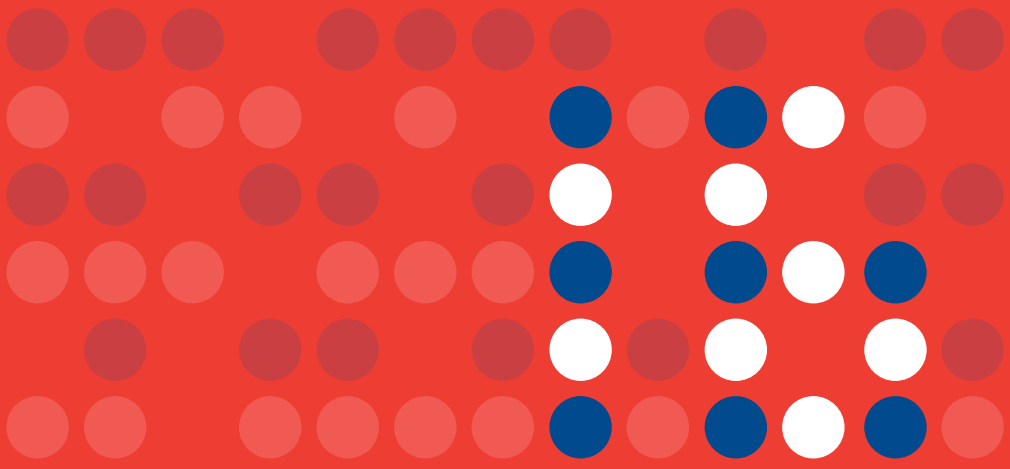
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2016

Summary and Recommendations

The Monitoring Report 2016 is now available online at www.hiv-monitoring.nl



Monitoring of HIV in the Netherlands

Each year, around the time of World AIDS Day on 1 December, Stichting HIV Monitoring (SHM) publishes the Monitoring Report. This 15th report provides a comprehensive overview of trends in the epidemic and treatment of infection with the human immunodeficiency virus (HIV) in the Netherlands. The Summary and Recommendations highlights the key findings and recommendations presented in the Monitoring Report.

The Monitoring Report 2016 is available online, in a fully searchable and downloadable PDF. In addition, all figures and tables included in the report will be made available in the form of a downloadable PowerPoint presentation. The report and accompanying figures can be found on our website, www.hiv-monitoring.nl.

Stichting HIV Monitoring

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

SHM comprehensively maps the HIV epidemic and HIV treatment outcomes in the Netherlands, thereby contributing to the knowledge of HIV. Working with all HIV treatment centres throughout the Netherlands, SHM has developed a solid 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.

In addition to receiving the national reports, healthcare professionals are provided with treatment centre-specific reports to enable them to monitor and optimise care provided in their centres. Moreover, SHM data are also made available upon request for use in HIV-related research, both in the Netherlands and internationally. The outcome of SHM's research and international collaborations provides tangible input into policy guidelines and further improves HIV care in the Netherlands.

For further information about SHM or to sign up for our newsletter, please visit our website: www.hiv-monitoring.nl or send us an email: hiv.monitoring@amc.uva.nl.

HIV Monitoring

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Foreword

This Summary and Recommendations highlights the key trends over time in the HIV epidemic in the Netherlands and makes a number of important recommendations based on the findings published in the Monitoring Report 2016 on human immunodeficiency virus (HIV) Infection in the Netherlands.

The full Monitoring Report is available online (www.hiv-monitoring.nl) and includes a section on the HIV Monitoring Programme, providing an update on the number of newly-registered HIV diagnoses, the changes over time in the characteristics of the HIV-positive population at the time of diagnosis, trends in prescription of combination antiretroviral therapy (cART), the effects of cART, the development of resistance to antiretroviral drugs, and morbidity and mortality in the HIV-positive population. This section also contains information on specific patient populations, including those with viral hepatitis co-infections and HIV-1-positive children and pregnant women. This year, we have further expanded the chapter on quality of care in the 26 HIV treatment centres in the Netherlands. The quality of care indicators are reported based on treatment centre size; treatment centres are invited to enquire about their individual indicator results. As in previous years, the Special Reports section includes a chapter on the results from the Amsterdam Cohort Studies and one on HIV in Curaçao.

