Monitoring Report 2014

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Contributing to the quality of HIV care

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001. Based in Amsterdam, SHM was appointed by the Dutch Minister of Health, Welfare and Sports *(Ministerie van Volksgezondheid, Welzijn en Sport)* as the national executive organisation for the registration and monitoring of HIV-infected patients in follow-up in Dutch HIV treatment centres.

Our mission:
To further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

www.hiv-monitoring.nl

HIV Monitoring

Colophon

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Monitoring Report 2014

Monitoring of Human Immunodeficiency Virus (HIV) infection in the Netherlands

The monitoring of HIV-infected adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 27 health institutes that are acknowledged by the Dutch Ministry of Health, Welfare and Sport as HIV treatment centres or subcentres. In addition, HIV-infected children and adolescents are monitored in four institutes that are recognised as paediatric HIV treatment centres.

In 2014 the following health institutes were involved as (sub)centres for adult HIV care (in alphabetical order of town):

1	Medisch Centrum Alkmaar (MCA)	Alkmaar
2	Flevoziekenhuis	Almere
3	Academisch Medisch Centrum- Universiteit van Amsterdam (AMC-UvA)	Amsterdam
4	HIV Focus Centre (DC Klinieken)	Amsterdam
5	Onze Lieve Vrouwe Gasthuis (OLVG)	Amsterdam
6	Sint Lucas Andreas Ziekenhuis	Amsterdam
7	Slotervaartziekenhuis	Amsterdam
8	Stichting Medisch Centrum Jan van Goyen (MC Jan van Goyen)	Amsterdam
9	VU Medisch Centrum (VUMC)	Amsterdam
10	Rijnstate	Arnhem
11	HagaZiekenhuis (locatie Leyweg)	Den Haag
12	Medisch Centrum Haaglanden (MCH, locatie Westeinde)	Den Haag
13	Catharina Ziekenhuis	Eindhoven
14	Medisch Spectrum Twente (MST)	Enschede
15	Universitair Medisch Centrum Groningen (UMCG)	Groningen
16	Kennemer Gasthuis	Haarlem
17	Medisch Centrum Leeuwarden (MC Leeuwarden)	Leeuwarden
18	Leids Universitair Medisch Centrum (LUMC)	Leiden
19	MC Zuiderzee	Lelystad
20	Maastricht UMC+ (MUMC+)	Maastricht
21	Radboud UMC	Nijmegen
22	Erasmus Medisch Centrum (Erasmus MC)	Rotterdam
23	Maasstad Ziekenhuis	Rotterdam
24	St Elisabeth Ziekenhuis	Tilburg
25	Universitair Medisch Centrum Utrecht (UMCU)	Utrecht
26	Admiraal De Ruyter Ziekenhuis	Vlissingen
27	Isala Klinieken (locatie Sophia)	Zwolle

Centres for the treatment and monitoring of paediatric HIV and AIDS were:

A	Emma Kinderziekenhuis, AMC-UvA	Amsterdam
B	Beatrix Kinderziekenhuis, UMCG	Groningen
C	Erasmus MC-Sophia	Rotterdam
D	Wilhelmina Kinderziekenhuis, UMCU	Utrecht


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15
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27
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A
5
6
14
11
18
7
8
12
9
25
D
10
C
22
23
21
26
24
13
20

Table of contents

Introduction

The Monitoring Report 2014 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 13th in the series published by the Stichting HIV Monitoring (SHM) since its founding in 2001. It provides a comprehensive review of trends over time in the HIV epidemic in the Netherlands and the effect of treatment.

Since 2002, SHM has officially been charged by the Dutch Ministry of Health, Welfare and Sport to monitor the HIV epidemic and the quality of HIV care in the Netherlands. Through the collection and maintenance of anonymised data from HIV patients in care in the 27 officially acknowledged HIV treatment centres throughout the country, our work contributes significantly to the knowledge of HIV. SHM also makes anonymised information available at both the centre and individual patient levels through a secure web-based environment, thereby enabling treating physicians to assess and improve patient care within their centres. As such, SHM importantly facilitates the assessment of the quality of care provided by the treatment centres. This has become a key component of these centres' formal certification according to the process developed jointly between the Harmonisation of Quality in the Healthcare Sector (*Harmonisatie Kwaliteitsbeoordeling in de Zorgsector,* HKZ) and the Dutch Association of HIV-treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB). Data from SHM can be used by individual treatment centres in collating and making available the key information required to support certification, whilst at the same time providing a nationwide benchmark. Moreover, once research proposals have been approved through appropriate procedures, treating physicians, as well as national and international researchers, can access aggregated data from all centres for scientific research purposes. Research conducted by SHM in collaboration with national and international research groups results in tangible advice geared to medical professionals, patients, government and healthcare at large.

The Monitoring Report, after the Summary and Recommendations, includes a section on the HIV Monitoring Programme, with detailed descriptions of the findings 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 (cART), 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.

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. A new addition this year is a chapter that aims to illustrate the potential for mathematical modelling and/or molecular epidemiology to improve our understanding of both the course of the HIV epidemic and its underlying dynamics, as well as the future consequences of an increasingly ageing population of patients with HIV in care. Finally, a web-based Appendix with supplementary tables and figures can be found on our website, www.hiv-monitoring.nl.

This year, we once again invited a small group of HIV treating physicians and experts in public health with an in-depth knowledge on relevant chapter topics to help shape content and act as reviewers. We are very grateful for their valuable input, which has further improved the report's clinical and public-health relevance. I thank them for their time and hope to continue this fruitful collaboration in the years ahead.

Finally, I would like to thank the HIV treating physicians, HIV nurse consultants and the staff of the diagnostic laboratories and facilities in the HIV treatment centres, along with the data collecting and monitoring staff both within and outside SHM. Without their ongoing motivation, tireless efforts and contributions, our work would be impossible. I also extend my gratitude to the patients 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 not only improve the care for people with HIV living in the Netherlands, but also provide guidance for prevention.

Professor Peter Reiss, MD

Director, Stichting HIV Monitoring

Summary & recommendations

Peter Reiss

The HIV epidemic in the Netherlands *(Chapter 1)*

As of June 2014, a total of 17,750 persons living with HIV in the Netherlands (17,558 adults, and 192 children and adolescents) were in care in one of the 27 designated HIV treatment centres. Of these 17,750, 91% (16,081) had started combination antiretroviral therapy (cART), and of these 16,081, 91% (14,602) 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. However, it is also important to realise that of the total 25,000 individuals that the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates were living with HIV in the Netherlands in 2012, 24% are likely to be unaware of their infection; this means that about 7,250 infected persons have not yet been diagnosed or linked to care and, importantly, still contribute to fuelling the epidemic.

In 2013, an estimated 1,100 patients newly entered care, which is comparable to the annual number reported in the last 3 years. In 2013, the majority (71%) of newly diagnosed infections were in men who have sex with men (MSM), 23% were acquired through heterosexual contact, 0.3% through injecting drug use (IDU), and 6% through other or unknown modes of transmission. Although the rate of newly diagnosed cases stabilised in the key affected population of MSM, and even steadily declined amongst MSM 35 to 44 years of age, it continued to increase in MSM both 25 years and younger and 55 years and older, as well as in heterosexuals 45 years and older. Of note, almost one quarter of all newly diagnosed patients entering into care in 2013 were 50 years or older. 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 whether individuals were diagnosed at a community health service or sexually-transmitted infections (STI) clinic, in a hospital or in a general practice.

The rates of testing for HIV appear to be increasing in certain settings. 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, although this increase is less pronounced in women and heterosexual men. This is reflected in the CD4 count, both at diagnosis and at start of cART, gradually having risen over time to a median of 417 and 360 cells/mm^3, respectively, in 2013. Of note, the likelihood of patients starting cART at higher CD4 counts has also clearly increased. Whilst in 2012, 29% of patients with a CD4 count of 500 cells/mm^3 had begun cART within 6 months of diagnosis, this proportion rose to 41% in 2013. Nonetheless, far too many patients continue to present late for care. In 2013, 43% of newly diagnosed patients presented late for care, i.e., with AIDS or a CD4 count less than 350 cells/mm^3, and 12% 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.

Improved transdisciplinary strategies that target all factors sustaining the epidemic are clearly 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 start combination antiretroviral therapy in a timely manner.

Combination antiretroviral therapy in adults and quality of treatment and care *(Chapters 2 and 3)*

Guidelines for the choice of first-line cART are closely adhered to in the Netherlands. Most patients who first initiated cART in 2013 and 2014 did so with a once-daily regimen, including tenofovir/emtricitabine as the backbone. The availability of novel single-tablet fixed-dose regimens, which combine tenofovir/emtricitabine with either the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine or the cobicistat-boosted integrase inhibitor elvitegravir, has clearly resulted in an increased use of these novel regimens.

Virological response to first-line cART has gradually improved during the era of cART: between 2011 and 2013, 87% of patients who first initiated cART achieved viral suppression to below the level of HIV-RNA quantification within 9 months. Importantly, earlier observations that patients younger than 30 years, those born outside the Netherlands, and those starting cART at a CD4 count >500 cells/mm^3 were less likely to achieve early viral suppression were no longer seen in those who had first begun treatment in the last three years. Of the patients who first initiated cART from 1999 onwards and were continuously on treatment and still in follow-up at 13.5 years, 94% had suppressed viraemia to less than 50 copies/ml.

Overall, 7.5% of the treatment-naïve 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.

International collaborative cohort analyses of the prevalence and incidence of patients experiencing triple-class virological failure (defined as failure of at least two nucleoside reverse transcriptase inhibitors (NRTI), one NNRTI and one ritonavir-boosted protease inhibitor), to which Stichting HIV Monitoring contributes data, have demonstrated an important improvement in the prognosis of such patients over time, both in terms of their

likelihood of achieving resuppression of viraemia and a reduced progression to AIDS and death. These trends are likely mainly driven by the availability of newer drugs with better tolerability, ease of use and limited cross-resistance, indicating the continued public health benefit of the introduction of new drugs.

