence and prevalence of a broad range of comorbidities and known risk factors for these comorbidities in HIV-positive individuals compared with HIV-negative individuals.

Another collaboration closely associated with the AGE_hIV cohort study, is the COBRA (*Comorbidity in relation to AIDS*) programme, which aims to further investigate these issues in collaboration with a number of European partners, for example by identifying reliable biomarkers of comorbidity and ageing in the context of HIV. As a COBRA partner, SHM collaborates with the AMC and provides the data collection infrastructure for monitoring the incidence and prevalence of a number of these comorbidities. The results obtained from this research may be used to inform and adapt national and international guidelines for prevention and management of comorbidities in ageing HIV-positive individuals. COBRA's EU funding formally ended March 1, 2017, but scientific productivity based on collected data and biomaterial continues.

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 in HIV prevention, treatment and care, including the community of people with, or at risk of, HIV (see the H-TEAM website for full list of participating organisations).

RIVM-CIB

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

OUR COLLABORATIONS IN 2018

to HIV and other sexually transmitted diseases such as infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as infectious diseases such as tuberculosis. For the purpose of national HIV surveillance work carried out by the RIVM-CIb and to fulfil RIVM-CIb's reporting requirements to the European Centre for Disease Prevention and Control (ECDC), the RIVM-CIb and SHM regularly exchange data collected through SHM's framework.

GGD Amsterdam

SHM has contributed 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. Although MOSAIC has formally ended, scientific productivity based on collected data and biomaterial continues.

SHM and GGD Amsterdam also work together on the *Amsterdam Cohort Studies* (ACS, reviewed earlier in this report) in collaboration with the AMC. The ACS are primarily funded through the RIVM-CIb. Since 2015, ACS funding has been included in the structural institute grant awarded to SHM by the ministry of Health, Welfare and Sport through the RIVM-CIb.

Finally, the GGD participated in the aMASE study, which was part of EuroCoord. This study aimed to identify barriers that migrant communities face when accessing healthcare, so that HIV prevention, diagnosis and prognosis may be improved in migrants in Europe. SHM provided clinical data required for the Netherlands' part of the study.

aMASAE was part of EuroCoord, the collaboration that encompassed all EU-funded cohort studies in the field of HIV and that ended in 2015. For the time being, scientific productivity within aMASE is continuing based on the last available joint dataset.

Pilot registration and monitoring of hepatitis C mono-infection

The National Hepatitis Plan adopted in 2016 sets out five key approaches by which to prevent further dissemination of viral hepatitis in the Netherlands and reduce related disease burden and mortality. One of the approaches is to improve surveillance and monitoring of HBV and HCV in order to gain insight into the cascade of care. The Dutch Society for Internal Medicine (*Nederlandse Internisten Vereniging*, NIV) and the Dutch Association of

OUR COLLABORATIONS IN 2018

Gastroenterologists and Hepatologists (*Nederlandse Vereniging Van Maag-Darm-Leverartsen*, NVMDL) established a steering committee that elected to work together with SHM to implement such a monitoring system. A working group was subsequently established, comprising representatives from NIV, NVMDL, the Dutch Association of HIV-Treating Physicians (NVHB) and SHM. As a first step, the working group has agreed to set up a pilot registration of individuals who are in care with a hepatitis C mono-infection and who have received direct-acting antiviral treatment. During 2017, the working group established the scope and implementation process of this pilot registration, which will take place at a select number of clinical centres. Data collection started in one of the pilot centres, namely Erasmus MC, at the end of 2018. The data collection pilot will be expanded in the remaining centres during the course of 2019.

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 was performed. EuroCoord formed 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.

EuroCoord was funded for a period of 5 years from 2011 onwards as part of the European Commission's 7th Framework Programme. Funding for EuroCoord and associated collaborations (see below) therefore ceased on 31 December 2015. Some of its associated collaborations (in particular, EPPICC and EuroSIDA) have succeeded in continuing parts of their research agendas through alternative funding mechanisms. Scientific productivity continues based on the last available joint dataset and collected biomaterial.

COHERE

The *Collaboration of Observational HIV Epidemiological Research in Europe* (COHERE) is a unique collaboration of 33 cohorts in Europe that aims to conduct epidemiological research on the prognosis and outcome of HIV-positive populations from across Europe, including children, pregnant mothers, and other adults.

OUR COLLABORATIONS IN 2018

COHERE was part of EuroCoord, the collaboration that encompassed all EU-funded cohort studies in the field of HIV and that ended in 2015. For the time being, scientific productivity continues based on the last available joint dataset.

Papers published by COHERE in 2018.

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 was to monitor the course of HIV infection from the time of infection onwards. The ACS participated in this study through their HIV seroconverted participants.

CASCADE was part of EuroCoord, the collaboration that encompassed all EU-funded cohort studies in the field of HIV and that ended in 2015. For the time being, scientific productivity within CASCADE is continuing based on the last available joint dataset.

Papers published by CASCADE in 2018.

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 of 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. 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 encompassed all EU-funded cohort studies in the field of HIV and that ended in 2015. EuroSIDA has since undergone reorganisation and secured alternative funding to continue this longstanding, highly successful collaboration.

Papers published by EuroSIDA in 2018.

OUR COLLABORATIONS IN 2018

RESPOND

In addition to its activities described above, EuroSIDA is also a founding partner of the newly-formed *International Cohort Consortium of Infectious Disease* (RESPOND). RESPOND is a non-interventional, non-randomised, open-label, multi-cohort observational study. The aim of RESPOND is to build a flexible and dynamic cohort consortium for the study of infectious diseases, including HIV, as a generic structure for facilitating multi-stakeholder involvement. This consortium builds on the collaborative work in HIV cohort studies that has taken place in Europe and beyond over the last 20 years and that has provided crucial information contributing to improvement of the lives of HIV-positive individuals. RESPOND will continue with a rigorous approach to answering questions with robust and reliable scientific methodologies, as well as having the flexibility and willingness to answer the most important questions of interest to the infectious diseases research community.

In 2018, together with other cohorts including EuroSIDA, SHM will contribute pseudonymised data from a number of ATHENA participants for designated RESPOND projects, alongside those ATHENA cohort participants already included in EuroSIDA.

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 living 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 encompassed 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). With EuroCoord having ended in 2015, EPPICC has successfully secured alternative funding to continue its research.

Papers published by EPPICC in 2018.

OUR COLLABORATIONS IN 2018

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 2018, Prof. Peter Reiss and Dr Ard van Sighem represented SHM in the ART-CC steering group.

Papers published by ART-CC in 2018.

D:A:D

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) was a prospective multi-cohort study that focused on the potential association between antiretroviral drugs and cardiovascular disease, liver and renal disease, and non-AIDS-defining malignancies.

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.

Papers published by D:A:D in 2018.

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 2018, a consortium consisting of SHM, the National Institute of Public Health in Warsaw, and the National and Kapodistrian University of Athens started a multi-year project on supporting the further development and integration of ECDC's HIV modelling tools. In addition, SHM is partner in a collaborative multi-year project led by Dr Annabelle Gourlay and Prof. Kholoud Porter from University College London to improve the monitoring of the HIV continuum of care in Europe.

Papers published by ECDC in 2018.

OUR COLLABORATIONS IN 2018

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 contribute to answering questions such as: when to start antiretroviral therapy, what antiretroviral regimen to use initially, and when to switch to another regimen. 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.

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.

Papers published by HIV-CAUSAL in 2018.

Imperial College London and Oxford University

SHM has had a longstanding collaboration since 2002 with the Department of Infectious Disease Epidemiology (DIDE), part of the Faculty of Medicine, Imperial College 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). Prof. Christophe Fraser currently coordinates the collaboration with SHM from his 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, and the Sanger Institute, UK, on a viral whole genome association study. The primary aim of this study is to identify viral virulence factors, which could ultimately shed new light on the pathogenesis of HIV.

SHM also continues to collaborate 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.

Papers published by BEEHIVE in 2018.

OUR COLLABORATIONS IN 2018

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.

Papers published by RDI in 2018.

Scientific output in 2018

Scientific output

IN 2018

In 2018, Stichting HIV Monitoring (SHM) received 2 new requests to make use of SHM's cohort data, 1 of which has been approved to date. During the year, 42 articles were published in international peer-reviewed journals. In addition, 47 abstracts were accepted for presentation at 17 meetings and conferences (28 posters and 19 oral presentations). An overview of research projects, publications and presentations can be found on our website.

42
peer-reviewed articles

47
presentations at 17 meetings

Completed research projects

I14087 Clinical experience with rilpivirine (KLIRI study)
Roelofsen E, Burger DM, Touw DJ, Gelinck LBS, Wilms EB, van Sighem AI.

I15065 Model based on clinical parameters to predict the natural history of severe liver fibrosis in HIV/HCV co-infected patients
Arends JE, Richter C, Lieveld FI, Reiss P, Smit C, Spanier M, van Erpecum KJ, Hoepelman IM.

I15090 Fibrosis progression after acute HCV infection in HIV-infected individuals
Van der Valk M, Kooij KW, Newsum AM, Smit C, Reiss P, Prins M, van der Meer J, MOSAIC study group, SHM hepatitis working group.

I15043 Cost-effectiveness of the Adherence Improving self-Management Strategy (AIMS) in HIV care: A model-based economic evaluation
De Bruin M, Prins J, Oberjé E, Hiligsmann M, Evers S, van Sighem AI.

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.

I16072 Comparison of the occurrence of HBV-related liver disease and (liver-related) mortality between patients with hepatitis B mono-infection and patients coinfected with hepatitis B and HIV in the Netherlands
Arends JE, Richter C, Lieveld FI, Reiss P, Smit C, Spanier M, van Erpecum KJ, Hoepelman IM.

Ongoing research projects

I05513 HIV Resistance Response Database Initiative (RDI)

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

Date of approval: 1 October 2005

The main activities of the RDI during 2018 using ATHENA data were as follows:

1. The development of new global models that do not require a genotype, for use in HIV-TRePS with the use of new treatment experience variables

Objectives

1. To develop models that do not require a genotype to predict virological response to antiretroviral therapy, with the maximum possible accuracy, as a potential treatment support tool within HIV-TRePS;
2. To evaluate the impact of therapy experience variables, namely time on therapy and line of therapy on model performance;
3. To include in the modelling any new drugs for which we have sufficient data in the RDI database and check the accuracy of the models for those drugs;
4. To evaluate the performance of the models with a substantial independent test set and with cases from resource limited settings, where the models have the greatest potential utility;
5. To benchmark the models against the predictive accuracy of genotyping with rules-based interpretation.