Once again, my thanks go to the HIV treating physicians and public health experts who acted as reviewers of the Monitoring Report 2016. We are very grateful for their valuable input. I would also like to thank the HIV treating physicians, HIV nurse consultants and staff of the diagnostic laboratories in the HIV treatment centres, along with the data collecting and monitoring staff both within and outside SHM. Without their ongoing motivation and tireless contributions, our work would be impossible. Finally, I extend my gratitude to those people living with HIV who generously agree to provide data to SHM. It is only through this partnership between both professionals and patients that we can further improve our insight into the many facets of HIV and HIV treatment, thereby continuing to improve the care for people living with HIV not only in the Netherlands, but also elsewhere around the world.

Professor Peter Reiss, MD

Director, Stichting HIV Monitoring

The HIV epidemic in the Netherlands

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

As of May 2016, a total of 18,866 persons living with HIV in the Netherlands (18,657 adults, and 209 children and adolescents) were known to be in care in one of the 26 designated HIV treatment centres. Of these 18,866, 95% (17,909) had started combination antiretroviral therapy (cART), and of these 17,909, 93% (16,739) had suppressed viraemia to below 100 copies/ml at the time of their last available HIV RNA measurement. These results are impressive when compared to figures from other parts of the world.

New diagnoses in 2015

In 2015, the majority (64%) of newly-diagnosed infections were in men who have sex with men (MSM), 28% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission. Of note, almost one quarter of all newly-diagnosed individuals in 2015 were 50 years or older. Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to approximately 900 new diagnoses in recent years. Although this decreasing trend continued in 2015, the projected number of diagnoses for that year (865) may have been underestimated as registration of HIV diagnoses for this year has not yet been finalised. Finally, overall, over 90 percent of persons newly diagnosed with HIV entered into specialised care within 6 weeks after diagnosis. There is little variation in these figures, regardless of where individuals were diagnosed.

CD4 count at diagnosis and start of cART

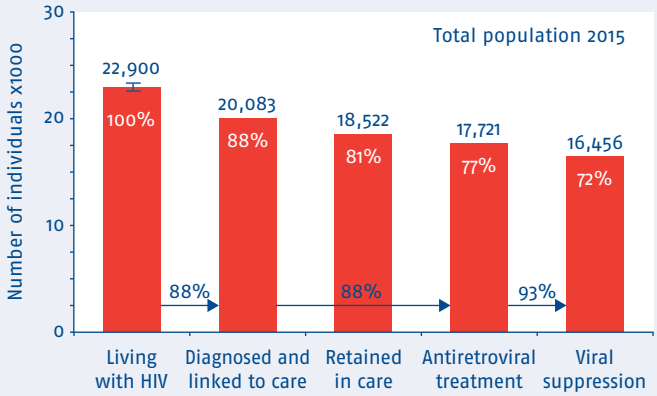
The rates of testing for HIV appear to be increasing in certain settings. Interestingly, the proportion of individuals with a previously negative HIV test has also increased (72% of MSM, 28% of other men and 42% of women diagnosed in 2015 had a known previous negative test). Moreover, fortunately, the proportion of individuals who are identified and start cART earlier in their infection (including during primary HIV infection) continues to increase, particularly amongst MSM. This is reflected in the CD4 count, both at diagnosis and at start of cART, gradually having risen over time to a median of 370 and 420 cells/mm^3, respectively, in 2015.

