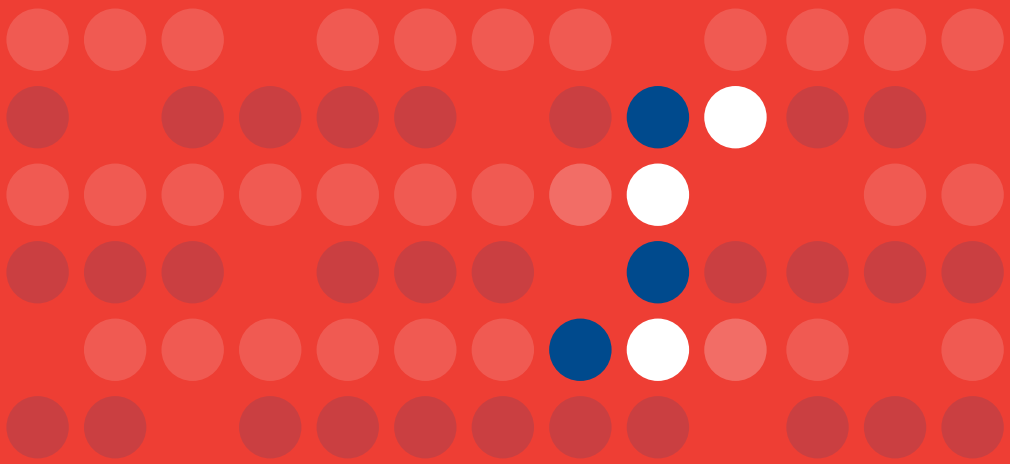
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2015

Summary and Recommendations

The Monitoring Report 2015 is now available for download at www.hiv-monitoring.nl



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 2015 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands.

The full Monitoring Report (available online) 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 infected population at the time of diagnosis, the effects of combination antiretroviral therapy, the development of resistance to antiretroviral drugs, and morbidity and mortality in the HIV-infected population. This section also contains information on specific patient populations, including those with viral hepatitis co-infections and HIV-1-infected children and pregnant women. A new addition this year is a chapter on quality of care in the 27 HIV treatment centres in the Netherlands, based on a number of quality of care indicators. 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.

In keeping with SHM's policy of reducing paper consumption, we will no longer be publishing the Monitoring Report 2015 as a printed book. Instead, it will be made 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.

My thanks go to the group of HIV treating physicians and public health experts who acted as reviewers of the Monitoring Report 2015. 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 also 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 patients registered in the Netherlands as of May 2015

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

New diagnoses in 2014

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

CD4 count at diagnosis and start of cART

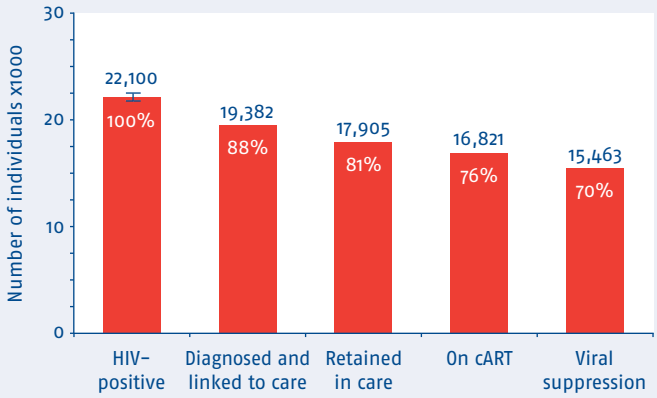
The rates of testing for HIV appear to be increasing in certain settings. Interestingly, the proportion of patients with a previously negative HIV test has also increased (73% MSM and 40% heterosexuals had a known previous negative test in 2014). Moreover, fortunately, the proportion of patients who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

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

Continuum of HIV care in 2014

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

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



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

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

Combination antiretroviral therapy in adults

First-line cART

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

Virological response

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

Virological failure

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

Importantly, genotypic sequence data are only available to SHM from a suboptimal proportion of patients, both at the time of virological failure as well as at time of HIV diagnosis prior to first

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

Immunological recovery

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

Tolerability of cART

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

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

Quality of care

Generally speaking, a number of different quality of care indicators showed limited variability across the 27 adult HIV treatment centres. Retention in care and viral suppression

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

Morbidity and mortality

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

Older age and co-morbidities

Not surprisingly, older age was an important risk factor for co-morbidities that are traditionally associated with ageing, notably cardiovascular disease and non-AIDS malignancies. In this context, it is important to note that the proportion of older individuals with newly diagnosed HIV entering care in the Netherlands is substantial; in 2014, 24% were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 42% currently older than 50 years (39% in 2013). Of particular concern is the increasing proportion of patients with multiple co-morbidities, the risk of which appears to be increased in those with HIV, as demonstrated amongst others by data from the AGEhiV Cohort Study, in which SHM collaborates with the Academic Medical Center, the Amsterdam Institute for Global Health and Development and the Public Health Service (GGD) in Amsterdam.