Methods

1. Three committees of 5 random forest (RF) models were developed to predict the probability of the follow-up viral load being less than 50 copies/ml.
2. The 'standard' committee was trained using the current standard variable set including the recently established 'expanded baseline windows' of 16 weeks for viral load and 24 weeks for CD4 counts and the new genotype-based adherence filter. The first experimental committee had one additional input variable – time-on-treatment time (ToT), i.e., the number of days since first antiretroviral therapy was initiated. The second experimental committee had two additional input variables – ToT plus the line of therapy (LoT), i.e., the number of different regimens in the patient's history up to and including the baseline failing regimen.
3. The accuracy of each of the committees and models was assessed during cross validation, with an independent RDI test set including a subset of the independent test set from a resource-limited setting.
4. The test sets included a substantial number of treatment change episodes (TCEs) that include a genotype, so the performance of these models that do not require a genotype could be compared to the predictive accuracy of genotyping with rules-based interpretation.
5. The predictions of the two sets of models and the actual virological responses for the test cases were used to plot receiver operating characteristic (ROC) curves and compared with use of the current committee of 10 standard RF models.

ONGOING RESEARCH PROJECTS

Summary of the results from independent testing
When tested with the independent test cases using the optimum operating point (OOP) developed in cross validation, the standard models achieved an area under the curve (AUC) of 0.82. The overall accuracy was 76%, sensitivity 71% and specificity 79%. The ToT models achieved an AUC value during testing of 0.84, with overall accuracy of 76%, sensitivity of 71% and specificity of 79%. The ToT+LoT models achieved an AUC value during testing of 0.84, with overall accuracy of 76%, sensitivity of 72% and specificity of 79%. There were no significant differences between the performance of the models.

Comparison to genotyping with rules-based interpretation
In this analysis, genotypic sensitivity scores were generated for the 652 TCEs with genotypes available, using three rules-based genotype interpretation systems in common use: ANRS, REGA and Stanford's HIVdb. Full sensitivity was scored as 1, partial as 0.5 and no response as 0. These scores were then used as predictors of response or failure and the performance compared to that of the models. The genotype systems achieved area under the receiver operating characteristics curve (AUROC) values of 0.530-0.54, compared with 0.82-0.84 using the models. All three genotype interpretation systems were significantly poorer at predicting responses than the models ($p<0.00001$).

Model performance with cases from sub-Saharan Africa
To evaluate the potential utility of the models in a resource-limited setting the test cases from sub-Saharan Africa were extracted as used as a stand-alone test set. As there were only 268 suitable cases, the results should be considered with caution. The baseline data from these cases were put through the models and their predictions of response compared with the responses observed in the clinic.

The AUC values were 0.75 for the standard models, 0.76 for the ToT models and 0.77 for the ToT & LoT models. Sensitivity was 71%, 67% and 71% respectively; specificity was 68%, 71% and 71% and overall accuracy 69%, 69% and 71%.
The performance of the ToT+LoT models was significantly better than that of the standard models for this small data set ($p=0.038$).

Discussion: The ToT models were slightly more accurate than the standard models, with a 2% increase in AUC to 0.84 in independent testing. The additional of line of therapy information did not improve the AUC (the primary outcome) any further.

All three sets of models were highly significantly more accurate than genotyping, which resulted in AUC scores of 0.53 to 0.54, amongst the poorest we have seen to date.
When the three sets of models were tested with a very small set of cases from sub-Saharan Africa, they performed slightly less well, achieving AUC values of 0.75, 0.76 and 0.77 for the standard, ToT and ToT+LoT models respectively. All three sets of models performed well, identifying alternative

ONGOING RESEARCH PROJECTS

regimens that were predicted to be effective for cases that failed on their new regimen in the clinic.

There were no significant differences between the three sets of models in full independent testing but the ToT+LoT models were just superior to the standard models for the sub-Saharan data.

2. A study of the concordance between models that make absolute predictions of plasma HIV-1 RNA levels over time vs. those that estimate the probability of a viral load <50 copies

Objective: To assess the degree of concordance between predictions of the absolute (A) models and the classifier (C) models.

Methods:

1. TCEs were extracted from data imported since the current A and C models had been developed (since Jan 1, 2018) using extraction criteria and input variables matched to the protocols for the A and C model development studies.
2. The TCEs were divided into responses and failures using a 50-copy cut off and the number in each category was noted.
3. For each category, the number of TCEs that were predicted to respond or fail by the C models were identified, resulting in four categories: responders correctly predicted, responders incorrectly predicted, failures correctly predicted, and failures incorrectly predicted.
4. Using <50 copies as the response cut-off, the number/percentage of cases in each of these four categories for which the A models made a congruent prediction were calculated.
5. Step 4 was repeated using 100, 200, 400 and 1,000 copies as the cut-off.
6. This was also repeated for the models developed in 2017, which use a genotype in their predictions.

The two types of model were developed to perform very different tasks, so some discordance was expected. In addition, since the A models have been trained using viral load data that only goes as low as 50 copies/mL, the predictions from these models 'bottom out' at that level – i.e. approach the 50-copy level and become asymptotic at that level. As a result, a simple examination of the number of cases that were predicted to produce a viral load below 50 copies by both sets of models is not helpful, since the predictions of the absolute models rarely, if ever, go below this level.

Nevertheless, this initial examination of concordance using different viral load thresholds for the absolute models could shed some light on the congruency of the two approaches.

The hope was that:

1. The great majority of responders correctly predicted to respond by the C models would have predictions of viral loads of <1,000 copies/mL (e.g. 90%), with this proportion reducing to near zero when the 50 copy cut-off for failures was used.

ONGOING RESEARCH PROJECTS

2. That close to 100% of the failures correctly predicted by the C models would have predictions of viral load >50 copies from the A models and that this proportion would decrease as successively higher thresholds for failure were applied.

Results: 94% of those responders correctly predicted by the C models had predictions from the A models of viral loads <1,000 copies. 84% of them had predictions <400, 70% <200 and 42% less than 100 copies/mL. As expected and explained above, very few of the predictions of the C models were below 50 copies – just 4% of these cases.

Of the 2,476 failures correctly predicted by the C models, 100% had predictions from A models over 50 copies/mL, as would be expected. This reduces to 92% <100, 71% <200, 56% <400 and 38% less than 1,000 copies/mL. As expected, the proportion of these failures predicted to fail by the A models decreased as the cut-off for failure was increased.

The results from the models using genotypes were even better with 98% of the responders that were correctly predicted by the C models receiving predictions of <1,000 copies from the A models, 89% at <400 copies, 80% at <200 and 46% at <100 copies/mL.

Of the 258 of 276 (93%) failures correctly predicted by the C models, 100% had predictions from A models over 50 copies/mL, as would be expected. This reduces to 97% <100, 84% <200, 66% <400 and 39% less than 1,000. Again, as expected, the proportion of these failures predicted to fail by the A models decreases as the cut-off for failure was increased.

A secondary analysis was performed to calculate the correlation between the predictions of the A models and the actual viral loads stratified by follow-up viral load (>50, >100, >200, >400 and >1,000 copies HIV RNA/mL). There were no significant differences between the correlations achieved for each section of data (i.e., no follow-up viral load threshold (above 50 copies) below which the models lost accuracy).

When the predictions of the A models were adjusted by subtracting 0.6 log, the level of concordance between the A and C models improved, suggesting a general tendency of the A models to over-estimate the follow-up viral load.

Conclusions: The results of this study show that there is an acceptable level of concordance between the predictions of the C and A models with well over 90% of respondents correctly predicted by the C models receiving predictions of viral load <1,000 copies by the A models and well over 80% less than 400 copies.

Nevertheless, there is inevitable diminution of accuracy of the A models as predictions approach the 50 copy lower limit. This would need to be explained to those using these models if the results of both the A and the C models were presented on the same report. An adjustment

ONGOING RESEARCH PROJECTS

of 0.6 log could be made before reporting the results, to improve the concordance between the two set of models. This will be considered further.

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

Ongoing.

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, Ong SH, Bakker M, Gras L, de Wolf F, Reiss P, Kellam P, Berkhout B, Fraser C, van der Kuyl AC.

Date of approval: 12 September 2012

Background: The *Bridging the Epidemiology and Evolution of HIV in Europe* (BEEHIVE) study started in April 2014 and runs until April 2019. The objectives of the study are to use the whole viral genomes to find determinants of disease severity, molecular epidemiology, and dual HIV-1 infections and to study minority variants. All participants were selected from 7 countries (Belgium, France, Finland, Germany, the Netherlands, Switzerland and the United Kingdom), were seroconverters or participants presenting with evidence of recent infection, and were diagnosed with HIV between 1985 and 2013.

Results: Inclusion of samples is complete (n=41 from Rotterdam, n=41 from Nijmegen, n=39 from the OLVG and n=24 from Zwolle); total nucleic acids were isolated from the samples with the method described in Cornelissen *et al.* 2017.
As the principal investigator of the BEEHIVE study, Prof. C Fraser, recently moved from Imperial College London to the Big Data Institute in Oxford, the sequence platform was changed to the Oxford Nanopore MinION platform. The final 450 samples will be sequenced on the latter platform. In 2017, 2,892 HIV genomes were sequenced using the Illumina MiSeq or HiSeq platform. To analyse these data, a new software tool, phyloscanner, which analyses pathogen diversity from multiple infected hosts, has been developed. Phyloscanner is a set of methods implemented as a software package; it can be used to detect contamination, multiple infections, recombination and transmission events. The description of the software package and the results were published in Molecular Biology and Evolution in 2018 (Wymant *et al.*).

ONGOING RESEARCH PROJECTS

In 2017, we also finished a minor project on evolution of HIV-1 Tat protein, the essential regulator of viral gene expression, in the BEEHIV dataset. We documented considerable variation in the length of the C-terminal domain of Tat in Dutch HIV-1 sequences, ranging from 77 to 124 amino acids over time. Subsequently, we set up functional assays to analyse whether this polymorphism correlates with changes in Tat activity. A revised manuscript describing our findings has recently been resubmitted to *Retrovirology*.

Conclusions: In 2017, the objectives of the BEEHIVE study were almost fulfilled.

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

Wensing AMJ, Boucher CAB, Brinkman K, Richter C, Bierman WFW, Ende van der ME, M Kasteren van MEE, Hoepelman AIM, Hofstra M.

Ongoing.

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

Ongoing.