The likelihood of individuals starting cART at higher CD4 counts has also clearly increased. Whilst in 2014, 73% of individuals with a CD4 count of 500 cells/mm^3 had begun cART within 6 months of diagnosis, this proportion rose to 81% in 2015. Nonetheless, far too many individuals continue to present late for care. In 2015, 45% of newly diagnosed individuals presented late for care, i.e., with AIDS or a CD4 count less than 350 cells/mm^3, and 29% presented with advanced HIV disease, i.e., with a CD4 count less than 200 cells/mm^3 or AIDS. Generally, the likelihood of presenting late for care or with advanced HIV disease was greater for men other than MSM, individuals originating from South and Southeast Asia and sub-Saharan Africa, and individuals aged 45 years or older.

Continuum of HIV care in 2015

By the end of 2015, 22,900 individuals were estimated to be living with HIV in the Netherlands, of whom 2,800 were still undiagnosed. On the basis of this estimated number of 22,900 people living with HIV, a continuum of HIV care has been constructed to depict engagement in HIV care in 2015 across a few key indicators, the last one being the number of individuals with suppressed viral load (See *Figure 1*). By the end of 2015, 20,083 individuals, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM. In total, 18,522 individuals were considered to still be in care. The majority of these individuals, 17,721 in total, had started cART, and 16,456 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 72% of the total estimated population living with HIV and 82% of those diagnosed and ever linked to care had a suppressed viral load.

Figure 1: *continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2015.*



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

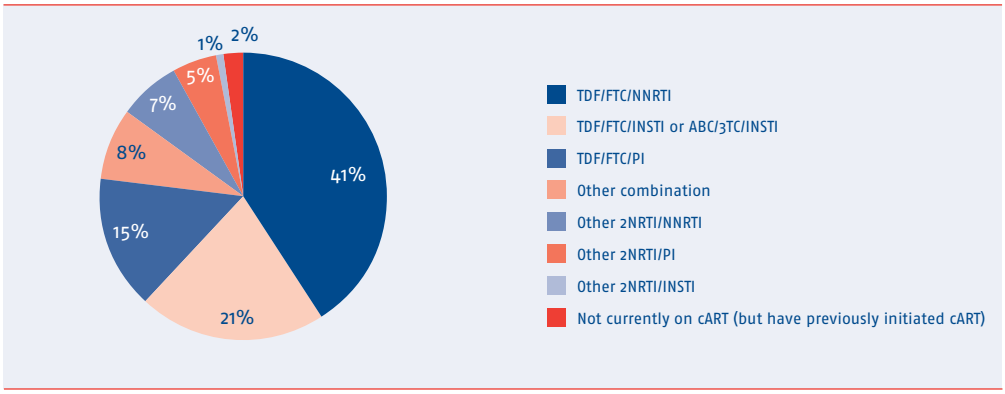
To achieve a significant decline in the rate of new infections, we continue to need improved transdisciplinary strategies for all factors sustaining the epidemic. These strategies should aim to simultaneously reduce the likelihood of HIV infection in key populations at risk, identify infected individuals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

Combination antiretroviral therapy in adults

In care and on cART in 2015

Initiation of cART following a diagnosis of HIV infection is taking place increasingly earlier in the Netherlands. In 2015, the majority of individuals who entered care and started cART in the Netherlands did so within a month after diagnosis. Concurrently, the median CD4 count at cART initiation has increased to 420 cells/mm^3. Among all HIV-positive individuals in care in 2015 who had ever started cART, the majority received a tenofovir-emtricitabine-based cART regimen combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI; 41%), a protease inhibitor (PI; 16%), or an integrase inhibitor (15%). Overall, integrase inhibitor-based cART was used by 27% of those in care in 2015: 14% received dolutegravir, 7% cobicistat-boosted elvitegravir and 6% raltegravir. cART use in 2015 in the Netherlands among HIV-positive individuals who started treatment is presented in *Figure 2*. Of those on cART with a plasma HIV RNA measurement in 2015, 97% had a suppressed viral load.

Figure 2: cART use in 2015 in the Netherlands among HIV-positive individuals who started treatment.