Cardiovascular risk

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

Non-AIDS malignancies

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

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

Hepatitis B and C co-infections

Screening for hepatitis B (HBV) and C (HCV) co-infection has, with time, increasingly become part of the standard of HIV care in the Netherlands. As a result, the presence or absence of HBV or HCV infection is now documented for virtually all HIV-positive patients in care in the Netherlands. Approximately 12% of patients had evidence of ever having been exposed to HCV, 6% were documented as having chronic infection and 1.6% had acute infection. Seven percent of patients were shown to have chronic HBV infection.

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

HCV & direct-acting antiviral agents

HCV genotype 1 infection was the most common genotype in patients with either chronic or acute HCV infection, and most patients with HCV infection were male and from the Netherlands or other European countries. Importantly, the incidence of acute HCV infection observed in 2014 amongst MSM remains high at a rate of 3.7 diagnoses per 1,000 person years (4.2 per 1,000 person years in 2013). This clearly indicates the need for continued preventive efforts in these men, including the use of the novel highly effective short-course well-tolerated 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.

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

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

HIV in pregnant women and in children

Pregnant women

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

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

Children & adolescents

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

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

The Amsterdam Cohort Studies

The Amsterdam Cohort Studies on HIV infection and AIDS (ACS) are unique prospective longitudinal cohort studies started in 1984-1985 and focused on MSM and injecting drug users (IDU) with HIV or at risk for HIV infection. As of 31 December 2014, 2,649 MSM and 1,680 IDU had been enrolled. The ACS continues to provide important insights into both viral and host, importantly including behavioural, factors that play a role in the transmission and pathogenesis of HIV and other (sexually transmitted) infections, including HCV, and that assist in rational design of public health interventions. Importantly, the ACS continues to provide highly reliable information on HIV and HCV incidence over time in the key affected populations. Among MSM, incident HCV infections are observed only among those who are infected with HIV; with respect to incident HIV infections, following a rise in infections after 1999, numbers have levelled off to around 1 case per

100 person years in 2014. Data on risk behaviour collected within the framework of the ACS continue to demonstrate that HIV-uninfected participants in the cohort report high rates of unprotected anal intercourse, primarily with steady, but also with casual partners.

Together with the AMC Department of Infectious Diseases, Department of Global Health, the Amsterdam Institute of Global Health and Development, and SHM, the GGD, including through the ACS, also importantly contributes to the ongoing follow up of HIV uninfected participants of the AGEhiV Cohort Study. This study, started in 2010, continues to provide very detailed information regarding the incidence of a broad range of ageing-associated co-morbidities, 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.

In collaboration with the RIVM-Centre for Infectious Disease Control (CIb), the GGD, the Jan van Goyen Medical Centre, the VU University Medical Center (VUmc), and the AMC, the ACS also collaborates in the H2M (HIV and HPV in MSM) study, which aims to compare the prevalence, incidence, and clearance of high-risk (hr) human papilloma-virus (HPV) infections between HIV-negative and HIV-infected MSM. Results thus far demonstrate that hrHPV infections are more common in HIV-infected than in HIV-uninfected men. This was true for both penile and anal infections. CD4 count (current or nadir) was found to have no effect on incidence or clearance.

Recent research published in 2014 includes the characterisation of envelope glycoproteins and broadly neutralising antibodies from two individuals in the ACS who produced broadly neutralising antibodies in their first year after seroconversion (elite neutralisers). Other highlights of research in 2014 using ACS data included a study that found that naturally-occurring HPV antibodies failed to confer protection against subsequent type-specific anal and penile HPV infection within one year in highly sexually-active adult MSM.

HIV on Curaçao

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

Monitoring of HIV in the Netherlands

Each year, around the time of World AIDS Day on 1 December, Stichting HIV Monitoring publishes the Monitoring Report. The 14th 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 2015 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-infected 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 patients. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care. In addition to 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

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