I14067 Predictive value of cardiovascular risk equations in the HIV-infected population receiving care in the Dutch HIV treatment centers

Van Zoest R, Law M, Sabin C, Vaartjes I, van der Valk M, Arends J, Reiss P, Wit F.

Date of approval: 2 June 2014

Background: A higher burden of cardiovascular disease (CVD) has been observed among people living with HIV (PLWH) when compared to HIV-negative controls, likely due to a complex interplay between traditional CVD risk factors and HIV-related factors such as persistent inflammation and immune activation, certain antiretrovirals, and damage to the immune system. As the age of the HIV-positive population increases, so does the CVD burden. CVD prevention strategies might be able to mitigate this burden.

CVD risk management guidelines recommend initiation of primary prevention based on a person's estimated risk. Accurate CVD risk

ONGOING RESEARCH PROJECTS

assessment is key in identifying those individuals who will benefit most from primary prevention. The Systematic COronary Risk Evaluation (SCORE), Framingham CVD Risk Score (FRS), and American College of Cardiology and American Heart Association Pooled Cohort Equations (PCE) are amongst the most commonly used CVD risk prediction algorithms. These general population-derived algorithms do not take into account any HIV-related CVD risk factors. In an attempt to more accurately predict CVD risk in PLWH, the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) Study algorithm was developed. Unlike SCORE, FRS and PCE, the D:A:D algorithm includes HIV-related variables such as CD4 count and exposure to certain antiretrovirals.

Since comprehensive assessment of CVD risk prediction algorithms is lacking in PLWH, the primary aim of the current study was to compare the performance of D:A:D, SCORE-NL (SCORE adjusted for national data), FRS, and PCE in the national AIDS Therapy Evaluation in the Netherlands (ATHENA) observational HIV cohort. Our secondary aim was to investigate whether we could improve the performance of SCORE-NL (used in the national guidelines) by assigning PLWH an additional CVD risk.

Methods: *Study population* For the current analysis we included data from ATHENA participants with ≥2 outpatient clinic visits between 1 January 2000 and 31 December 2016 who met the following inclusion criteria: HIV-1-positive, aged ≥18 years, no pre-existing CVD, initiated first combination antiretroviral therapy (cART) regimen >1 year ago, with available data on smoking status, total/HDL cholesterol, blood pressure, and CD4 count.

Baseline was defined as the first outpatient visit after meeting the above-mentioned inclusion criteria. CVD was the primary outcome and follow up was censored at the earliest of: 10 years after baseline, 31 December 2016 or last outpatient visit prior to 31 December 2016, death, or loss to follow up.

CVD risk prediction algorithms We compared four commonly used algorithms: D:A:D, SCORE-NL, FRS, and PCE.

D:A:D predicts the five-year risk of incident CVD and has been developed using pooled datasets of 11 HIV cohorts across 212 clinics in Europe (including part of the ATHENA cohort), Argentina, Australia, and the United States (US). For appropriate comparison with other algorithms we also calculated ten-year risk, using the same algorithm, but including the Cox ten-year instead of the five-year survival estimate at the mean values of the predictors included in the D:A:D algorithm (provided by the authors).

SCORE was originally developed to estimate ten-year risk of fatal CVD in Europe using a pooled dataset of general population cohorts from 12 European countries. In the current analysis we used SCORE-NL, which uses age-specific conversion factors to translate ten-year CVD mortality risk into ten-year CVD mortality and morbidity risk.

ONGOING RESEARCH PROJECTS

Dutch guidelines recommend using SCORE-NL to estimate an individual's CVD risk. We also evaluated a self-adapted version of SCORE-NL by assigning PLWH an additional CVD risk by artificially increasing a person's age (as is currently done in patients with diabetes or rheumatoid arthritis). We investigated an arbitrarily chosen age increase of five or ten years in PLWH (referred to as SCORE-NL+5Y and SCORE-NL+10Y, respectively).

FRS estimates the ten-year probability of a first CVD event based on data collected in the US-based Framingham Heart Study and the Framingham Offspring study.

More recently, the ethnicity-specific and sex-specific PCE was developed to estimate the ten-year risk for a first atherosclerotic CVD event using a pooled dataset of general population cohorts from the US.

Definitions Each algorithm studied comprises different CVD risk factors and endpoints. We used algorithm-specific CVD endpoints within the current analysis.

Blood pressure, total cholesterol, HDL cholesterol, and CD4 count were measured as part of standard care, and measurements prior to baseline were used to estimate CVD risk. For most participants, smoking status was not updated over time. Therefore, we assumed that smoking status remained constant over time. Diabetes was defined as (1) use of antidiabetic medication, or (2) a reported diagnosis of diabetes mellitus in a patient's clinical record combined with either fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), non-fasting plasma glucose ≥11.1 mmol/L (200 mg/dL) or HbA1c ≥48 mmol/mol (6.5%). Family history of CVD was collected at entry into ATHENA and was defined as having a first degree relative who experienced myocardial infarction or stroke before the age of 50 years; individuals with missing data were assumed to have no family history of CVD. Ethnicity was based on an individual's region of origin and subsequently categorised into four groups: (1) white/Caucasian (the Netherlands, North America, Australia, central Europe, eastern Europe), (2) black (sub-Saharan Africa, Caribbean), (3) Hispanic (Latin America), and (4) other (north-Africa, Asia-Pacific, south-east Asia).

Statistical analysis Statistical analyses were performed using Stata (version 12; StataCorp, College Station, Texas, USA), except for the Greenwood-Nam-D'Agostino (GND) goodness-of-fit test, which was performed with R, version 3.5.1. At baseline, we calculated and categorised an individual's CVD risk for each algorithm as recommended for clinical practice.

The Kaplan-Meier method was used to obtain estimates of observed CVD events accounting for variable follow-up time. Model discrimination (the ability to differentiate people who developed CVD from those who did not) was evaluated

ONGOING RESEARCH PROJECTS

using Harrell's C-statistics. Harrell's C-statistic values between 0.50-0.59 were considered poor, 0.60-0.69 moderate, 0.70-0.79 acceptable, and 0.80-1.00 very good to excellent. Model calibration (the extent to which the algorithm accurately reflects observed CVD risk) was assessed using the mean observed-versus-expected ratio (O:E ratio), calibration plots and the GND goodness-of-fit-test. For the calibration plot and GND test we divided the cohort into deciles of predicted CVD risk for each algorithm. Groups were collapsed when they contained <5 events to ensure calculation of a stable GND chi-squared statistic.

Sensitivity analyses A number of sensitivity analyses were performed to assess the robustness of the results:

A. Using cumulative incidence function to estimate the number of observed events, considering non-CVD deaths as competing events;
B. Excluding data from PLWH who contributed to the D:A:D study (n=8,826);
C. Substituting the D:A:D algorithm by a recalibrated algorithm in which data from ATHENA participants were excluded (provided by the authors);
D. Restricting the analysis to those aged 40 to 70 years old.

Results: *Characteristics of the study population*
Data from 16,070 PLWH were included in the main analysis, representing 63% of the total population in care in the Netherlands and registered with ATHENA between January 2000 and December 2016. Common reasons for exclusion were insufficient follow up or missing data.

Participants had a median age of 43 years (interquartile range, 36-50), 82.4% were male, 94.5% used cART, and 88.6% had HIV-RNA <200 copies/mL. Depending on the algorithm used, between 2.4 and 11.4% of individuals were predicted to have a CVD risk ≥20%.
The algorithms used different endpoints and hence follow up and number of events varied between algorithms. During 88,929, 88,623, 87,310, and 89,271 person-years of follow up (PYFU), a CVD incidence of 6.5, 6.9, 8.6 and 5.8/1,000 PYFU was observed, for D:A:D, SCORE-NL, FRS and PCE, respectively.

Performance of CVD risk prediction algorithms
All algorithms yielded acceptable discrimination (Harrell's C-statistics ranged from 0.73 to 0.79).

On a population level, D:A:D, SCORE-NL, and PCE slightly underestimated CVD risk (O:E-ratios 1.35, 1.38, and 1.14, respectively), whereas FRS somewhat overestimated CVD risk (O:E ratio 0.92). The slight overestimation of CVD risk by FRS was mainly observed in those with ≥20% predicted risk (O:E ratios, 1.06, 0.94, and 0.78 in those with a predicted risk of <10%, 10-20%, and ≥20%, respectively). D:A:D, SCORE-NL, and PCE underestimated CVD risk in the low and intermediate risk groups (O:E ratios: D:A:D, 1.34 [<10%] and 1.37 [10-20%]; SCORE-NL, 2.20 [<10%] and 1.20 [10-20%]; PCE, 1.55 [<7.5%]). While risk

ONGOING RESEARCH PROJECTS

prediction in those with high predicted risk was rather accurate for D:A:D and PCE, SCORE-NL clearly overestimated CVD risk (O:E-ratios, 0.99 [≥20%], 1.09 [≥7.5%], and 0.65 [≥20%], respectively). D:A:D, FRS, and PCE best fitted our data, as reflected in the calibration plots and GND test statistics (GND chi-squared, 30.00 [D:A:D], 34.22 [FRS], 24.57 [PCE], 119.22 [SCORE-NL]). Yet, all algorithms yielded a statistically significant lack of fit (GND $p<0.05$).

The mean O:E-ratio of SCORE-NL changed from 1.38 to 0.86 by assigning PLWH an additional CVD risk equivalent of a five-year increase in age. Though risk prediction was more accurate in those with a predicted CVD risk <10% (O:E ratio changed from 2.20 to 1.41), CVD risk prediction deteriorated in those with CVD risk ≥20% (O:E ratio changed from 0.65 to 0.54). A ten-year increase in age led to an overestimation of CVD risk over the whole range. Overall, model fit worsened by increasing CVD risk (GND chi-squared = 119.22 [SCORE-NL]; 169.01 [SCORE-NL+5Y]; 621.81 [SCORE-NL+10Y]).

Sensitivity analyses Sensitivity analyses using cumulative incidence functions to obtain the estimated number of observed events, using a recalibrated D:A:D algorithm (excluding ATHENA participant data), and applying stricter age limits did not substantially modify the results. However, excluding data from PLWH who contributed to the D:A:D study yielded a good model fit for D:A:D, FRS and PCE (GND $p>0.05$).