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

Initial regimen

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

Virological response

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

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

HIV drug resistance

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

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

Immunological response

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

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

Quality of care

Generally speaking, a number of different quality of care indicators showed limited variability across the 26 adult HIV treatment centres. Retention in care and viral suppression rates in the first 6 months on cART, as well as during long-term use of cART, were high across all centres, regardless of size. Across most of the centres, an increasing proportion of

individuals are starting cART sooner after entering into care, confirming that treatment centres are following new guidelines to offer cART to anyone with newly-diagnosed HIV, regardless of their CD4 count. Despite the increasing number of individuals starting cART within 6 months after entering care, some centres could further improve this figure among those individuals who enter care with CD4 cell counts above 350 cells/mm^3.

Variation in HCV screening

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

Morbidity and mortality

Mortality rates remain low in HIV-positive individuals in care in the Netherlands. There has been a sustained decline in death from AIDS, with a shift towards death from other causes. Non-AIDS comorbidities, including non-AIDS-defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease, comprise a sizable fraction of those other causes. Of note, however, the proportion of individuals dying of AIDS (26% of the total number of deaths) remained substantial between 2007 and 2015. This was largely driven by late presentation and late entry into care, and once again stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

Older age and comorbidities

Not surprisingly, older age was an important risk factor for comorbidities that are traditionally associated with ageing, notably cardiovascular disease and non-AIDS malignancies. In this context, it is important to note that the proportion of older individuals with newly-diagnosed HIV entering care in the Netherlands is substantial; in 2015, 23% were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 45% currently older than 50 years (42% in 2014, 39% in 2013). Of particular concern is the increasing proportion of individuals with multiple comorbidities, the risk of which appears to be increased in those with HIV, as demonstrated, for example, by data from the AGE$_h$IV Cohort Study, in which SHM collaborates with the Academic Medical Center, the Amsterdam Institute for Global Health and Development and the Public Health Service (GGD) in Amsterdam.

Cardiovascular risk

Despite the increasing age of the HIV-positive population, the proportion at high or very high cardiovascular risk only increased slightly over the period 2000-2015. This suggests that cardiovascular risk management may have improved over time. Significant room for further improvement remains, however, given the suboptimal use of statin therapy, antihypertensive therapy and anti-platelet therapy as secondary prevention following a myocardial infarction or ischaemic stroke, and the low uptake of these medications in the prevention of primary cardiovascular disease.

Non-AIDS malignancies

The crude incidence of non-AIDS malignancies in the Netherlands has remained stable over time, but the absolute number and proportion of deaths due to these malignancies has increased. In men we observed a decline in age-standardised incidence of non-AIDS malignancies, including anal cancer, possibly as a result of a reduction in risk factors such as smoking, screening and treatment for early (pre-malignant) stages of anal cancer, and a higher proportion of individuals living with higher CD4 cell counts in more recent years. The most common non-AIDS malignancies continue to be lung, anal, and head and neck cancers as well as Hodgkin's lymphoma, although the proportion of individuals diagnosed with other non-AIDS malignancies increased with increasing age.

Awareness of the role of modifiable, often lifestyle-related risk factors, like smoking, and their management by both physicians and people living with HIV offer important hope of ensuring a lower comorbidity burden and resilient ageing. This is particularly relevant for older individuals or those with another strong comorbidity risk factor, and applies not only to conditions such as cardiovascular disease and diabetes mellitus, but also to measures to prevent cancer, chronic kidney disease and bone loss. At the same time there is clearly room for improvement in the use of known effective biomedical interventions for primary and secondary cardiovascular disease prevention according to general guidelines.

Hepatitis B and C co-infections

Screening for hepatitis B (HBV) and C (HCV) co-infection has become part of the standard of HIV care in the Netherlands. As a result, the presence or absence of HBV or HCV infection is now documented for virtually all HIV-positive individuals in care in the Netherlands. Approximately 12% of individuals had evidence of ever having been exposed to HCV, 6% were documented as having chronic infection and 2% had acute infection. Seven percent of individuals were shown to have chronic HBV infection.