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 2013, 13% of patients in care had a last available CD4 measurement less than 350 cells/mm^3. Patients who start cART at a CD4 count of more than 350 cells/mm^3 and have sustained fully suppressed viraemia after 8 years, including patients aged over 50 at the time of treatment initiation, are likely to achieve long-term CD4 counts similar to those in the general population. Similar trends were observed in the patients' ability to achieve a CD4/CD8 ratio greater than 1, which may be a marker of reduced residual immune activation whilst on suppressive cART. A median CD4/CD8 ratio above 1 was achieved after 3.5 and 8 years of suppressive cART, if CD4 cell counts at the start of cART were ≥500 cells/mm^3, and between 350 and 500 cells/mm^3, respectively. Further analyses, including in collaboration with other cohorts, are ongoing to address whether CD4/CD8 ratios independent of CD4 counts are associated with an increased risk of morbidity, including from non-AIDS events.

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. MSM, women and older patients were more likely to change their initial regimen because of toxicity. This likelihood was higher in MSM, especially when treatment was started at CD4 counts above 500 cells/mm^3.

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

Morbidity and mortality *(Chapters 1, 2 and 4)*

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 (NADM), cardiovascular disease (CVD) and chronic liver disease, comprise a sizable fraction of those other causes. Of note, however, the proportion of patients dying of AIDS (nearly 25%) remained substantial between 2007 and 2013. Once more, this seems to be 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. It is interesting to note that a recent analysis by the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), to which SHM is an important contributor, showed that the incidence of AIDS-defining illnesses was higher in individuals with a current CD4 count of 500 to 749 cells/mm^3 compared to those with a CD4 count of 750 to 999 cells/mm^3; in addition, the incidence did not decrease further at higher CD4 counts, even in patients suppressed on cART. These findings suggest that immune reconstitution may not be complete until the CD4 count increases to more than 750 cells/mm^3.

Similarly high CD4 counts achieved on cART, for example by commencing treatment at higher levels than the current average in the Netherlands, will contribute to preventing the most frequently-observed non-AIDS co-morbidities. However, the extent of this contribution remains to be determined. In particular, analyses of the most recent SHM dataset tend to show that prior AIDS and/or low nadir or current CD4 count are independently associated with an increased risk of cardiovascular disease, diabetes mellitus, chronic kidney disease and non-AIDS malignancies.

As expected, older age was also found to be an important risk factor for these co-morbidities that are traditionally associated with ageing. In this context, it is important to note that the proportion of older individuals with newly diagnosed HIV entering care in the Netherlands continues to increase over time; in 2013, 24% were 50 years or older compared to 20% in 2012. At the same time, the age distribution of the overall patient population with HIV in care in the Netherlands has also changed, with 39% currently older than 50 years (37% in 2012). 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. 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, show that both the presence of multiple co-morbidities and individual cases of hypertension, cardiovascular disease, peripheral arterial disease and chronic kidney disease are significantly more prevalent amongst those with HIV than in an uninfected control population of a similar age distribution. Besides older age, smoking and a positive family history (for hypertension, myocardial infarction, diabetes mellitus, or hypercholesterolaemia), duration of time spent with a CD4 count less than 200 cells/mm^3, increasing levels of markers of inflammation and innate immune activation, central obesity and longer prior exposure to ritonavir at total doses of ≥400 mg daily were independently associated with the prevalence of co-morbidity.

Ageing of the population in care may also explain why cardiovascular risk assessment using the algorithm developed by the Data Collection on Adverse Events of Anti-*HIV* Drugs (D:A:D) study group indicates a gradual increase from 12.8% in 2007 to 14.9% in 2013 in the proportion of patients at either high (5-10%) or very high (≥10%) risk of developing coronary

heart disease in the next 5 years. Although cardiovascular-risk management seems to have improved over time, the observation that over half of patients at high or very high risk were not known to be using a statin clearly indicates further room for improvement.

Whilst the overall incidence of non-AIDS-defining malignancies in the population with HIV in care has remained stable over time since the introduction of cART, the absolute number and proportion of deaths due to these malignancies has increased. Given the known markedly increased risk of anal cancer in HIV-infected MSM, the observation that the overall incidence of anal cancer slowly decreased over time from 1.2 cases per 1,000 person years in 2002-2003 to 0.6 cases per 1,000 person years in 2012-2013 is relatively reassuring. The gradual increase in CD4 count at time of HIV diagnosis and start of cART, which has been most notable amongst MSM, may have contributed to this trend. Collaborative analyses conducted on far larger datasets as part of the D:A:D study are needed to provide the statistical power to address the possible contribution of prolonged exposure to particular antiretrovirals on the risk of developing (individual) non-AIDS malignancies, including anal cancer.

Awareness of the role of modifiable, often lifestyle-related risk factors, like smoking, and their management by both physicians and HIV-infected 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 *(Chapter 5)*

Screening for hepatitis B (HBV) and C (HCV) co-infection has, with time, increasingly become part of the standard-of-care in the Netherlands. As a result, the presence or absence of HBV or HCV infection is now documented for virtually all HIV-infected patients in care in the Netherlands. Approximately 12% of patients had evidence of ever having been exposed to HCV, 6% were documented as having chronic infection and 1.5% had acute infection. Seven percent of patients were shown to have chronic HBV infection.

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 recent years amongst MSM remains high, having risen from 0.54 cases per 1,000 person years in 2003 to 5.5 per 1,000 person years in 2011, and 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 novel highly effective combination therapies for HCV.

An estimated 29% of HIV-infected patients overall and 24% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. Thus, it is important that efforts are undertaken to increase successful vaccination rates amongst this subgroup of patients.

Co-infected patients with a longer duration of infection were at increasing risk of progressing to chronic liver disease, including hepatocellular carcinoma (HCC). Ten years after a known diagnosis of viral hepatitis, HCC had developed in 3% of patients with chronic HCV and 1% of patients with chronic HBV. Of note, the likelihood of dying from chronic liver disease from 2000 onwards had declined in patients with chronic HBV, probably due to increasing use of tenofovir as part of combination therapy for HIV.

The uptake of HCV treatment has markedly increased in recent years. Among the HIV/HCV co-infected patients currently known to be in care, 59% have ever been exposed to treatment for their HCV infection. Among patients treated with a combination of pegylated interferon alpha (peg-IFN alpha) and ribavirin (RBV), only 39% overall could be considered cured. The direct-acting antivirals boceprevir or telaprevir became available in the Netherlands early in 2012. Combining either of these agents with peg-IFN alpha and RBV has improved response rates for HCV genotype 1 infection, yet the results remain suboptimal. Moreover, these regimens are associated with clinically significant toxicities and drug-drug interactions with cART. Of the 1,187 HCV/HIV co-infected patients who receive ongoing care in one of the Dutch HIV treatment centres, a total of 907 (76%) remain in need of effective HCV therapy, 485 of whom have never yet received HCV treatment and 422 in whom prior treatment was unsuccessful.

The availability of combinations of direct-acting pan-genotypic antivirals against HCV that are much better tolerated and more efficacious is eagerly awaited. It is hoped that these combinations, which will potentially allow the use of interferon-free regimens, will contribute to further reducing the burden of severe chronic liver disease, hepatocellular carcinoma and liver-related mortality amongst persons living with HIV. In addition, joined with additional preventive measures, they may contribute to reducing the rate of incident HCV infection among the key affected population of MSM.

HIV in pregnant women and in children *(Chapters 6 and 7)*

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.

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.
More and more of these children, however, are transitioning into adult care. Around 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 *(Chapter 9)*

This year, the Amsterdam Cohort Studies on HIV infection and AIDS (ACS) is celebrating its 30th anniversary as unique prospective longitudinal cohort studies started in 1984-1985 and focused on MSM and IDU with HIV or at risk for HIV infection. As of 31 December 2013, approximately 2,500 MSM and 1,600 IDU had been enrolled. The ACS continues to provide important insights into both viral and host (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 less than 1 case per 100 person years in 2013. 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.

In collaboration with the RIVM-Centre for Infectious Disease Control (CIb), the Public Health Service Amsterdam, 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 papillomavirus (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 oral, penile, and anal infections. Analyses of the incidence of hrHPV infections over the two-year follow-up period are underway. Other highlights of recent research include the observation that the reconstitution of CD4+ T cells following the start of cART is independent of the presence of X4-HIV variants, and the finding that HVC/HIV-coinfected individuals, compared to HIV-monoinfected individuals, not only have an increased risk of liver-related, but also of AIDS-related death.

HIV on Curaçao *(Chapter 10)*

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. A temporary discontinuation in data collection followed

the retirement of the previous data collector on the island, but with the help of SHM, a new data collector has recently been trained. In recent years, HIV-infected 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, combination antiretroviral therapy is being started at increasingly higher CD4 cell counts. The quality of monitoring and treatment offered to HIV-infected patients has also improved considerably. However, adherence to treatment and retention in care remain suboptimal.