Conclusions: Within this largely well-treated HIV-positive population in the Netherlands, all assessed CVD risk prediction algorithms reasonably distinguished individuals who developed CVD from those who did not. Though all algorithms yielded a statistically significant lack of fit, D:A:D, PCE, and FRS best predicted CVD risk, with calibration being considerably poorer for SCORE-NL. Assigning PLWH an additional CVD risk equivalent to a five-year increase in age (SCORE-NL+5Y) improved CVD risk prediction by SCORE-NL in the low to intermediate CVD risk group (<20%), but led to a more pronounced overestimation in those with high CVD risk. D:A:D, PCE, FRS, and SCORE-NL+5Y would all be suitable for use in clinical practice, with the caveat of slightly under-predicting CVD risk in the low CVD risk group.

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, Spinhoven P, van Luenen S.

Date of approval: 23 September 2014

Medical data: The medical data (time since HIV diagnosis, medication use, CD4 cell count, and viral load) were obtained from SHM in 2017. These data were used to describe the sample and for the moderation analysis (i.e., is time since HIV diagnosis a moderator of intervention effect?).

ONGOING RESEARCH PROJECTS

Background: The goal of the study was to investigate moderators of intervention effect of a guided Internet-based self-help intervention for people with HIV and depressive symptoms. This study was part of a randomized controlled trial where the intervention was found to be effective in reducing depressive symptoms, compared to an attention-only control group.

Methods: The intervention consisted of guided online cognitive behavioral therapy. Demographic characteristics (e.g., age), HIV characteristics (e.g., duration of HIV), and psychological characteristics (e.g., coping self-efficacy) were investigated as potential moderators of intervention effect.

Results: In 2015, 188 people with HIV and depressive symptoms were included in the study: 97 were randomised to the intervention group and 91 to the control group. One moderator of intervention effect was found: coping self-efficacy. Participants with low coping self-efficacy improved more in the intervention group than in the control group, and participants with high coping self-efficacy improved in both groups.

Conclusions: The results indicate that the intervention may be provided to all people with HIV and depressive symptoms. It may be especially important for people with HIV and low coping self-efficacy to start with the intervention, since they do not improve in the control group with only minimal attention.

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

Reitsema M, van Hoek AJ, Mangen MJ, van Benthem B, Wallinga J, op de Coul E, 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. To control HIV, several preventive measures are being considered or employed, such as increased HIV testing and pre-exposure prophylaxis (PrEP). We assessed the impact of these measures on HIV transmission and their cost-effectiveness. To investigate the impact of HIV prevention measures on the transmission of other sexually transmitted infections (STIs), we examined also the transmission of *N. gonorrhoeae* (NG) in the model.

Methods: We developed an individual-based model that describes the formation of sexual relationships between MSM and the transmission of HIV and NG. Parameters relating to sexual behaviour were estimated from data from the Amsterdam Cohort Study and the Network Study among MSM in Amsterdam. Parameters relating to HIV progression were estimated from data from Stichting HIV Monitoring (SHM). Frequency of HIV/STI testing was estimated from data of the

ONGOING RESEARCH PROJECTS

national database of STI clinics in the Netherlands. The model was calibrated to data on HIV diagnoses from SHM and gonorrhoea positivity rates from STI clinics. In the model, we assumed that from 2015 onwards, all HIV treatment centres in the Netherlands follow the new guidelines for immediate initiation of cART after diagnosis.

Subsequently, we developed an economic model. We used an activity-based costing approach, identifying all individual activities involved in HIV testing and HIV care (such as, nurse time, doctor time, lab activities, medicine) and assigning the costs of each activity involved to each 'product' (such as an HIV test or hospital visits) according to the actual consumption of each activity in each product. Direct healthcare costs were calculated using this approach and included costs of medical consultations, costs for laboratory tests, and cART medication. Effects of the interventions were expressed in quality-adjusted life-years (QALY) gained.

The incremental cost-effectiveness ratio (ICER) was calculated, showing the additional costs per QALY gained with the intervention, compared to the current situation. Costs were expressed in 2016 euros. According to Dutch guidelines, costs were discounted by 4% and effects by 1.5%. The analyses were carried out from a healthcare payer perspective, considering only healthcare costs relating to HIV testing and HIV care.

Results: *Impact of increased HIV/STI testing*
We carried out analyses with different increases in HIV/STI testing. We examined a moderate increase in the percentage of MSM who get tested every six months (from 20% currently to 50%) among all MSM; or only among MSM who had ≥10 partners in preceding six months; or MSM who had a gonorrhoea diagnosis in preceding 12 months; or MSM who had condom-less anal sex (CAI) in the preceding six months. We also examined scenarios where the time intervals between tests were reduced by 50%.

The following three scenarios were the most effective in preventing HIV transmission: halving the time between tests among all MSM who get tested, increasing the percentage of six-monthly testers among all MSM or only among MSM who had CAI. Over ten years, these scenarios resulted in 1362, 1319, or 1232 averted new HIV infections, but 663, 584, or 423 additional HIV tests were needed per averted HIV infection, respectively. These scenarios also resulted in the highest numbers of averted *N. gonorrhoeae* infections.

Increasing six-monthly testing among all MSM resulted in 1380 averted HIV infections, 715 QALYs gained, €26 million additional costs, and an average ICER of €36,700 per QALY gained. This was not cost-effective, with the €20,000 willingness-to-pay threshold employed in the Netherlands. Increasing six-monthly testing among MSM with ≥10 partners resulted in 799 averted HIV infections and 367 QALYs gained; this scenario resulted in lower costs than those with the current testing rates and was cost-saving.

ONGOING RESEARCH PROJECTS

Impact of PrEP Criteria for PrEP eligibility in the model follow the recent Dutch guidelines on PrEP use. We examined several scenarios of how a nationwide PrEP programme could be implemented. We examined PrEP programmes with or without risk compensation, in the form of reduced condom use. With PrEP, the HIV incidence rate was reduced from 0.192 infections per 100 PY in 2017 to 0.092 per 100 PY in 2027, assuming no risk compensation, or to 0.083 per 100 PY with risk compensation. The prevalence of gonorrhoea was also reduced due to PrEP; with risk compensation, gonorrhoea prevalence was higher than that without risk compensation. A PrEP programme without risk compensation resulted in 1,482 QALYs gained and €12.3 million less costs than the current situation without PrEP, making the PrEP programme cost-saving. PrEP with risk compensation resulted in 1,380 QALYs gained and €1.0 million less costs, and an average ICER of €1,925 per QALY gained.

Conclusions: Our analyses indicate that considerable reductions in HIV transmission can be achieved with increased HIV/STI testing and PrEP. Moreover, both these measures can lead to reductions in gonorrhoea transmission, since HIV testing is usually accompanied by STI testing and PrEP guidelines recommend three-monthly gonorrhoea testing. Our findings indicate that increasing the percentage of MSM being tested every six months among those with recent gonorrhoea or those with ≥10 partners in the preceding six months is efficient in terms of tests needed to prevent a new HIV infection. Increased HIV/STI testing may be cost-effective only if targeted to MSM with many partners. PrEP for high-risk MSM can be cost-effective even with moderate levels of risk compensation. Nevertheless, our findings suggest that combinations of prevention measures or strategies also targeting low-risk MSM might be necessary to reduce the number of new HIV infections to zero.

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

Rokx C, Gupta R, Rijnders B, Shafer B, Gregson J, Tang M, Hamers R, Raizes E, Crawford K, Marconi V, Hill A, Hosseinipour M, Clumeck N, Kanki P, Lockman S, 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: Tenofovir disoproxil fumarate (TDF) genotypic resistance defined by K65R/N and/or K70E/Q/G occurs in 20% to 60% of individuals with virological failure (VF) on a WHO-recommended TDF-containing first-line regimen. However, the full spectrum of reverse transcriptase (RT) mutations selected in individuals with VF on such a regimen is not known.

ONGOING RESEARCH PROJECTS

Methods: To identify TDF regimen-associated mutations (TRAMs), we compared the proportion of each RT mutation in 2,873 individuals with VF on a WHO-recommended first-line TDF-containing regimen to its proportion in a cohort of 50,803 antiretroviral-naive individuals. To identify TRAMs specifically associated with TDF-selection pressure, we compared the proportion of each TRAM to its proportion in a cohort of 5,805 individuals with VF on a first-line thymidine analogue-containing regimen.

Results: We identified 83 TRAMs including 33 NRTI-associated, 40 NNRTI-associated, and 10 uncommon mutations of uncertain provenance. Of the 33 NRTI-associated TRAMs, 12 - A62V, K65R/N, S68G/N/D, K70E/Q/T, L74I, V75L, and Y115F - were more common among individuals receiving a first-line TDF-containing compared to a first-line thymidine analogue-containing regimen.

Conclusions: These 12 TDF-selected TRAMs will be important for monitoring TDF-associated transmitted drug-resistance and for determining the extent of reduced TDF susceptibility in individuals with VF on a TDF-containing regimen.

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

Popping S, Verbon A, Nichols BE, Boucher C, Vijver van de D, Geerlings S, Reiss P, Sighem van A, Kroon FP, Brinkman K.

Date of approval: 24 June 2015

Background: Cost-effectiveness analyses are used to provide the most health benefits at the lowest costs for HIV care. Quality adjusted life years (QALYs), are key in assessing health benefits in a cost-effectiveness analysis. Unfortunately, QALYs available in literature are outdated and obtained at a time when antiretroviral drugs were more toxic and CD4 treatment thresholds were low.

The first part of this study aims to measure QALY scores using the validated EuroQol-5-dimension questionnaire (EQ-5D-5L) among HIV-positive individuals. We will assess the QALY scores among different groups of people living with HIV (PLWHIV). In addition, the measured QALY scores will be combined with cost and clinical data to assess the cost effectiveness of HIV care.

The second part of the study aims to assess the additional cost of late presenters in HIV care. In Europe, as many as 50% of HIV-positive individuals present late to care. Late presentation is associated with high morbidity from AIDS-defining malignancies and opportunistic infections which may substantially increase the cost of care.

Methods: To measure the QALY scores, a longitudinal observational study was initiated at the Erasmus Medical Center outpatient clinic. Consecutive HIV-positive adult individuals are

ONGOING RESEARCH PROJECTS

eligible to fill out the EQ-5D-5L questionnaire during their doctor's appointment. We measured the compliance and feasibility of the EQ-5D-5L in the first two months of the study (pilot phase). Since June 2016, patients at the HIV outpatient clinic have been asked to fill-out the EQ-5D-5L. In addition, since December 2018, patients who consented to the electronic study have received an email with a personal link to the online EQ-5D-5L. The gemstracker software, facilitated by the Erasmus MC, is used to send out and collect the EQ-5D-5L questionnaires. PLWHIV who did not consent to the electronic form, could still participate in the study by filling out the EQ-5D-5L forms at the outpatient clinic.