Overall, individuals with HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. For individuals with chronic HBV diagnosed after 2000, liver-related deaths have been significantly reduced, likely as a result of increasingly effective treatment for HBV through the use of tenofovir-containing cART.

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

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

HCV & direct-acting antiviral agents

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

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

The rapidly expanding availability of novel interferon-free regimens for HCV, together with optimised screening for HCV co-infection with time will hopefully limit the impact of HCV co-infection on long-term liver-related morbidity and mortality. To reduce the rate of incident HCV infection among the key affected population of MSM, regular screening for HCV among successfully-treated individuals is recommended for early detection of HCV re-infections, in combination with preventive behavioural interventions aimed at MSM.

HIV in pregnant women and in children

Pregnant women

Universal first trimester screening for HIV in pregnant women and the increasingly effective use of cART during pregnancy has made perinatal transmission of HIV extremely rare in the Netherlands, although cases of incident HIV infection following a negative first trimester screen have been documented later during pregnancy. Moreover, approximately 7% of HIV-positive pregnant women do not have fully suppressed viraemia around the time of delivery.

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

Children

Treatment outcomes for children living with HIV in the Netherlands and receiving care in one of the four designated paediatric treatment centres are generally favourable. These outcomes include long-term immunologic responses to cART, particularly in vertically-infected children who have started treatment below two years of age.

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

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

The Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS started shortly after the first cases of AIDS were diagnosed in the Netherlands, enrolling men who have sex with men (MSM) in a prospective cohort study from October 1984 onwards. A second cohort involving people who use drugs (PWUD) was initiated in 1985. The ACS aims to investigate the prevalence and incidence of HIV-1 infection and AIDS, the associated risk factors, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. More recently, ACS research has broadened to include the epidemiology of other blood-borne and sexually transmitted infections (STI) and their interaction with HIV.

Together with the AMC Department of Infectious Diseases, Department of Global Health, the Amsterdam Institute of Global Health and Development, and SHM, the Public Health Service Amsterdam (in part through the ACS), also importantly contributes to the ongoing follow up of HIV-uninfected participants of the AGE$_h$IV Cohort Study. This study, started in 2010, continues to provide very detailed information regarding the incidence of a broad range of ageing-associated comorbidities, as well as regarding risk factors and biomarkers associated with these conditions. It thereby provides important information to complement SHM's more general nationwide collection of data on clinical non-AIDS outcomes.

Within the ACS, different institutes collaborate to bring together the data and biological sample collections and to conduct research. Research highlights in 2015 within the ACS research programme include ongoing work into high-risk human papillomavirus (hrHPV) infections in MSM. Using the cohort from a previous study, H2M (HIV and HPV in MSM), that compared the prevalence, incidence, and clearance of hrHPV between HIV-negative and HIV-positive MSM, the H2M2 study was initiated in 2015 to identify potential predictors for high-grade anal intra-epithelial neoplasia in the HIV-infected MSM population. In addition, a second new study (the H2M3 study) aims to study long-term incidence and clearance of anal and penile hrHPV infections. Other research within the ACS research programme included work on the envelope glycoprotein (Env) trimer, whereby the conformation of soluble Env trimers was stabilised in closed, ground states. These closed trimers may be useful components of vaccines aimed at inducing broadly neutralizing antibodies. Finally, ACS research identified an important cellular component involved in HIV replication, namely the GTPase-activating protein-(SH3 domain)-binding protein 1 (G3BP1) that restricts HIV-1 replication.

HIV in Curaçao

SHM continues to provide assistance to Stichting Rode Kruis Bloedbank with data collection and monitoring of individuals with HIV in care at the St Elisabeth Hospital in Willemstad in Curaçao. In recent years, HIV-positive individuals in Curaçao appear to be diagnosed increasingly earlier in their infection, as shown by a declining proportion of patients presenting late for care. As a consequence, combination antiretroviral therapy is being started at increasingly higher CD4 cell counts. Although early start of treatment appears to be possible, long-term continuous follow up should be guaranteed to optimise the effect of treatment.