Monitoring programme report

1. The HIV epidemic in the Netherlands

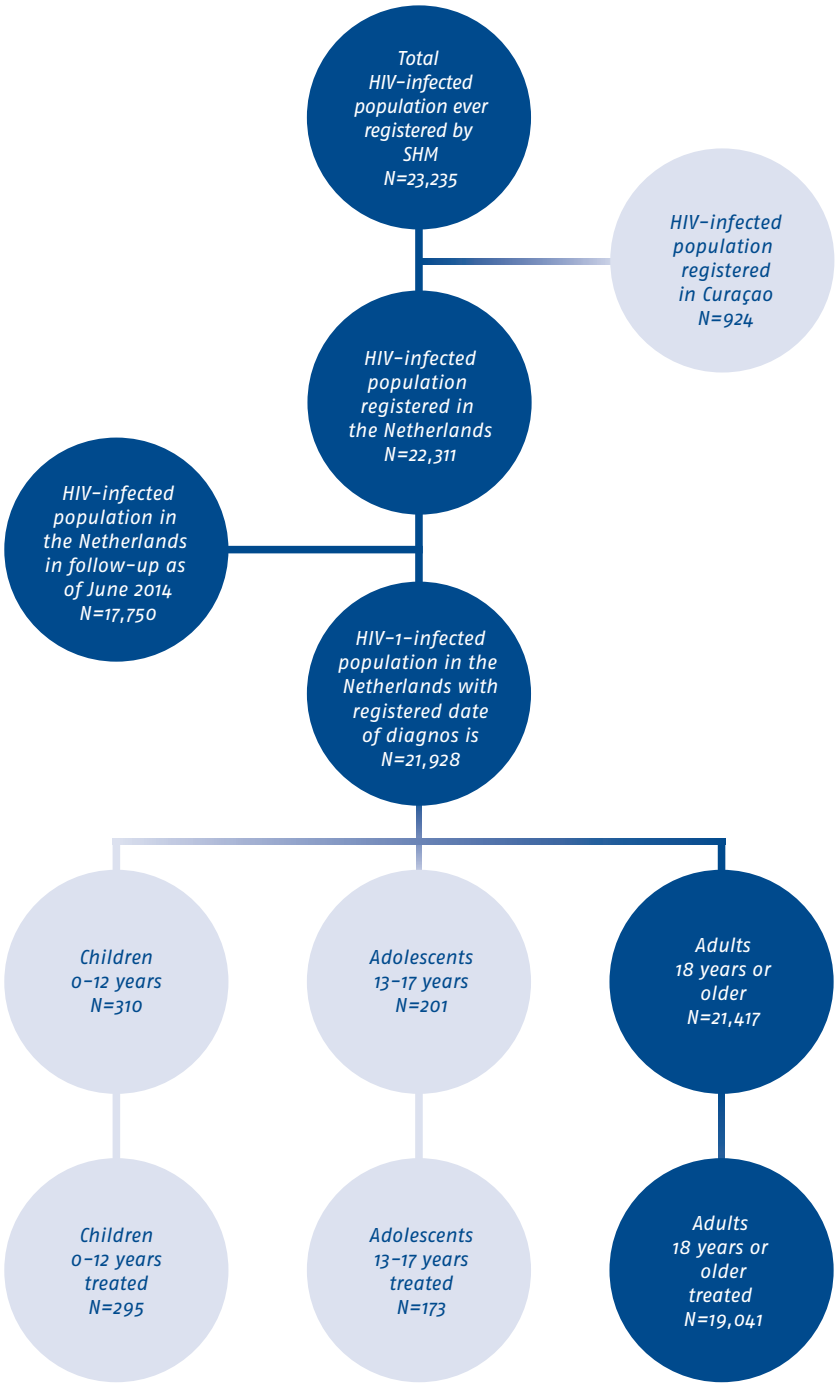
Ard van Sighem and Eline op de Coul

Introduction

For more than 10 years, Stichting HIV Monitoring (SHM) has collected demographic and clinical information from almost all patients infected with human immunodeficiency virus (HIV) who have been in care since 1996 in one of the 27 HIV treatment centres in the Netherlands. One of SHM's main achievements is a detailed knowledge of the characteristics of the HIV-infected population and its evolution over time. This chapter focuses mainly on the adult HIV-infected population, whilst children and adolescents are described in more detail in *Chapter 6*.

As of June 2014, 23,235 HIV-infected patients had ever been registered by SHM; of those, 22,311 were followed in one of the HIV treatment centres in the Netherlands *(Figure 1.1)*, with a total follow-up time since diagnosis of 203,759 person years. The remaining 924 patients were registered in the St. Elisabeth Hospital in Willemstad, Curaçao, and are discussed in more detail in *Chapter 10*. Of the 22,311 patients, the majority were infected with HIV-1 (21,999; 99%). A small group of patients, 95 in total, were infected with HIV-2, whilst 61 patients had antibodies against both HIV-1 and HIV-2. Serologic results were not yet available in the SHM database for 156 recently registered patients. Although the majority of the 1143 patients newly registered since June 2013 were diagnosed in 2013 or 2014, 22% of those newly registered were diagnosed in or prior to 2012.

Figure 1.1: Overview of the HIV-infected population registered by Stichting HIV Monitoring (SHM) as of June 2014.



Population – in care

Patients in clinical care

In total, 17,750 (80%) of the 22,311 registered patients, comprising 17,558 adults and 192 minors (less than 18 years of age), were still under clinical observation *(Figure 1.1; Table 1.1; Web Appendix 1.1)* as of June 2014. Of the 4,561 patients who were no longer in clinical care, 2,271 (50%) had died, and 975 (21%) had moved abroad. Patients were considered to be in clinical care if data were available in 2013 or 2014 and they were known to be alive. This definition reflects present-day clinical practice in which some patients who respond well to treatment and have no complications from treatment are seen only once a year by their treating physician[1].

Table 1.1: Characteristics of the 17,750 HIV-infected patients in clinical care as of June 2014. An extended version of this table is available on the SHM website (Web Appendix Table 1.1).

	Men (n=14,271, 80%)		Women (n=3,479, 20%)		Total (n=17,750)	
	n	%	n	%	n	%
Transmission						
MSM	10,753	75	–	–	10,753	61
Heterosexual	2,273	16	3,035	87	5,308	30
IDU	252	2	96	3	348	2
Blood (products)	146	1	91	3	237	1
Other/unknown	847	6	257	7	1,104	6
Current age (years)						
0–12	57	0	60	2	117	1
13–17	38	0	37	1	75	0
18–24	271	2	93	3	364	2
25–34	1,729	12	655	19	2,384	13
35–44	3,435	24	1,177	34	4,612	26
45–54	5,105	36	951	27	6,056	34
55–64	2,645	19	369	11	3,014	17
≥65	991	7	137	4	1,128	6
Region of origin						
The Netherlands	9,558	67	1,010	29	10,568	60
Sub-Saharan Africa	1,037	7	1,469	42	2,506	14
Western Europe	845	6	129	4	974	5
South America	942	7	316	9	1,258	7
Caribbean	559	4	177	5	736	4
Other	1,282	9	372	11	1,654	9
Unknown	48	0	6	0	54	0

	Men (n=14,271, 80%)		Women (n=3,479, 20%)		Total (n=17,750)	
	n	%	n	%	n	%
Years aware of HIV infection						
<1	599	4	81	2	680	4
1–2	1,717	12	286	8	2,003	11
3–4	1,798	13	349	10	2,147	12
5–10	4,135	29	967	28	5,102	29
>10	5,913	41	1,757	51	7,670	43
Unknown	109	1	39	1	148	1

Legend: *MSM=men who have sex with men; IDU=injecting drug use.*

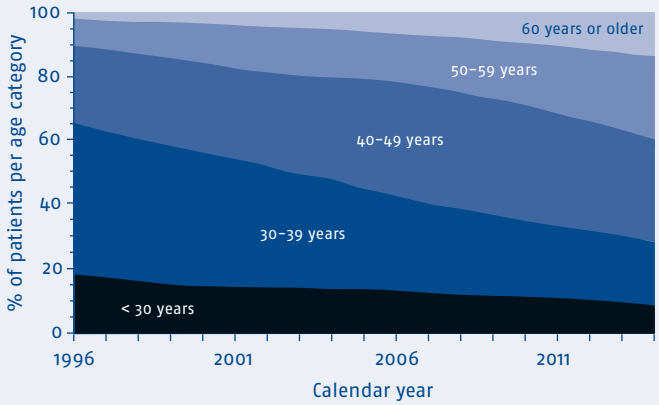
Retention in care

Of the 14,072 patients who enrolled in HIV care during the past 10 years, 732, or 5%, were lost to care before 2013 and were not reported as having died or moved abroad. Retention in care was highest for patients of Dutch origin: 96% were estimated to be still in care after 10 years. Of the patients of Sub-Saharan African origin, 71% of men and 81% of women were still in care after 10 years, as were 87% of men and 90% of women originating from other regions. Retention in care improved with increasing age at the time of entry into care: for every additional 5 years of age at the time of entry, patients were 8% less likely to be lost to care.

Ageing population

The median age of the population in clinical care currently stands at 47 years (interquartile range [IQR], 39-54) and has been increasing since 1996 *(Figure 1.2)*. This increase in age is mainly a result of the improved life expectancy of HIV-infected patients after the introduction of combination antiretroviral therapy (cART). In addition, patients are being diagnosed at increasingly older ages, as will be discussed later in this chapter. As a result, almost two out of five patients currently in care (39%) are 50 years or older, including 43% of men and 26% of women; 13% of the patients are 60 years or older *(Web Appendix Table 1.1)*. As the HIV-infected population ages, it is to be expected that the number of patients with age-related comorbidities will increase in coming years, thereby complicating the management of their HIV infection (see *Chapter 4*).

Figure 1.2: Increasing age of the HIV-infected population in clinical care over calendar time. In 1996, 19% of the patients in care were younger than 30 years of age, whereas 9% were 50 years or older. In 2014, these proportions were 8% and 39%, respectively, whilst 13% of patients in care were 60 years of age or older. The proportion of patients in clinical care as of 1 June of each calendar year is shown according to those who were <30 years of age, 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 years or older.



Duration of infection

On average, patients in clinical care as of June 2014 received their HIV diagnosis 10.3 years previously. Thus, a large group (43%) of those in care have been living with HIV for more than 10 years, whilst 9% had done so for more than 20 years. The average time since diagnosis was 9.8 years for MSM, 9.6 years for heterosexual men, and 10.7 years for heterosexual women. The majority of injecting drug users (85%) received their HIV diagnosis more than 10 years ago, which reflects the greatly decreasing number of new infections occurring via this route.

Treatment combinations

All together, 91% of the patients in care were treated with cART, compared with 87% in last year's report[1]. The most frequently prescribed currently used regimens, which accounted for 64% (2013: 57%) of all treatment combinations, were a combination of tenofovir/emtricitabine and either efavirenz (24%; 2013: 26%), nevirapine (15%; 2013: 15%), ritonavir-boosted darunavir (9%; 2013: 7%), rilpivirine (8%; 2013: 3%), or ritonavir-boosted atazanavir (8%; 2013: 8%). A backbone of tenofovir/emtricitabine was used by 74% (2013: 70%) of the patients, whilst abacavir/lamivudine was used by 12% (2013: 12%) and zidovudine/lamivudine was used by 6% (2013: 8%). Additional drugs in the regimen included efavirenz, used by 28% (2013: 32%) of the patients, nevirapine (23%; 2013: 25%), atazanavir (12%; 2013: 13%), darunavir (16%; 2013: 13%), rilpivirine (8%; 2013: 3%), and raltegravir (8%; 2013: 7%).