All collected QALY scores are combined with clinical data using the SHM cohort. In addition, we combine the QALY scores with cost. QALY difference between patient groups, start of treatment, and treatment duration will be analysed. Furthermore, QALY data will be compared to the general Dutch population and to the UK population of PLWHIV. In addition cost-effectiveness analysis of HIV care will be performed.

For the second part of the study, we used SHM data from individuals who first initiated ART between 1 July 2012 and 1 July 2013 to investigate the cost of late presenters. In addition, we will compare this to individuals who first initiated ART between 1 July 2014 and 1 July 2016. Costs of ART, hospitalisation, outpatient visits, co-medication and HIV-laboratory tests were calculated. Factors independently associated with high non-ART costs, were determined by multivariable logistic regression, including parameters with P<0.1 from the univariable analysis.

Results: From June 2016 until January 2019 a total of 1297 EQ-5D-5L questionnaires were filled out. From those, 96 were with the electronic version, with a compliance of 70%. The compliance with the paper version was measured in the pilot phase and showed a high compliance of 90%.

We included 918 patients, of whom 333 filled out a second questionnaire and 42 a third and 4 a fourth questionnaire. 78.1% of our patients were male. The median age at moment of enrolment was 49.0 (38.0-56.0). Most PLWHIV had MSM (55.5%) as mode of transmission followed by heterosexual contact (34.1%). Of PLWHIV who filled out the EQ-5D-5L 44.9% were of non-Dutch origin. From this group 24.7% originated from sub-Saharan Africa, 22.2% from south America, and 18.1% from the Caribbean.

Preliminary results show a high median QALY score of 0.87 (interquartile range 75.0-90.0) which is comparable to the Dutch population. Our results show limited problems with mobility, self-care, or daily activities for HIV-infected individuals. However, almost a third of the HIV-infected individuals experience pain/discomfort or anxiety/depression problems. Similar results are found in the UK population, where PLWHIV scored lower on anxiety/depression than the general population.

ONGOING RESEARCH PROJECTS

We are currently compiling a combined dataset with clinical data, QALYs and cost. Further analyses will follow.

For the second part of the study:
A total of 1,149 individuals were included with a median age of 40 years (interquartile range (IQR) 30-47) and median CD4 nadir of 330 cells/µl (IQR 229-420). 652 (56.7%) patients were late presenters and 226 (19.7%) presented with advanced disease. Nearly half (42.5%) of patients with advanced disease were of non-Dutch origin, compared with 32% in the total cohort. The mean cost per patient was €13,919 (standard deviation (SD) €8,301) of which €11,208 (SD €4,258) represented ART cost and €2,711 (SD €7,186) non-ART costs. Higher non-ART cost were calculated in individuals with advanced disease, €6,403 (SD €14,631), ascribed to more hospitalisation and, to a lesser extent, comedication. Few patients drive the non-ART cost resulting in a high SD. The ART cost was similar regardless of infection stage at entry into care. Factors that contributed independently to higher non-ART cost include CD4-cell count, AIDS-defining illness, regimen switching, and malignancies.

Conclusions: The EQ-5D is an adequate tool to measure QALY scores during outpatient consultations for HIV-infected individuals. Obtained QALY scores are similar to the Dutch population, however PLWHIV have a lower score on the anxiety/depression module.
Late presenters are considered to be more costly. Higher costs are mainly ascribed to the non-ART costs, due to hospitalisation and, to a lesser extent, co-medication.

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, Wit FWNM, Rokx C, Leyten EMS, Lowe SH, Brinkman K, Bierman WFW, van Kasteren MEE, Postma AM, Bloemen VCM, Bouchtoubi G, Hoepelman AIM, van der Ende ME, Reiss P, Rijnders BJA.

Date of approval: 2 March 2016

Background: Use of integrase inhibitor-containing cART is associated with a fast HIV-RNA decline and increase of CD4 cells. These factors are also associated with development of IRIS: a pathological inflammatory response against antigens of opportunistic infections (OI). Whether use of integrase inhibitors (INI) increase the risk of IRIS is unknown, as phase 3 studies only include few late presenters.

ONGOING RESEARCH PROJECTS

Methods: Observational study in the ATHENA cohort. Patients who initiated cART after 03-2009 and who had CD4 T-cells <200 cells/mm^3 were selected if they met one of the following criteria: 1) OI prior or after initiation of cART, 2) use of corticosteroids <12 months after start cART, or 3) died <12 months after start cART. Manual chart review was performed to further investigate whether they developed IRIS. IRIS was defined according to the predefined definition of French *et al.* ($IRIS_{FRENCH}$) or as diagnosed by the treating physician ($IRIS_{CLINICAL}$). The two primary endpoints of this study were the incidence of $IRIS_{FRENCH}$ and $IRIS_{FRENCH+CLINICAL}$.

Results: A total of 672 patients met the criteria. As we had collected data of 356 patients in 2016, the charts of the remaining 416 patients were reviewed in 2017. Baseline characteristics of patients who initiated an INI-containing cART regimen (n=155) did not differ from those who initiated a non-INI-containing cART regimen (n=517). Cox regression showed that use of INI was independently associated with $IRIS_{FRENCH}$ and $IRIS_{FRENCH+CLINICAL}$ (HR 1•91, 95% CI 1•17-3•10, p<0•01 and HR 1•80, 95% CI 1•25-2•60, p<0•01). Only raltegravir, but not elvitegravir and dolutegravir, was associated with IRIS: HR 3•18 (95% CI 2•03-4•98, p<0•01).

Conclusions: We found that use of raltegravir is associated with development of IRIS in cART-naïve HIV-infected late-presenters. This might be a biased result, as raltegravir was prescribed to specific patient populations. These results have to be confirmed in a large randomised controlled trial before conclusions can be drawn from these findings.

I16060 Evaluation of dolutegravir use in the treatment of HIV in the Netherlands: focus on switchers and adverse events

Bollen P, Hakkers CS, Boender TS, van Crevel R, Brouwer AE, Hoepelman AIM, Reiss P, Wit FNMW, Arends JE, Burger D.

Date of approval: 30 August 2016

Background: Unexpectedly high rates of neuropsychiatric adverse events (NPAEs) and drug discontinuation have been reported with the use of dolutegravir-based combination antiretroviral treatment (cART) for HIV in observational studies compared to randomised controlled trials.

Methods: We included all HIV-1 positive adults, enrolled in the AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort, first initiating dolutegravir-based or elvitegravir-based cART between December 2013 and February 2016. cART discontinuation rates for 1) any reason, 2) adverse events (AE), and 3) NPAEs were determined separately for cART-naive and cART–experienced patients. Associations between patient characteristics, the specific integrase-inhibitor used, and time-to-cART discontinuation, were evaluated through multivariable Cox proportional hazards models.

ONGOING RESEARCH PROJECTS

Results: 3,416 patients were included of whom 1,051 (31%) were cART-naive and 2,365 (69%) were cART–experienced. cART-experienced patients were more likely to discontinue both dolutegravir-based and elvitegravir-based cART for any reason and for AE than cART-naive patients (log-rank; p<0.0001). Factors associated with discontinuation due to AE, independent of the use of dolutegravir-based or elvitegravir-based cART, were being of non-western origin and having CD4 cell-count <200 or ≥500 cells/mm^3 for cART-naive individuals and being aged ≥60 years, ever or current use of psychotropic drugs, and a history of discontinuing prior cART due to AE for cART-experienced patients. Discontinuation due NPAEs in cART-experienced patients was associated with age ≥60 years.

Conclusion: In the Netherlands, patient characteristics contribute more to the risk for dolutegravir or elvitegravir-based cART discontinuation for AE than the particular integrase-inhibitor used. Especially cART–experienced ageing populations seem susceptible for discontinuation for AE and NPAE after start of dolutegravir- or elvitegravir-based cART.

I16091 Longitudinal virological outcomes and factors associated with virological failure in HIV infected young adults in the Netherlands 1996–2016

Weijsenfeld AM, Wit FWNM, Pajkrt D.

Date of approval: 16 December 2016

Background: Achieving and maintaining viral suppression in young adults (18-24 years) living with HIV is challenging. Overall HIV viral suppression rates are lower in young adults than in older adults. Longitudinal data provide valuable insight into dynamics of viral suppression and variables of potential influence on HIV virological failure (VF), but is scarce in young adults living with HIV on combination antiretroviral therapy (cART).

Methods: We analysed data from the Dutch national HIV database of 816 young adults living with HIV on cART in the Netherlands from 2000-2015. VF was defined as two consecutive detectable plasma HIV-1 viral load (VL) measurements >200 copies/ml. Generalised linear mixed model analyses were used to assess HIV VF over time and identify risk factors associated with VF.

Results: VF during the study follow up occurred at least once in 26% of cases. The probability of experiencing VF decreased over the study period per calendar year (odds ratio [OR] 0.78, 95% confidence interval [CI];0.72; 0.85). Factors significantly associated with VF were being infected through heterosexual contact (OR 5.20, CI 1.39-19.38) and originating from Latin America or the Caribbean (OR 6.59, CI 2.08-20.92). Smaller, yet significant risk factors for VF were being infected through a blood transfusion or a needle accident (OR 9.93, CI 1.34-73.84, and having started with cART with a nadir CD4 count >500 cells/µl (OR 11.36, CI 2.03-63.48).

ONGOING RESEARCH PROJECTS

Conclusions: In our large cohort of young adults, the risk of VF has diminished over 15 years. Specific subgroups were identified as being at risk for suboptimal treatment.

I17093 The impact of mutations on the effectiveness of abacavir/lamivudine/dolutegravir regimens prescribed in treatment-experienced patients (The M184V/I – DTG study)

Olearo F, Kouyos R, Bonnet F, Yerly S, Wandeler G, Stoeckle M, Baettig V, Cavassini M, Gayet-Ageron A, Scherrer A, Schmid P, Bucher HC, Günthard H, Böni J, D'Armino A, Zazzi M, Bellecave P, Cazanave C, Daffau P, Rijnders B, Reiss P, Wit F, Calmy A.

Date of approval: April 2017

Background: To assess the impact of the M184V/I mutation on the risk of virological failure (VF) in patients with suppressed viremia on combination antiretroviral therapy switching to abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG).

Methods: A retrospective observational study based on prospectively collected data. We included treatment-experienced adults with HIV from five European cohorts who switched to ABC/3TC/DTG while having ≤150 copies/mL of HIV-1 RNA and at least one available plasma genotypic resistance test. Primary outcome was time to first VF (defined as two consecutive HIV-1 RNA measurements >50 copies/mL or one HIV-1 RNA measurement >50 copies/mL accompanied by a change in antiretroviral therapy before the next HIV-1 RNA measurement). We also analysed a composite outcome considering the presence of VF or virological blips, defined as an isolated detectable HIV-1 RNA >50 copies/mL followed by a return to virological suppression with any change in antiretroviral therapy.

Results: One thousand six hundred and twenty-six patients were included in the analysis (median follow up: 289 days; interquartile range: 154-441). Patients with evidence of M184V/I (n=137) were older and had a longer duration of virological suppression before the switch. The incidence of VF per 1000 person-years after the switch was 29.8 (11.2-79.4) in patients with documented M184V/I versus 13.6 (8.4-21.8) in patients without a documented M184V/I. In the propensity score weighted analysis, M184I/V was not associated with VF nor the composite endpoint (hazard ratio:1.5 [95% CI: 0.49-4.71]; hazard ratio: 1.66 [95% CI: 0.93-2.96], respectively).

Conclusions: Virosuppressed treatment-experienced patients switching to ABC/3TC/DTG have low VF rate within one year. Unweighted analysis indicates twice the VF rate with past M184V/I, however the effect is not statistically significant after controlling for multiple factors.

ONGOING RESEARCH PROJECTS

I17095 Evaluation of diagnosis, referral and treatment of acute HIV-1 infection at the Amsterdam STI clinic: trends over time

Dijkstra M, van Rooijen M, Hillebregt MM, van Sighem AI, Smit C, De Bree G, Hogewoning A, Heijman E, Hoornenborg E, Prins M, Prins J, Schim van der Loeff M, de Bree GJ.

Date of approval: 24 November 2017

Background: Immediate start of antiretroviral therapy (cART) during acute HIV infection (AHI) is beneficial for patients and reduces onward transmission. An AHI trajectory among men who have sex with men (MSM) was implemented in Amsterdam in 2015; MSM diagnosed with AHI were referred to start cART within 24 hours. We evaluated the AHI trajectory by comparing MSM diagnosed through the AHI trajectory and through routine strategies regarding the proportion of AHI (Fiebig I-II) among HIV diagnoses and the time between diagnosis and viral suppression.

Methods: Data from 1,013 MSM (2008-2017) newly diagnosed at the Sexual Health Clinic were linked with data from HIV treatment centres by a Trusted Third Party. We compared time between HIV diagnosis and viral suppression using the log-rank test for four cART-initiation policies: (1) start cART at CD4 <500 cells/mm^3 (2008-2011); (2) start cART at CD4 <500 cells/mm^3 and in patients with AHI (2012-2015); (3) universal start of cART (2015-2017); and (4) immediate start of cART, AHI trajectory (2015-2017).

Results: In 2015-2017, the proportion of AHI among HIV diagnoses was 52.6% (10/19) in the AHI trajectory and 4.2% (5/118) using routine diagnostic procedures. The median time between diagnosis and viral suppression for cART-initiation policy 1, 2, 3, and 4 was 569 (IQR 259-1031), 228 (IQR 129-435), 95 (IQR 63-136), 55 (IQR 31-72) days respectively, p<0.001.

Conclusions: Implementation of the AHI trajectory, along with changes in treatment guidelines, resulted in a higher proportion of AHI diagnoses and a decreased time between HIV diagnosis and viral suppression.

Publications

IN 2018

ATHENA

Health-related quality of life of people with HIV: an assessment of patient related factors and comparison with other chronic diseases
Engelhard EAN, Smit C, van Dijk PR, Kuijper TM, Wermeling PR, Weel AE, de Boer MR, Brinkman K, Geerlings SE, Nieuwkerk PT.
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Preconception use of cART by HIV-positive pregnant women increases the risk of infants being born small for gestational age
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PLoS One. 2018 Jan 19;13(1):e0191389. doi: 10.1371/journal.pone.0191389. eCollection 2018.

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Smit M, van Zoest RA, Nichols BE, Vaartjes I, Smit C, van der Valk M, van Sighem A, Wit FW, Hallett TB, Reiss P; Netherlands AIDS Therapy Evaluation in The Netherlands (ATHENA) Observational HIV Cohort.
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AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile
Boender TS, Smit C, van Sighem A, Bezemer D, Ester CJ, Zaheri S, Wit FWNM, Reiss P; ATHENA national observational HIV cohort.
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Trends in human immunodeficiency virus diagnoses among men who have sex with men in North America, Western Europe, and Australia, 2000-2014
Chapin-Bardales J, Schmidt AJ, Guy RJ, Kaldor JM, McGregor S, Sasse A, Archibald C, Rank C, Casabona Barbarà J, Folch C, Vives N, Cowan SA, Cazein F, Velter A, an der Heiden M, Gunsenheimer-Bartmeyer B, Marcus U, Op de Coul ELM, van Sighem A, Aldir I, Cortes Martins H, Berglund T, Velicko I, Gebhardt M, Delpech V, Hughes G, Nardone A, Hall HI, Johnson AS, Sullivan PS.
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< Back to page 56

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Liver decompensation in HIV/hepatitis B coinfection in the cART era does not seem increased compared to hepatitis B mono-infection
Lieveld FI, Smit C, Richter C, van Erpecum KJ, Spanier BWM, Gisolf EH, Vrolijk JM, Siersema PD, Hoepelman AIM, Reiss P, Arends JE.
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Rozhnova G, Heijne J, Bezemer D, van Sighem A, Presanis A, De Angelis D, Kretzschmar M.
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AGE$_h$IV

HIV-1 status is independently associated with decreased erectile function among middle-aged men who have sex with men in the era of cART
Dijkstra M, Van Lunsen RHW, Kooij KW, Davidovich U, Van Zoest RA, Wit FWMN, Prins M, Reiss P, Loeff MFSV; AGEhIV Cohort Study Group.
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Francesco D, Verboeket SO, Underwood J, Bagkeris E, Wit FW, Mallon PWG, Winston A, Reiss P, Sabin CA; Pharmacokinetic and clinical observations in PeoPle
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Reduced forced vital capacity among HIV-infected middle-aged individuals
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ART-CC

Antiretroviral pill count and clinical outcomes in treatment-naïve patients with HIV infection
Young J, Smith C, Teira R, Reiss P, Jarrín Vera I, Crane H, Miro JM, D'Arminio Monforte A, Saag M, Zangerle R, Bucher HC; Antiretroviral Therapy Cohort Collaboration (ART-CC).
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Increased non-AIDS mortality among persons with AIDS defining events after antiretroviral therapy initiation
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BEEHIVE

Easy and accurate reconstruction of whole HIV genomes from short-read sequence data
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< Back to page 67

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CASCADE

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COBRA

No evidence for accelerated ageing-related brain pathology in treated HIV: longitudinal neuroimaging results from the Comorbidity in Relation to AIDS (COBRA) project

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The 'COmorBidity in Relation to AIDS' (COBRA) cohort: Design, methods and participant characteristics

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Do people living with HIV experience greater age advancement than their HIV-negative counterparts?

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COHERE

Global trends in CD4 count at start of antiretroviral treatment: collaborative study of treatment programs

IeDEA and COHERE Cohort Collaborations.
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< Back to page 65

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Rohner E; AIDS-defining Cancer Project Working Group of IeDEA, COHERE in EuroCoord. The ATHENA (AIDS Therapy Evaluation in the Netherlands) national observational HIV cohort.
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D:A:D

Abacavir use and risk of recurrent myocardial infarction
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Gender differences in the use of cardiovascular interventions in HIV-positive persons; the D:A:D Study
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< Back to page 67

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Ryom L, Lundgren JD, El-Sadr W, Reiss P, Kirk O, Law M, Phillips A, Weber R, Fontas E, d'Arminio Monforte A, De Wit S, Dabis F, Hatleberg CI, Sabin C, Mocroft A; D:A:D study group.
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ECDC

Substantial heterogeneity in progress toward reaching the 90-90-90 HIV target in the WHO European region
Porter K, Gourlay A, Attawell K, Hales D, Supervie V, Touloumi G, Rosinska M, Vourli G, van Sighem A, Pharris A, Noori T; ECDC Dublin Declaration Monitoring Network.
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EPPIC

Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle- and high-income countries in Europe and Thailand: A cohort study
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< Back to page 67

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< Back to page 65

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< Back to page 68

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Earlier HIV diagnosis in Amsterdam after implementation of an early HIV infection awareness campaign
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van Sighem A.
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Models for case surveillance settings – ECDC model
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< Back to page 56

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Acute hepatitis C infection among HIV-positive adults in the Netherlands: a capture-recapture analysis of two national databases
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PrEP for MSM can result in reductions in HIV transmission and can be cost-effective, even with a small decrease in condom use
Reitsema M, van Hoek AJ, Wallinga J, van Benthem B, van Sighem A, Schim van der Loeff M, Xiridou M.
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Earlier HIV diagnosis among men who have sex with men in Amsterdam following interventions to increase awareness of early HIV infection
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The impact of frequent HIV testing on HIV transmission among MSM
Reitsema M, Visser M, van Benthem B, Wallinga J, van Sighem A, Schim van der Loeff M, Heijne J, Xiridou M.
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The paediatric continuum of HIV care in the Netherlands: from diagnosis in childhood to viral suppression in adulthood
Smit C, Wolfs T, Boender TS, van Rossum A, Reiss P, on behalf of the ATHENA observational cohort.
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Substantial decline in virological failure after combination antiretroviral treatment (cART) initiation in treatment-naïve HIV-positive adults in the Netherlands from 1996 to 2016
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Evaluating progress towards triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in the Netherlands, 2012-2015
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Does HIV-seroconversion affect the serum N-glycans profile, one possible biomarker of ageing? Insights from a longitudinal study
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Cost-effectiveness of increased HIV testing among Dutch MSM
Mangen MJ.
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The HIV continuum of care in Austria from 2010 to 2016: data and challenges
Leierer G, van Sighem A, Rieger A, Schmied B, Sarcletti M, Ollinger A, Haas B, Egle A, Rappold M, Zangerle R.
HIV Glasgow 2018, Glasgow, UK, 28-31 October 2018

Financial report

Income

In 2018, Stichting HIV Monitoring's (SHM) total income was €3,819,205. The majority of this income came from the structural institute grant for both HIV monitoring in the Netherlands and the Amsterdam Cohort Studies (ACS) that is awarded each year to SHM by the Centre for Infectious Disease Control Netherlands 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 2018, the total institute grant awarded for both purposes (HIV monitoring and ACS) amounted to €3,716,525. During the course of 2018, the wage-sensitive part of both components of the institute grant was increased by 2.96%, equivalent to €77,006. Of this, €23,982 was allocated to the ACS institute grant, and the remaining €53,024 to HIV monitoring in the Netherlands. Since the institute grant for 2018 was not spent in its entirety and the deferred grant revenue had reached its maximum level as of 31 December 2018, SHM expects to have to repay €23,686 to the RIVM. This will bring the total institute grant for 2018 to €3,769,845.