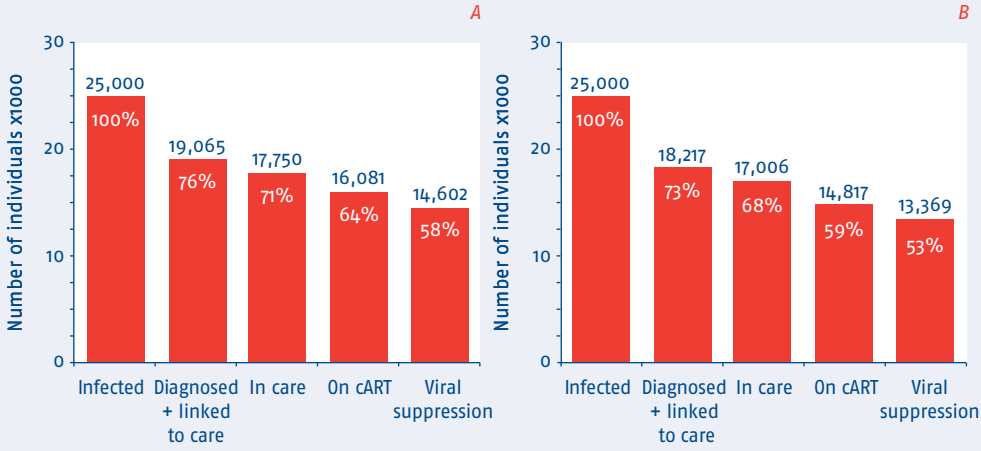
Clinical condition

The median current CD4 count was relatively high at 600 (IQR, 447-780) cells/mm^3, partly as a result of treatment and partly as a result of earlier diagnosis, as shown later in this chapter. CD4 counts were similar between men and women, although men infected via heterosexual contact had lower CD4 counts than their female counterparts (*Web Appendix Table 1.1*). For all patients in care, the most recent viral load measurement was below 500 copies/ml for 85% and below 100 copies/ml for 82%. About one-fifth (22%) of the patients had ever been diagnosed with an AIDS-defining disease; 56% of these patients were diagnosed with AIDS concurrently with their HIV diagnosis.

Continuum of HIV care

According to recent estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS), between 20,000 and 34,000 people were living with HIV in the Netherlands in 2012 [2]. On the basis of an approximate number of 25,000 people living with HIV, a continuum or 'cascade' of HIV care has been constructed to depict engagement in HIV care across a few key indicators, the last one being the number of individuals with suppressed viral load (*Figure 1.3*) [3]. It should be noted that in the Netherlands the total number of diagnosed HIV-infected individuals is unknown; only the number of diagnosed patients who are linked to care and registered by SHM can be reliably determined. Patients were considered to have viral suppression if their most recent HIV RNA measurement was below 100 copies/ml. With such low RNA levels, the probability of transmission of HIV is very low, so new infections would be prevented [4]. Overall, 58% of the total infected population and 77% of those diagnosed and linked to care had a suppressed viral load. Likewise, 61% of the estimated total population with HIV had RNA levels below 500 copies/ml (*Web Appendix Figure 1.1*).

Figure 1.3: (A) Continuum of HIV care for the total estimated HIV-infected population in the Netherlands as of June 2014. According to UNAIDS, between 20,000 and 34,000 people were living with HIV in the Netherlands in 2012. In total, 19,065 patients were ever linked to care, registered by SHM, still alive, and not reported as having moved abroad (22,311 registered patients minus 2,271 patients who died minus 975 patients who moved abroad). Of these patients, 17,750 were still in care and 16,081 had started combination antiretroviral treatment (cART). In total, 14,602 patients of the patients in care had a most recent RNA measurement below the limit of quantification or below 100 copies/ml. (B) Continuum of HIV care as presented in the Monitoring Report 2013[1].



Legend: cART=combination antiretroviral therapy.

Population – diagnosis

HIV-1-infected individuals

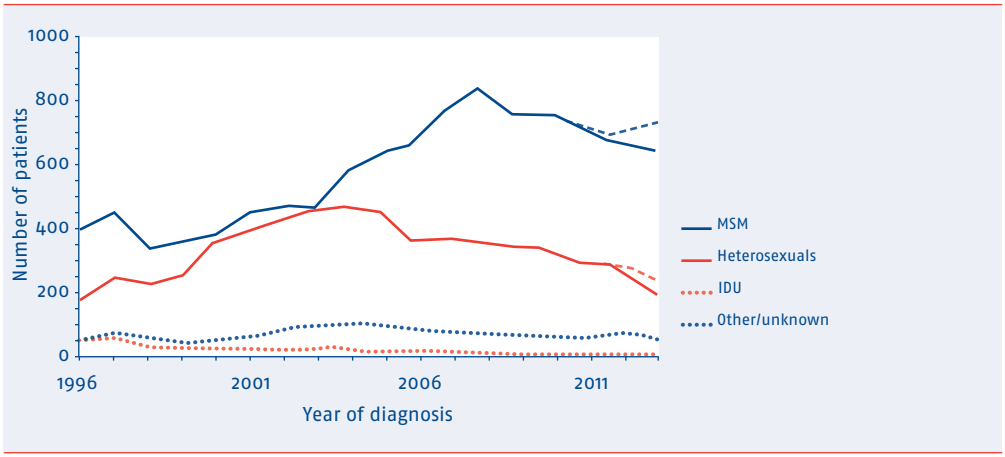
Having briefly discussed the HIV-infected population currently in clinical care, we will now focus on the 21,417 patients who were diagnosed with HIV-1 as adults with a recorded date of diagnosis (*Figure 1.1*). The majority of these patients were MSM (12,653 [59%]); the rest were infected mainly via heterosexual contact (2,977 men [14%] and 3,620 women [17%]) (*Web Appendix Table 1.2*). For 741 (3%) of the patients, the reported mode of transmission was injecting drug use, whilst 261 patients (1%) were infected by exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 5% (1,165) infections.

No further increase

Since the 1990s, the annual number of new diagnoses amongst MSM steadily increased from approximately 400 to well above 800 in 2008 (*Figure 1.4*). From 2009 onwards, however, the registered number of diagnoses has been considerably lower, ranging

between 700 and 750 per year, thus marking an end to the trend of an increasing number of diagnoses[1]. In fact, the increase may have slowed down as early as 2006, since the number of new diagnoses in 2007 and 2008 may have exceeded the long-term trend due to the introduction of opt-out testing for HIV at sexually transmitted infections (STI) clinics across the country at about that time[5]. Nevertheless, it appears that the increase in frequency of testing and in the proportion of patients diagnosed early in the course of their infection, which is discussed later, has not yet been sufficient to have induced a clear reduction in the number of new HIV infections and a resulting convincing decline in the number of new diagnoses.

Figure 1.4: *Annual number of new HIV-1 diagnoses amongst adults, according to transmission risk group. In 2013, men who have sex with men (MSM) accounted for 71% of new diagnoses, infections via heterosexual contact for 23%, infections via injecting drug use (IDU) for 0.3%, and infections via other or unknown modes of transmission for 6% of the annual tally. The dotted lines indicate the projected number of diagnoses when the backlog in registration of HIV cases (3% in 2012, 11% in 2013) is taken into account.*



Legend: *MSM=men who have sex with men; IDU=injecting drug users.*

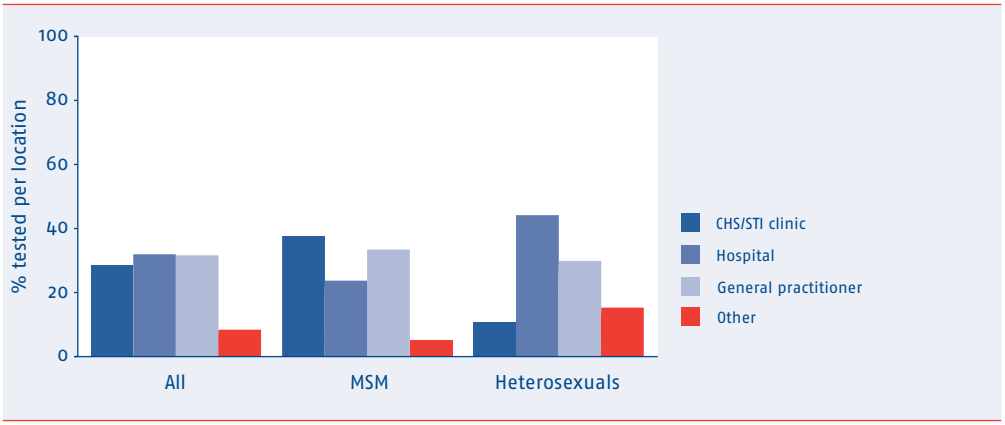
In the heterosexual population, the annual number of new diagnoses has declined to approximately 300 cases per year in the last few years. This decline, as shown later in this chapter, is largely the result of a reduced number of diagnoses in migrant populations. Injecting drug use is rarely reported any longer as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs.

Testing location

For 95% of patients diagnosed in 2008 or later, information on the location of testing was available. Overall, 29% received their first HIV-positive test result at a community health service or STI centre, 32% at a hospital, and 31% at a general practice (*Figure 1.5*). Amongst those

tested at community health services or STI clinics, 89% were MSM, 5% were heterosexual men, and 5% were heterosexual women. These numbers are comparable with those directly reported by STI clinics in 2013: 88% MSM, 4% heterosexual men, and 7% women[6].

Figure 1.5: Proportion of patients diagnosed from 2008 onwards stratified by location of testing and mode of transmission.



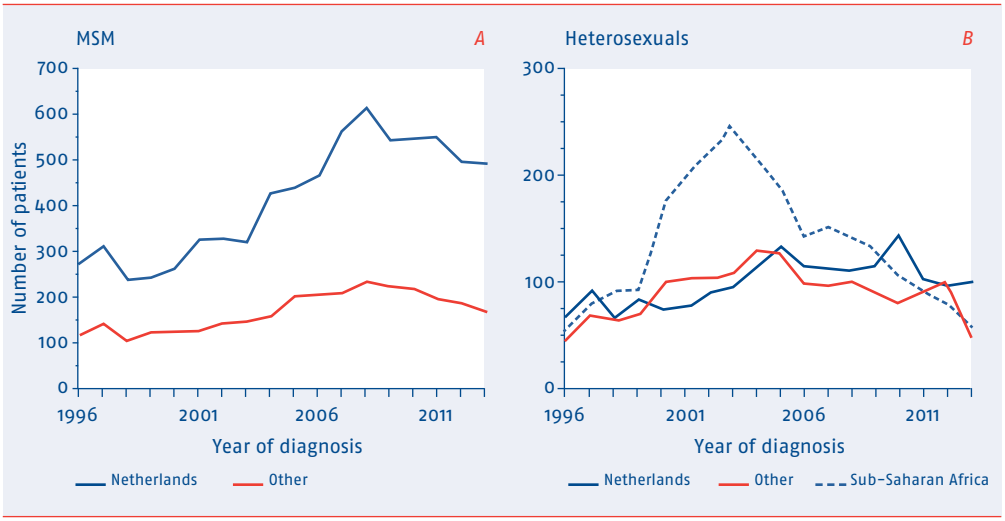
Legend: MSM=men who have sex with men; CHS=community health service; STI=sexually transmitted infection.

More patients of Dutch origin

In total, 72% of the patients infected via homosexual contact originated from the Netherlands, 10% from other European countries, 7% from South America, and 3% from the Caribbean (*Figure 1.6A*). In recent years, the proportion of MSM of Dutch origin has increased to 75% (*Web Appendix Table 1.3*). Minor changes over time have been observed in the proportion of patients from South America, which was 7% of the annual tally in the period before 2011 and 5% thereafter, and in the proportion of patients of Western European origin, which was 8% before 2011 and 5% thereafter.

In the heterosexual population, only 32% originated from the Netherlands, whilst 41% originated from Sub-Saharan Africa, 10% from South America, 5% from the Caribbean, and 4% from South and Southeast Asia (*Figure 1.6B*). However, the number of new diagnoses amongst Sub-Saharan Africans dropped sharply after 2003, probably partially as a result of stricter immigration laws that came into effect in the Netherlands at about that time. After 2010, 39% of the diagnosed heterosexual population was of Dutch origin, and 30% originated from Sub-Saharan Africa.

Figure 1.6: Annual number of diagnoses amongst (A) men who have sex with men (MSM) and (B) patients infected via heterosexual contact stratified by country of origin. Of the 12,653 MSM, 9,058 (72%) originated from the Netherlands, 1,294 (10%) from other European countries, 826 (7%) from South America, and 426 (3%) from the Caribbean. Amongst the 6,597 heterosexual patients, 2,641 (40%) originated from Sub-Saharan Africa, 2,120 (32%) from the Netherlands, 652 (10%) from South America, 361 (5%) from the Caribbean, and 280 (4%) from South and Southeast Asia. Note: data collection for 2012 and 2013 has not yet been finalised.



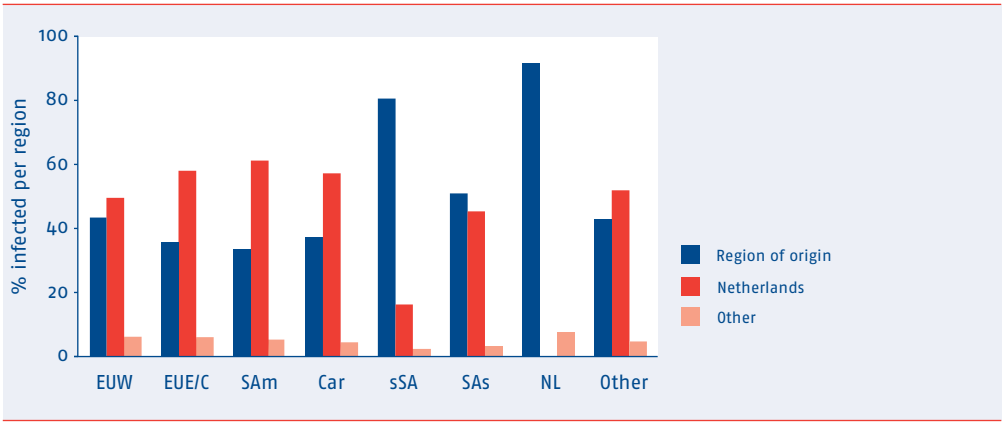
Legend: MSM=men who have sex with men

Geographical region of infection

For 15,678 (73%) of the diagnosed adult patients, the most likely country of infection was reported. The majority of the patients born in the Netherlands (93%) reported having been infected in the Netherlands (*Figure 1.7*). Although most of the patients born in Sub-Saharan Africa were infected in their region of origin (82%), 16% of these patients were probably infected in the Netherlands. The majority of patients from other regions, except those from South and Southeast Asia, were infected in the Netherlands.

As may be expected from the heterogeneity in the geographic region of origin, there were also major differences in the regions of infection between the major transmission groups. The majority of MSM (88%) were infected in the Netherlands. Moreover, the majority of patients infected via injecting drug use (81%) were infected in the Netherlands, whilst 10% of them reported having been infected in other Western European countries. The reported distribution across regions of infection was compatible with the HIV-1 subtype of the infected patients. Overall, 93% of MSM and 89% of drug users for whom the HIV-1 subtype was known were infected with subtype B virus, which is the dominant subtype found in Western countries.

Figure 1.7: Proportion of HIV-1-infected adults per region of origin who were infected in their own region of origin, the Netherlands, or elsewhere.



Legend: *EUW=Western Europe; EUE/C=Eastern and Central Europe; SAm=South America; Car=Caribbean; sSA=Sub-Saharan Africa; SAs=South and Southeast Asia; NL=the Netherlands; Other=other regions of origin.*

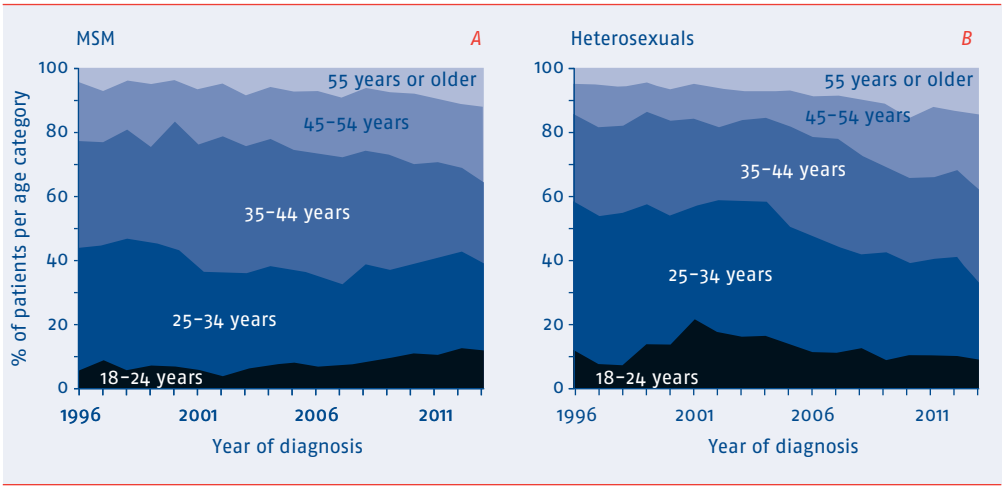
Of the 4,627 heterosexual patients with a reported region of infection, 47% were infected in the Netherlands, whilst 35% reported having been infected in Sub-Saharan Africa. Of the 928 Dutch heterosexual men who reported a country of infection, 73% were infected in the Netherlands, 12% in South and Southeast Asia, and 9% in Sub-Saharan Africa. Of the 770 Dutch women infected via heterosexual contact, 89% reported having been infected in the Netherlands and 6% in Sub-Saharan Africa, whereas less than 1% were infected in South and Southeast Asia.

Increasingly older age at time of HIV diagnosis

The age at which patients are diagnosed with HIV has been slowly increasing over time. In 1996, the average age at the time of diagnosis was 37 years; in 2013, it was 41 years. Over the entire period from 1996 through 2013, 15% of adults who received a diagnosis of HIV were 50 years or older; in 2013, 24% were 50 years or older. There were, however, considerable age differences between MSM and heterosexual men and women. MSM born in the Netherlands were diagnosed at a mean age of 40 years, whilst those of foreign origin were diagnosed at 35 years. Amongst heterosexual patients of Dutch origin, the average age at the time of diagnosis was 39 years for women and 43 years for men. Heterosexual patients born in Sub-Saharan Africa (women: 31 years; men: 35 years) or elsewhere (women: 35 years; men: 41 years) were substantially younger than their Dutch counterparts.

For MSM, the age distribution at the time of diagnosis has gradually changed over time, whilst for heterosexuals there were no notable changes up to 2003 (*Figure 1.8*). Thereafter, the age of heterosexuals at diagnosis started to increase concomitantly with the decreasing number of diagnoses amongst patients from Sub-Saharan Africa, who were generally younger than heterosexuals of Dutch or other origin.

Figure 1.8: Age distribution at the time of diagnosis amongst HIV-1-infected men who have sex with men (MSM) (A) and heterosexual men and women (B). Between 1996 and 2013, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 23% to 36%, whilst these proportions were 14% and 38% for heterosexuals. During the same period, the proportion of patients between 25 and 34 years of age decreased from 38% to 27% for MSM and from 47% to 24% for heterosexuals.



Young adults

The number of diagnoses amongst young adults less than 25 years of age and infected via heterosexual contact was approximately 75 in the early 2000s and decreased to 19 in 2012, or to 9% of the annual tally (*Figure 1.8; Web Appendix Figure 1.2*). Amongst MSM, both the number and the proportion of diagnoses amongst young adults increased over time and, in 2013, young adults accounted for 12% of the annual tally, or 78 diagnoses.