In addition, SHM participates in various national and international scientific collaborations involving observational cohort studies for which additional funding and contributions are received.

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). The grant for monitoring HIV in the Netherlands was set at €3,216,525 for 2018. Together with the above-mentioned wage-sensitive increase of €53,024 and after deducting the reimbursement of €23,686, the total institute grant for monitoring HIV in the Netherlands will amount to €3,245,863.

The RIVM officially established the final amount for the 2017 institute grant on 26 October 2018. As of 31 December 2017, the approved deferred VWS grant revenue stood at €366,420. In the 2017 annual accounts, the deferred grant reserve was nil. This revenue will be added to the 2018 annual accounts, in accordance with the RIVM's specification.

STRUCTURAL INSTITUTE GRANT FOR THE AMSTERDAM COHORT STUDIES

Since 1984, the ACS have been carrying out multidisciplinary research into the epidemiology, psychosocial determinants, natural course and pathogenesis of HIV-1 infection and, more recently, other blood-borne and sexually-transmitted diseases. The collaborating institutes, including the Academic

INCOME

Medical Center (AMC) in Amsterdam, the Public Health Service of Amsterdam (*Geneeskundige en Gezondheidsdienst*, GGD Amsterdam), and SHM, make use of data and body samples provided by HIV-1 positive individuals and people at high risk of acquiring 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 is responsible for the financial administration of the ACS and submits the application to the RIVM for the ACS' annual structural institute grant of €500,000. In 2018, an increase to the wage-sensitive part of the institute grant was applied retrospectively from 2015 onwards. This amounts to a total indexation of €23,982, as a result of which the grant awarded for the ACS in 2018 amounted to €523,982. In addition, the collaborating institutes within the ACS make a contribution to the coordination, management and financial management costs. GGD Amsterdam and the AMC each contribute individually to the storage of patient data and samples.

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 2018, SHM received €47,397 as income from HIV monitoring-related collaborations. This income is €77,027 less than that earned through collaborations in 2017. In 2018, SHM contributed to the following scientific collaborations:

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

The ECDC framework contract, which is divided into three parts, continued in 2018 and runs through to May 2022. A total sum of €72,380 has been reserved for SHM, €1,571 of which can be allocated to the 2018 financial year.

2. Comorbidity and Ageing with HIV (AGE_hIV)

In 2018 SHM received a sum of €27,126 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 ageing HIV-positive

INCOME

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 Amsterdam UMC, AMC site.

3. EuroSIDA and RESPOND study

In 2018, SHM supplied data for EuroSIDA and the RESPOND study, for which we received €8,081.

4. Other collaborations

SHM charged personnel costs (€4,389) relating to training and support to Stichting Rode Kruis Bloedbank in Curaçao. Personnel costs of €4,110 were also charged to AIGHD for data management work relating to the HIV Transmission Elimination Amsterdam (H-TEAM) initiative.

OTHER INCOME

In total, SHM received €1,964 from other sources of income. This sum represented compensation for SHM's contribution to organising the AIDS 2018 conference.

Expenditure

In 2018, SHM's total expenses were €4,132,160. Three main expense categories for 2018 are outlined below:

1. PERSONNEL COSTS

A substantial portion of SHM's expenses comprises personnel costs. In 2018, personnel costs once again represented the largest expense for SHM at €2,468,441, equivalent to 59.7% of the total expenditure. As per 31 December 2018, SHM had a total of 45 employees (with an average of 36.8 full-time equivalents [FTEs]). This number does not include employees of HIV treatment centres that carry out their own data collection and data entry and for which the treatment centres receive a payment from SHM.

2. MATERIAL COSTS

In 2018, material costs amounted to €701,115 and comprised license and maintenance costs for the national HIV monitoring database, housing costs, administration and consultancy costs, and other operational costs. Depreciation of the investment in the new data entry system commenced in February 2018. The new system, known as DataCapTree, went live on 5 February 2018.

3. PAYMENTS

Amsterdam Cohort Studies payment

SHM will transfer the RIVM funding earmarked for the ACS (€500,000) and the wage-sensitive increase of €23,982 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.

Payments to HIV treatment centres

SHM employees now carry out data collection and entry for 16 treatment centres. In 2018, SHM paid the remaining HIV treatment centres that carry out their own data collection and entry of data into SHM's database a sum of €58.51 per patient per year, based on the number of patients in active follow up on 31 December 2017. In 2018, a number of these hospitals requested data collection assistance from SHM. The associated costs were deducted from the payment made by SHM to the hospitals in question for patient data collection and entry. In addition, HIV treatment centres received a sum as a contribution towards the costs of collecting and storing patients' plasma.

In 2018, SHM paid HIV treatment centres a total of €526,727 for patient data collection and entry and for storage of patients' samples. An amount of €88,105 was deducted from the above-mentioned sum for the assistance in data collection provided by SHM employees.

Operating result

The operating result (€-313,408) indicates that the total costs in 2018 exceeded SHM's income. The depreciation costs associated with the development of the new data entry system, DataCapTree, (€217,031) will be deducted from the designated reserve earmarked for this project. A sum of €12,933 will be added to the deferred grant revenue, bringing this reserve to its maximum of 10% of the institute grant (€379,353). The remainder of the operating result (€-109,310) will be deducted from the general reserve.

RESERVES

SHM's total financial reserves (i.e., the deferred grant revenue, eligible costs reserve, general reserve, and designated reserve) amounted to €3,680,940 on 31 December 2018.

1. Deferred VWS grant reserve

As of 31 December 2018, the accumulated deferred grant revenue had reached the maximum permitted amount of 10% of the awarded institute grant and amounted to €379,353. The deferred grant revenue is intended to guarantee operational continuity over a certain period of time.

2. Eligible costs reserve

From 2002 through 2007, SHM built an eligible reserve of €382,206. This sum arose through financing from the Healthcare Tariffs Board (*Tarieven Gezondheidszorg*) and, later, the Dutch Healthcare Authorities (Nederlandse Zorgautoriteit). In 2020, SHM intends to release this reserve to the general reserve.

3. Designated reserve

In 2018, depreciation costs for the DataCapTree IT project (€217,031) were charged against the designated reserve. Consequently, as per 31 December 2018, the designated reserve earmarked for this project amounted to €1,063,270.

4. General reserve

The general reserve is not earmarked for a specific purpose and, on 31 December 2018, amounted to €1,856,111.

CONTINGENCY RESERVE AS OF 31 DECEMBER 2018

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.

Balance sheet

AFTER APPROPRIATION OF PROFITS

Assets	31-Dec-18 (€)	31-Dec-17 (€)
Fixed assets		
Intangible fixed assets	956,387	1,128,727
Tangible fixed assets	17,156	9,219
Total fixed assets	**973,543**	**1,137,946**
Current assets		
Accounts receivable	2,814	3,735
Receivables and accrued assets	186,972	175,167
Liquid assets	3,681,608	3,997,933
Total current assets	**3,871,394**	**4,176,835**
Total assets	**4,844,937**	**5,314,781**

Liabilities	31-Dec-18 (€)	31-Dec-17 (€)
Capital reserves		
Deferred grant revenue	379,353	0
General reserve	1,856,111	2,331,841
Eligible costs reserve	382,206	382,206
Designated reserve	1,063,270	1,280,301
Total capital reserves	**3,680,940**	**3,994,348**
Short-term liabilities		
Accounts payable	227,837	362,359
Short-term liabilities and accrued expenses	936,160	958,074
Total short-term liabilities	**1,163,997**	**1,320,433**
Total liabilities	**4,844,937**	**5,314,781**

Profit and loss account

Profits	2018 (€)	Budget 2018 (€)	2017 (€)
Structural institute grants	3,769,845	3,716,500	3,660,247
Other grants and financial contributions	47,397	210,700	124,424
Other revenue	1,964	500	21,114
Total profits	**3,819,205**	**3,927,700**	**3,805,785**
Operating costs			
Personnel costs	2,468,441	2,452,200	2,396,557
Depreciation of fixed assets	221,333	266,200	6,120
Other operating costs	479,965	531,500	632,978
Project-related costs	-183	7,000	4,266
Payments	962,604	932,500	908,441
Total operating costs	**4,132,160**	**4,189,400**	**3,948,362**
Year result	**-312,955**	**-261,700**	**-142,577**

Financial profit and loss	2018 (€)	Budget 2018 (€)	2017 (€)
Interest and similar revenue	681	5,000	2,968
Interest and similar expenses	-1,134	-1,500	-1,040
Total financial profit and loss	**-453**	**3,500**	**1,928**
Year result	**-313,408**	**-258,200**	**-140,649**

Appropriation of year result *The year result was distributed as follows:*	2018 (€)	2017 (€)
Added/ charged to deferred grant revenue	12,933	-53,013
Added/ charged to designated reserve for data entry system	-217,031	0
Added/ charged to the general reserve (i.e., other results of the separate SHM components)	-109,310	-87,636
	-313,408	**-140,649**

Risk disclosure

SHM's governing board and director/deputy 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

A culture of respectful and honest conduct forms the foundation for preventing any form of fraudulent conduct. SHM strives to foster such a culture within the organisation and has taken certain measures 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 improper use of SHM property. Furthermore, SHM has a 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 it are an important part of SHM's risk management. 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 residual risk.

2019 Budget

The budget for 2019 was adopted by SHM's governing board on 18 October 2018. The actual realisation for 2019 will differ from this budget. The most important components of the 2019 budget are described in further detail below.

BOARD RESOLUTIONS

As of May 2018, SHM had registered 20,675 individuals. Here, the term registered refers to all people for whom data were collected during the past two years. These included 225 children and 260 individuals who had died. Excluding those who had died, as of May 2018, a total of 20,415 registered individuals were still in care. This represents an increase of 593 compared with May 2017.