Entry into care

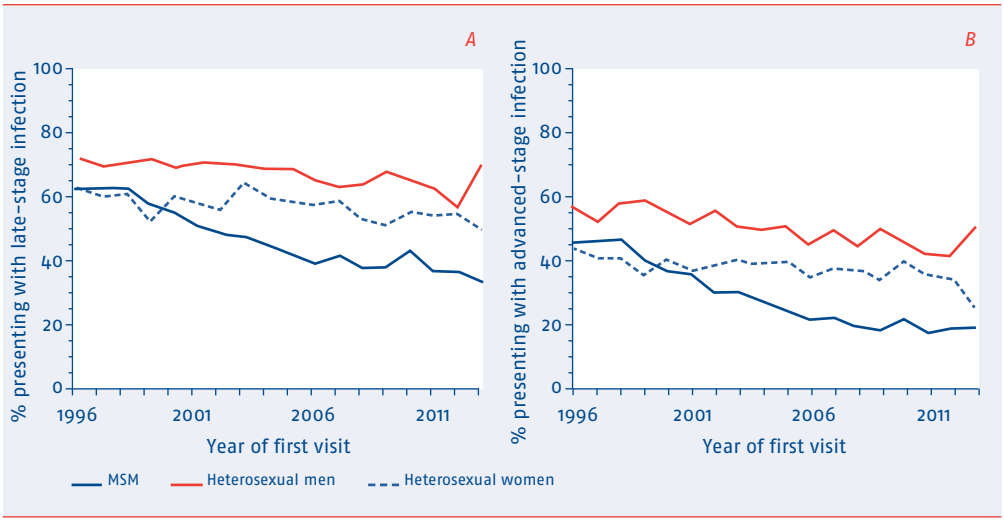
Of all patients diagnosed with HIV in 2008 or later for whom the location of testing was known, 83% had entered into care within 4 weeks, and 89% had entered care within 6 weeks of receiving their diagnosis. Overall, 90% of patients who received their first HIV-positive test at a community health service or STI clinic were in care within 6 weeks, as were 94% of those who tested HIV-positive in a hospital, 91% of those diagnosed at a general practice surgery, and 64% of those diagnosed at other locations. The proportion in care

within 6 weeks was similar for MSM (90%) and for heterosexuals (89%). For heterosexuals, the proportion in care within 6 weeks did not differ by age at the time of diagnosis. On the other hand, more than 92% of MSM diagnosed at 35 years of age or older were in care within 6 weeks, compared with only 83% of young adults.

Late presentation

Overall, 53% of the patients were late presenters, i.e., individuals either presenting for care with a CD4 count below 350 cells/mm^3 or presenting with an AIDS-defining event regardless of CD4 count[7]. Although the proportion of late presenters has decreased over time, in 2013 43% of patients entered clinical care late in their infection (*Figure 1.9; Web Appendix Figure 1.3*). Of those entering care in recent years (2010 or later), 12% had already been diagnosed with AIDS. In addition, the proportion of patients presenting for care with advanced HIV disease, i.e., with a CD4 count below 200 cells/mm^3 or AIDS, has decreased over time and was 25% in 2013. In total, 29% of the patients entering care from 1996 onwards had CD4 counts of 500 cells/mm^3 or higher, 19% had CD4 counts between 350 and 499 cells/mm^3, 20% between 200 and 349 cells/mm^3, and 32% below 200 cells/mm^3.

Figure 1.9: *Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of entry into care. From 1996 onwards, 53% presented with late HIV disease: men who have sex with men (MSM) 45%, heterosexual men 68%, heterosexual women 58%, injecting drug users (IDU) 63% (data not shown). Overall, 34% were advanced presenters: MSM 26%, heterosexual men 50%, heterosexual women 37%, and IDU 46%. Late stage infection: CD4 counts below 350 cells/mm^3 or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm^3 or having AIDS.*



Legend: *MSM=men who have sex with men*

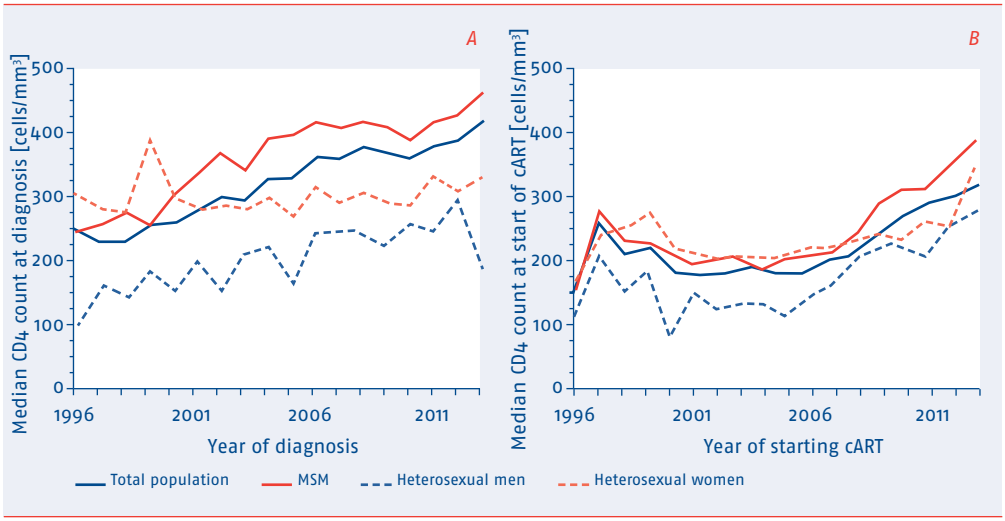
Among patients entering clinical care in 2010 or later, 38% of MSM, 64% of heterosexual men, and 55% of heterosexual women presented with late-stage HIV infection. Patients of sub-Saharan African origin infected via heterosexual contact were more likely to present with a late-stage infection (65%) compared with their peers of Dutch origin (53%). Late-stage infection at the time of entry into care was most often found in heterosexual patients originating from South and Southeast Asia, of whom 75% were late presenters. In this same group, 69% presented for care with advanced HIV infection, compared to 39% of Sub-Saharan Africans and 36% of Dutch heterosexual patients.

Late presentation was also more common in patients entering care at older ages. Late presentation was seen in 54% of MSM and 67% of heterosexuals entering care at 45 years of age or older, compared with 28% of MSM and 45% of heterosexuals entering care at ages younger than 25 years. Although testing behaviour and frequency may differ between these two age groups, the relatively shorter period of sexual activity of those diagnosed at younger ages also accounts for these observed differences. Late-stage infection was also observed more often in patients who received their HIV diagnosis in 2008 or later at a hospital (66%) compared with those who were tested at a general practice surgery (44%), a community health service or STI clinic (28%), or another testing location (42%).

Increasing CD4 cell counts

Between 1996 and 2013, median CD4 counts in the total adult population at the time of diagnosis increased from 250 to 416 cells/mm^3 (*Figure 1.10A*). This overall increase was mainly the result of a rise in CD4 counts in both MSM and heterosexual men, whereas CD4 counts in women remained virtually unchanged.

Figure 1.10: Changes over time in median CD4 counts (A) at HIV diagnosis and (B) at the start of combination antiretroviral therapy (cART). Between 1996 and 2013, CD4 counts at the time of diagnosis increased from 250 (interquartile range [IQR], 80–437) to 416 (IQR, 200–610) cells/mm³ in the total adult population. The increase was most apparent for men who have sex with men (MSM): 245 (IQR, 80–450) cells/mm³ in 1996 and 464 (IQR, 290–640) cells/mm³ in 2013. During the same period, CD4 counts in heterosexual men increased from 100 (IQR, 26–390) to 190 (IQR, 60–405) cells/mm³, whereas CD4 counts in heterosexual women were 300 (IQR, 120–500) cells/mm³ and did not change over time. (B) In the total population, CD4 counts at the start of cART rose to 260 (IQR, 130–400) cells/mm³ shortly after cART became available, decreased to a plateau approximately 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2013, CD4 counts were 360 (IQR, 240–490) cells/mm³ in the total population, 382 (IQR, 290–520) cells/mm³ in MSM, 271 (IQR, 90–390) cells/mm³ in heterosexual men, and 330 (IQR, 207–470) cells/mm³ in heterosexual women.



***Legend:** MSM=men who have sex with men; cART=combination antiretroviral therapy*

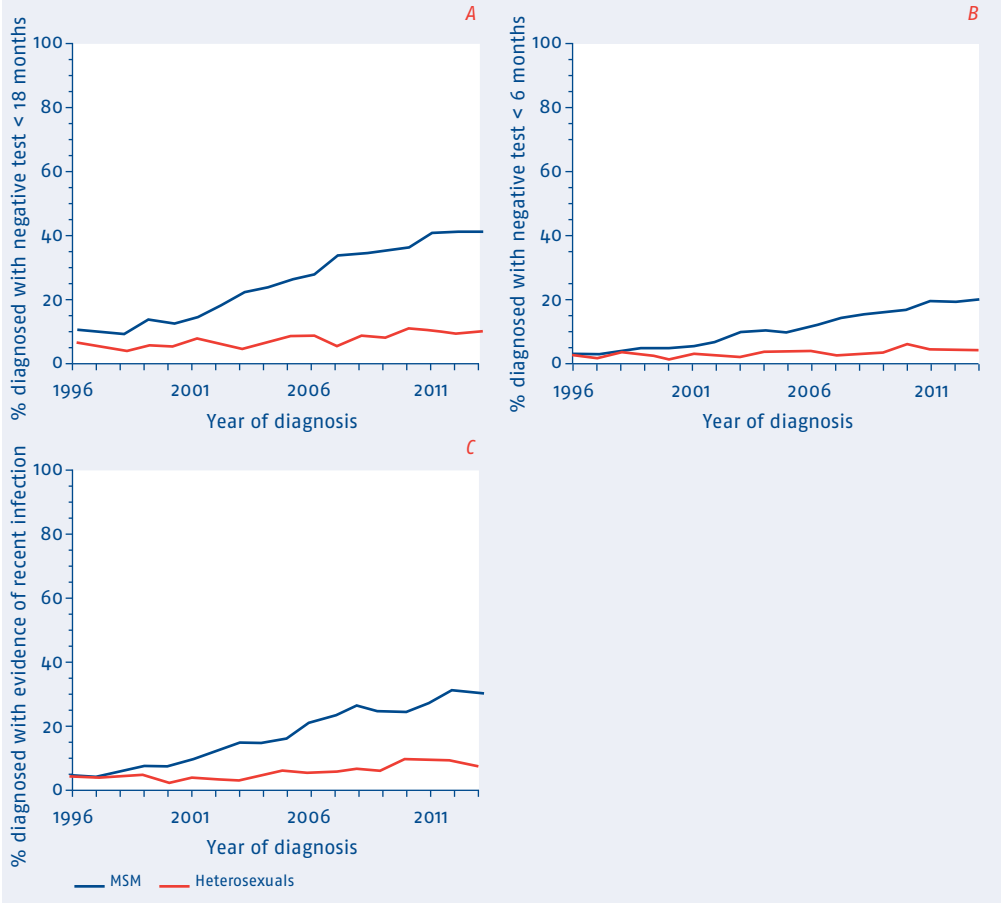
Earlier diagnosis

The increase in CD4 counts at diagnosis, in conjunction with a decreasing proportion of late presenters, suggests that, on average, patients are being diagnosed increasingly earlier in the course of their HIV infection. For individual patients, however, the CD4 count at diagnosis may not always be a reliable marker of time since infection. In a large European cohort of seroconverters, for instance, one-quarter of newly-infected patients had CD4 counts below 350 cells/mm³ within only 1 year after seroconversion[8].

A further, and arguably better, indication of earlier diagnosis is the increase in the proportion of MSM who were diagnosed with evidence of a recent infection, either because they had a known negative HIV test 6 months, at most, before their first positive test or because they had symptoms typical for acute HIV infection (*Figure 1.11; Web Appendix Figure 1.4*). Among MSM diagnosed in 2010 or later, 40% had a negative test in the 18 months before diagnosis, whilst 18% had a negative test in the 6 months before diagnosis. More than one-quarter of

the diagnosed MSM (28%) had a negative test in the 6 months preceding diagnosis or had additional evidence of a recent infection. Only 9% of the heterosexuals had a negative test in the 18 months before diagnosis, whilst 9% of these patients had evidence of having acquired their infection at most 6 months before diagnosis.

Figure 1.11: *Proportion of patients diagnosed and having (A) a last negative HIV test at most 18 months before diagnosis, (B) a last negative HIV test at most 6 months before diagnosis, and (C) a last negative HIV test at most 6 months before diagnosis or other evidence of a recent infection, including symptoms related to acute infection or a known moment of risk exposure. Altogether, 41% of men who have sex with men (MSM) and 9% of heterosexuals (men 7%, women 11%) diagnosed in 2013 had a last negative test at most 18 months before diagnosis, whereas 19% of MSM and 3% of heterosexuals (men 3%, women 4%) had a last negative test at most 6 months before diagnosis. The proportion of patients diagnosed in 2013 with a last negative test at most 6 months before diagnosis or other evidence of a recent infection was 31% for MSM and 8% for heterosexuals (men 8%, women 8%).*



Legend: *MSM=men who have sex with men*

Increasing frequency of testing

Since both the proportion of recent infections and CD4 counts at diagnosis have increased amongst those diagnosed with HIV, testing for HIV has apparently become more common. An additional indication for this is the increasing proportion of patients with a previously negative HIV test (*Web Appendix Figure 1.4*). In 2013, 68% of MSM and 31% of heterosexuals diagnosed with HIV had a previous test with a negative result. The proportion with a previously known negative test was highest amongst those diagnosed at a community health service or STI clinic (77%), compared with 38% of those diagnosed in a hospital, 56% of those tested at a general practice, and 59% of those diagnosed elsewhere.

Population – start of cART

Treated population

Of the 21,417 adult patients with an HIV-1 infection, 19,041 patients had started cART by June 2014. The majority of these patients (87%) started cART whilst being antiretroviral therapy-naïve. For the entire group of adults, the total follow-up time since start of cART was 148,323 person years.

Treatment combinations

According to the current guidelines, the recommended preferred first-line antiretroviral regimens in therapy-naïve patients include tenofovir/emtricitabine in combination with efavirenz, ritonavir-boosted darunavir, or ritonavir-boosted atazanavir[9]. For patients first initiating cART in 2013 and 2014, these regimens accounted for 54% of all first-line regimens compared to 59% in last year's report: 28% included efavirenz, 19% included boosted darunavir, and 7% included boosted atazanavir. An additional 9% of the patients started with a combination of tenofovir/emtricitabine and nevirapine, and 18% with tenofovir/emtricitabine and rilpivirine. Like efavirenz, rilpivirine is also available as a fixed-dose combination, although only for patients with a viral load below 100,000 copies/ml[10-12]. As rilpivirine is generally associated with fewer side effects than efavirenz, many patients prefer to start with rilpivirine, despite the requirement of taking it with food. As a result, rilpivirine has now become a more frequently prescribed first-line antiretroviral drug than efavirenz, which accounted for 48% of first-line regimens in 2012 and dropped to 35% in 2013[1,13].

In 2013 and 2014, 39 patients (3%) started tenofovir/emtricitabine in combination with raltegravir. Although this combination is included in preferred first-line regimens in the US Department of Health and Human Services (DHHS) guidelines, it is not recommended by the Dutch guidelines because raltegravir is to be used twice daily, whilst national guidelines favour once-daily regimens. The more recent fixed-dose combination of elvitegravir, cobicistat, and tenofovir/emtricitabine was used as the first cART regimen by 6% of the patients.

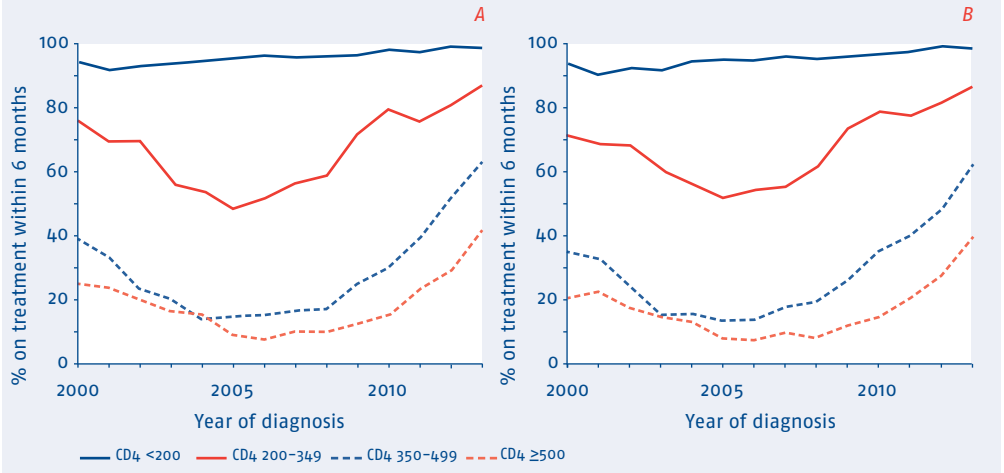
The large majority (93%) of first-line regimens included tenofovir/emtricitabine. Only a small proportion of patients started with zidovudine/lamivudine (4%) or abacavir/lamivudine (3%).

Earlier start

In the past few years, cART has been started increasingly earlier in the course of HIV infection, as evidenced by higher CD4 counts at the start of treatment since the mid-2000s (*Figure 1.10B*). In 2013, median CD4 counts at the start of treatment had increased from 326 cells/mm³ in 2012 to 360 cells/mm³. All together, 20% of patients started treatment at CD4 counts already below 200 cells/mm³, 26% started at CD4 counts between 200 and 349 cells/mm³, 30% started at CD4 counts between 350 and 499 cells/mm³, and 24% started at CD4 counts of 500 cells/mm³ or higher.

The main reason for starting treatment too late appears to be a late diagnosis, because most patients who are able to start treatment on time do so. Patients with less than 200 CD4 cells/mm³ at diagnosis or at the time of entry into care almost immediately started treatment: within 6 months after diagnosis more than 95% had started cART (*Figure 1.12; Web Appendix Figure 1.5*). The proportion of patients who started treatment within 6 months was smaller for those with higher CD4 counts, but it has rapidly increased in recent years, reflecting changes in treatment guidelines and an increasing tendency to start treatment at higher CD4 counts.

Figure 1.12: *(A) Proportion of patients who started combination antiretroviral treatment (cART) within 6 months after HIV diagnosis stratified by CD4 count at the time of diagnosis. (B) Proportion of patients who started cART within 6 months after entry into care stratified by CD4 count at the time of entry into care. Patients were considered only if they had more than 6 months of follow-up after diagnosis or entry into care. Of all patients diagnosed in 2012, 99% (99% in 2013) of those with CD4 counts below 200 cells/mm³ had started cART within 6 months after receiving their diagnosis, whilst 81% (88% in 2013) of those with CD4 counts between 200 and 349 cells/mm³, 52% (63% in 2013) of those with CD4 counts between 350 and 499 cells/mm³, and 29% (41% in 2013) of those with CD4 counts of 500 cells/mm³ or above had begun cART within 6 months of diagnosis.*



Immediate start of treatment

The most recent DHHS guidelines recommend starting treatment irrespective of CD4 counts, although currently this recommendation is mainly based on expert opinion and indirect evidence[9]. Nonetheless, the increase in recent years in the proportion of patients with more than 500 cells/mm^3 who were on treatment within 6 months of diagnosis suggests that this strategy of immediate treatment is also being increasingly adopted in the Netherlands (*Figure 1.12*).

Short-term treatment outcomes

In the entire group who started cART, median CD4 counts increased from 231 cells/mm^3 at the start of treatment to 370 cells/mm^3 after 24 weeks. An increase of similar magnitude, albeit at higher CD4 counts, was observed in patients starting treatment in 2010 or later, namely 318 cells/mm^3 at the start of cART and 460 cells/mm^3 at 24 weeks. All together, 88% of the patients achieved suppression of viral load to unquantifiable levels or below 500 copies/ml within 24 weeks, whilst 81% had HIV RNA levels below 100 copies/ml. A more comprehensive overview of treatment outcomes is presented in the next chapter.