In 2019, the number of registered individuals is predicted to increase by 1.3% compared with 2018. This increase is based on the average increase in the number of HIV-positive individuals over time since 2004. Since 2004, the rate of increase has been dropping and it is expected to become negative for the first time in 2021. As a result, the number of individuals in care is expected to decline from that year 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 on age-related comorbidity and associated risk factors and medication use. In particular, interactions between antiretroviral drugs and comedication prescribed for comorbidities may adversely affect the effectiveness of HIV treatment. Moreover, comorbidity and multimorbidity, as well as poly-pharmacy, may also reduce treatment compliance in people living with HIV, further underlining the importance of collecting high-quality data on this topic. 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 [other than the traditionally registered AIDS-defining malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma]), it is also necessary to collect information on chronic liver disease, which is frequently, but not exclusively, associated with hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection. Moreover, with the advent of the now rapidly expanded 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.

2019 BUDGET

In recent years, SHM has invested in measures to allow efficient and effective registration of relevant data on HBV and HCV, including the use of DAAs in HCV treatment and the impact of this treatment. In the future, this investment 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 described in the 2017 and 2018 working plan and following an intensive preparatory period involving drafting a statement of requirements, carrying out market research, reference visits, negotiations and a legal review, SHM's board and the RIVM approved the development and implementation of a LogicNets-based system to replace the data entry system, Oracle Clinical (for which AMC's support was due to terminate on 1 January 2018). The project, which involved a collaboration between LogicNets, ICT automatisering, SHM and the AMC's ADICT (abbreviated to 'LISA'), officially started on 24 May 2016 and was successfully completed on time on 5 February 2018. The tailor-made LogicNets data entry system, named DataCapTree, went live on 5 February 2018.

DataCapTree is built on a decision-support system. In other words, collection of information is guided by decision trees programmed within the system. This should mean that data collectors will spend less time on the data collection process. A total of 107 data collection protocols have been developed for the full data collection process, of which 36 essential protocols were built, tested and accepted by all test groups by the time the system went live.

Data collection in Oracle Clinical ended on 31 December 2017. During January 2018, data collectors received training at the SHM head office and locally at their data collection site. On 5 February 2018, data collection subsequently started in the new system, with the 36 tested and accepted protocols. Up until early 2019, the remaining protocols will continue to go into production on a rolling basis, following test and acceptance by all test groups. Once all the protocols are live, it will be possible to carry out an evaluation of the system and an effect measurement. Depending on the findings of the evaluation, an update of the system may be scheduled in 2019. In addition, functional adjustments will also be carried out in 2019 and, where necessary, the system will be expanded.

At the end of 2019, the complete system will have been in use for a full year and it will be then be possible to measure the anticipated improvement in efficiency in the various data collection processes. In preparation, a method by which to measure the effect of DataCapTree will be developed during the course of 2019.

Another part of the LISA project involved the construction of a new and more modern structure within the data warehouse to allow for the possibility of

2019 BUDGET

importing data from external sources in the future. This functionality means SHM will be prepared for future developments that may allow more data to be imported directly from the HIV treatment centres' clinical data warehouses. SHM plans to carry out a pilot study in 2019 to test and develop this functionality.

In contrast to the previous situation with Oracle Clinical, functional management of the new data entry system is now carried out by SHM. This means that SHM is able to programme new query lists and data entry screens independently. This functionality and associated work processes will be further defined in 2019. Finally, in 2019, the possibility of adding new protocols will be put to the test in practice when SHM implements the pilot project for the registration of viral hepatitis C mono-infection.

GRANTS/OTHER FINANCIAL CONTRIBUTIONS IN 2019

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 2019. In 2018, the RIVM awarded SHM a sum of €3,216,525. In addition, on 5 September 2018, the wage-sensitive part of the 2018 grant was indexed by 2.96%, providing a structural addition of €77,006. This brings the total 2018 institute grant for HIV monitoring in the Netherlands to €3,293,531. The 2019 budget was based on this sum.

The institute grant for the 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 Amsterdam UMC, AMC site, and GGD Amsterdam. SHM 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.

Following the National Health Council's advice and the associated National Hepatitis plan to register viral hepatitis, a steering committee set up by the Dutch Society for Internal Medicine (*Nederlandse Internisten Vereniging,* NIV) and the Dutch Association of Gastroenterologists and Hepatologists (*Nederlandse Vereniging Van Maag-Darm-Leverartsen,* NVMDL) reached consensus in 2017 to work together with SHM to collect high-quality data on people with a hepatitis mono-infection. Consequently, in the third quarter of 2018, SHM started a pilot registration of people in care with a hepatitis C mono-infection. The costs of this pilot study, estimated to be €124,900, will be financed by the working group of internists/infectious disease specialists and gastroenterologists with hepatitis expertise that was established by the NIV.

2019 BUDGET

Contributions totalling €103,000 have been budgeted for the following projects in which SHM is involved: AGE$_h$IV, ECDC, H-TEAM, CIPHER/ EPPICC, Curaçao data collection, and EuroSIDA-RESPOND (to which SHM contributes data and expertise).

STAFFING IN 2019

The budgeted number of SHM staff for 2019 is equivalent to 37.4 FTEs. Compared with 2018, this represents an increase of 0.8 FTEs. This increase is mainly due to the appointment of additional data collectors for the hepatitis C pilot study.

EXPENSES IN 2019

The budget for 2019 takes into account the salary increases announced in the newly-approved 2018-2020 collective labour agreement (CAO) for university medical centres in the Netherlands. As such, SHM has included a 3% salary increase as of 1 January 2019 in the budget. SHM also follows 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 2019, the gross salaries will amount to €2,024,600. A total of 16.2% of the gross salaries, equivalent to €309,700, has been budgeted for social security contributions. This rate is based on the 2018 budget realisation. The budgeted sum for pension costs for 2019 is €188,200, which is equivalent to nine percent of the gross salaries.

A sum of €101,200 has been budgeted for 2019 to cover other personnel costs, comprising travel expenses (home-office commute and business travel), training, occupational health and safety services, and staff insurances.

The budget approved by SHM's governing board for the LISA/DataCapTree IT project, namely €1,291,000, was not exceeded. The investment amounted to €1,285,000 and depreciation of these costs will be spread across 5 years, starting from 5 February 2018 (the date on which the system went live). The depreciation costs will be charged against the designated reserve for this project.

The estimated costs for 2019 for the use and maintenance of all automation systems (LogicNets system, data warehouse, website hosting, development and maintenance, administration software, and office IT equipment) are €5,400 lower than in 2018 (€204,000 versus €209,400) due to implementation of DataCapTree. In 2017, when the AMC's Oracle Clinical system was still in use, these costs amounted to €361,200.

2019 BUDGET

Other operating costs for 2019 (housing, consultants, office supplies, reporting, and conferences) are more or less equivalent to those of 2018 (€275,000 versus €271,800).

Payment to those HIV treatment centres that carry out data collection themselves will decrease in 2019 because SHM will no longer refund the fee for support and coordination. As a result, a sum of €500,000 has been budgeted for these payments, compared with €526,700 in 2018.

In 2019, the ACS institute grant of €500,000 that is expected to be paid to SHM will be paid out fully to the two organisations that carry out this study, namely Amsterdam UMC, AMC site, and GGD Amsterdam.

FINANCIAL RESULTS

SHM's estimated financial result for 2019 is €-257,000.

This 2019 financial result is distributed across the following SHM activities and projects:

HIV monitoring in the Netherlands	-37,030
LISA/DataCapTree IT project	-257,000
Other projects	37,030
Total result for 2019	**-257,000**

2019 BUDGET

Profits	Budget 2019 (€)
VWS / RIVM grant for HIV monitoring in the Netherlands	3,293,500
VWS / RIVM grant for ACS	500,000
Project-based grants and financial contributions	203,000
Other revenue	20,200
Total profits	**4,016,700**
Operating costs	
Salary, social security, & pension costs	2,581,200
Other personnel costs	42,500
Subtotal personnel costs	*2,623,700*
Depreciation of fixed assets	266,000
IT expenses	204,000
Third party services	62,500
Subtotal third party costs	*266,500*
Housing expenses	111,000
Travel and conference expenses	43,000
Reporting	24,500
Office expenses	27,500
Project-specific expenses	6,500
Subtotal other operating costs	*212,500*
Payments Amsterdam Cohort Studies	500,000
Payments HIV treatment centres	405,500
Subtotal payments	*905,500*
Total operating costs	**4,274,200**
Year result	**-257,500**
Financial profit and loss	
Interest and similar revenue	2,000
Interest and similar expenses	-1,500
Total financial profit and loss	**500**
Year result	**-257,000**

Note: The negative financial result for 2019 is due to the incidental depreciation and other costs related to the new LISA/DataCapTree data entry system.

Appendix

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, human immunodeficiency virus (HIV), 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 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.

TERMINOLOGY & DEFINITIONS

CD4 (T4) cell
CD4+ T-lymphocyte, or T4 cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by HIV. 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.

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.

DAAs
Direct-acting antivirals (DAAs) are new-generation drugs that treat hepatitis C virus infection by targeting specific steps in the hepatitis C virus life cycle. There are different classes of DAAs, defined by their mechanism of action and therapeutic target.

DNA
Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert its own genetic material 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*).

TERMINOLOGY & DEFINITIONS

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 affects the liver and 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 Vereniging
Dutch HIV association.

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 don't directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs the half-life of interferon. Pegylated interferon alpha is used to treat chronic hepatitis C infection.

Mono-infection
When a person has only one infection.

TERMINOLOGY & DEFINITIONS

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 (ARV) 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
A measure of time used in medical studies that combines the number of persons and their time contribution (e.g., in years) to the study. In the ATHENA cohort, person years generally refer to the cumulative number of years that individuals were followed by SHM.

TERMINOLOGY & DEFINITIONS

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.

Pseudonymisation
Pseudonymisation is a privacy-enhancing technique that replaces personal identifiers with coded data. Certain identifiers (such as gender and age) are included in the record, but personal information is removed or replaced by a randomised string of characters. The data collected from people living with HIV are stored in SHM's database in a pseudonymised form. Pseudonymisation takes place within the HIV treatment centre and the key to the code is only available to the HIV treating physician.

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

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

RIVM
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.

TERMINOLOGY & DEFINITIONS

Sustained virologic response (SVR12 or SVR24)
A measure of the response to hepatitis C virus (HCV) treatment. SVR12 or SVR24 indicates an undetectable level of HCV in blood 12 or 24 weeks, respectively, after completion of antiviral therapy for chronic HVC 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.

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

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

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

VWS
Dutch ministry of Health, Welfare and Sport.

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

HIV Monitoring