Population – HIV-2

HIV-2-infected population

In total, 95 of the 22,311 registered patients, including 45 men and 50 women, were infected with HIV-2. The majority (76, or 80%) of these patients were infected via heterosexual contact. HIV-2 is endemic in Western Africa, and 61 patients originated from this region, mostly from Ghana (25 patients) or Cape Verde (23 patients). Only 21 patients were born in the Netherlands. A total of 67 patients were still in clinical care, 14 patients had died, and 5 had moved abroad. The mean age of the patients still in care was 54 years, and 72% were 50 years or older.

The mean age at the time of diagnosis was 44 years, which was considerably higher than for HIV-1-infected patients. For the 80 patients who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis was 290 (90-669) cells/mm^3. From 1996 onwards, 48% of the patients were late presenters, and 41% presented for care with advanced HIV disease. The distribution of CD4 counts at entry into care appeared to be more bimodal than for HIV-1-infected patients: 39% had CD4 counts below 200 cells/mm^3, 40% had CD4 counts of 500 cells/mm^3 or higher, whilst relatively few patients (21%) had CD4 counts between 200 and 499 cells/mm^3.

Treatment

By June 2014, 55 patients had ever started cART. Of the 38 patients who were still being treated, 18 used a backbone of abacavir/lamivudine, 8 tenofovir/emtricitabine, and 7 zidovudine/lamivudine. Additional drugs in the regimen included ritonavir-boosted darunavir in 15 patients, ritonavir-boosted lopinavir in 10 patients, and atazanavir in

7 patients (all ritonavir-boosted, except one). At start of cART, 22 patients had HIV-2 RNA levels above 500 copies/ml, whilst 13 had levels below 500 copies/ml.

Of the 67 patients who were still in care, 49 had a most recent viral load measurement below 500 copies/ml, 3 had a viral load above 500 copies/ml, and for 15 patients no HIV-2 RNA result was available. In total, 29 patients had not, or not yet, started treatment. These patients still had high CD4 counts (median, 790 (520-900) cells/mm^3), and none had an HIV-2 viral load above 500 copies/ml (11 not determined).

International collaborations

Since HIV-2 is relatively rare and is mainly found in Western Africa, the effect of antiretroviral treatment on outcome has not been studied in detail. A Collaboration on HIV-2 Infection (ACHIeV2e) was established in 2005 as a collaboration of 13 observational cohorts in Europe and Africa, including SHM, with the aim of studying the natural history and response to treatment in HIV-2-infected patients. In a recent paper, the group compared short-term treatment outcomes in 44 patients starting a regimen of three nucleoside reverse-transcriptase inhibitors (NRTIs) and 126 patients starting a ritonavir-boosted protease inhibitor (PI/r)-containing regimen[14]. During the first 12 months after start of treatment, patients on PI/r-regimens had improved rates of viral suppression and higher CD4 cell increases than those starting with triple NRTI regimens.

Conclusion

In recent years, the overall annual number of new HIV diagnoses in the Netherlands has stabilised around 1100. In general, the trend of an increasing number of new diagnoses amongst MSM, which had been observed since the turn of the millennium, has come to an end. Despite a steady decline in new diagnoses amongst MSM between the ages of 35 and 44 years, the number of new diagnoses continues to increase amongst young adult MSM and in MSM 55 or older. Diagnoses in patients infected via heterosexual contact are decreasing, mainly due to reductions in immigration from HIV-endemic regions. However, amongst heterosexuals aged 45 or older, the number of diagnoses is slowly increasing.

HIV-infected patients are being diagnosed increasingly earlier in the course of their infection. A shrinking proportion of patients are diagnosed with CD4 counts below 350 cells/mm^3 and, conversely, the proportion diagnosed with evidence of a recent infection is increasing. These changes are more pronounced, however, amongst MSM than amongst heterosexual men and women.

In addition, in recent years, testing for HIV has appeared to become more frequent, because patients with a positive test are more likely to have had a previous negative test. Testing rates appear to be highest amongst patients who received a positive test result at community

health services or STI clinics and lowest in those tested in a hospital. The population that tested positive for HIV in a hospital also had the highest proportion of late testers. These observations illustrate that patients tested at community health services or STI clinics are more likely actively seeking testing for HIV on a regular basis than patients diagnosed in a hospital.

Patients tested early in their infection generally start treatment earlier and before CD4 counts have dropped to below 350 cells/mm^3. In the most recent years, treatment uptake has also increased in patients with CD4 cells above this threshold. As a result, 82% of patients in care and 58% of the total estimated population of persons living with HIV in the Netherlands, including those not yet diagnosed, have a suppressed viral load. The true proportion may even be higher because of reporting delays.

Recommendations

Despite all these positive developments (i.e., more testing, earlier diagnosis, earlier start of treatment, and a large proportion of patients with viral suppression), the annual number of new HIV diagnoses still fails to show a convincing, significant decline amongst either MSM or heterosexuals. To fully curb the epidemic, testing and treatment need to be scaled up, and a reduction in sexual risk behaviour should be promoted, as this is expected to have an even greater impact on the number of new infections [15,16].

2. Response to combination antiretroviral therapy (cART)

Luuk Gras, Kees Brinkman, Jan Prins and Peter Reiss

Introduction

The primary goal of cART is to prevent disease progression of HIV[17]. Another goal is the prevention of onward HIV transmission. This transmission has been shown to be more likely with higher HIV RNA levels in studies in HIV-serodiscordant heterosexual couples[18-20]. A recent randomised controlled trial in HIV-serodiscordant couples in which the HIV-infected partner had a CD4 cell count between 350 and 500 cells/mm^3 confirmed that the immediate start of ART is effective at preventing primary clinical events, AIDS, and tuberculosis[21], as well as transmission of HIV[22], compared to deferring treatment until the CD4 count has dropped to ≤250 cells/mm^3. Thus, in addition to preventing disease progression in HIV-infected individuals, cART also has a public health benefit in terms of preventing onward HIV transmission.

However, the strength of the guideline recommendation to start cART decreases at higher latest CD4 cell counts[9,23]. Studies seem to agree on the benefit of cART when started between 350 and 500 CD4 cells/mm^3, but they are less consistent regarding the benefit of starting cART when the CD4 cell count is still above 500 cells/mm^3[24-27]. One disadvantage of an earlier start of cART may be longer exposure to antiretroviral drugs, some of which are associated with development of cardiovascular disease[28-30], loss of bone density[31-33], renal disease[34-36], and liver disease[37,38]. Short-term toxicity is less frequently seen with newer drugs[39-41], but certain complications may take longer to emerge. Another disadvantage of an early start of cART is the longer inconvenience of daily intake of lifelong medication. Especially when individuals are not yet experiencing any effects of HIV infection and have high CD4 cell counts, such inconveniences and adverse events may lead to less willingness to initiate cART[42] and less-than-optimal adherence to therapy[43], followed by an enhanced risk of virological failure, emergence of resistant virus[44-46], and ultimately, HIV disease progression[47].

However, since untreated HIV increases the risk of several non-AIDS-defining diseases, newer drugs are generally better tolerated, and the effect of early cART is beneficial in prevention of HIV transmission, most guidelines either recommend starting cART or recommend considering its start when CD4 cell counts are 500 cells/mm^3 or higher. US guidelines on when to start cART, which are generally followed by the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB), currently recommend starting cART in all HIV-infected individuals. This implies that all HIV-infected individuals should be given the option of starting treatment immediately after diagnosis[9].

The Strategic Timing of AntiRetroviral Treatment (START) trial (an ongoing randomised controlled trial to evaluate the role of immediate cART in patients with a CD4 count >500 cells/

mm³ versus treatment delay until the CD4 count falls to ≤350 cells/mm³) will help to further, and more robustly, answer the question of optimal timing for cART initiation, including the magnitude of its effect on preventing different non-AIDS morbidities[9,48].
In this chapter we describe trends over time in the use of cART, trends in the virological and immunological response to cART, as well as trends in toxicity related therapy changes, according to demographic and clinical characteristics at the start of treatment.

Demographic and clinical characteristics at the start of cART

Of the 21,928 treated and untreated individuals with an HIV-1 infection and a known date of diagnosis (*Figure 1.1*) registered by Stichting HIV Monitoring (SHM), 18,896 were 16 years of age or older when they started cART between January 1995 and December 2013. Of these, 2,598 were mono- or dual ART-experienced at the start of cART, and 16,298 were ART-naïve. The individuals described in this chapter include 179 individuals younger than 18 years of age at HIV diagnosis who are also described in Chapter 6.
We divided patients according to calendar year of starting cART: 6,047 started between 1,995 and the end of 2001, 5,296 between 2002 and the end of 2007, 6,408 between 2007 and the end of 2012, and 1,145 in 2013 (*Table 2.1*). Patients starting in 2014 are not included because their follow-up is currently too short to allow meaningful reporting of their virological and immunological response to cART.

Table 2.1: *Baseline characteristics of 18,884 patients starting combination antiretroviral therapy (cART) between 1 January 1995 and 31 December 2013.*

							Year of starting cART	
	1995–2001		2002–2007		2008–2012		2013	
Total (n, %)	6,047	100.0	5,296	100.0	6,408	100.0	1,145	100.0
DEMOGRAPHIC CHARACTERISTICS								
Male gender (n, %)	4,900	81.0	3,850	72.7	5,411	84.4	997	87.1
Age at start of cART (median, IQR)	37.5	32.0–44.4	38.5	31.8–45.6	40.5	32.9–48.1	41.3	32.2–49.1
Transmission risk group (n, %)								
MSM	3,512	58.1	2,505	47.3	4,214	65.8	810	70.7
Heterosexual contact	1,675	27.7	2,218	41.9	1,769	27.6	272	23.8
IDU	420	6.9	155	2.9	77	1.2	8	0.7
Blood or blood products	127	2.1	73	1.4	49	0.8	13	1.1
Vertical transmission	1	0.0			8	0.1	2	0.2
Unknown	312	5.2	345	6.5	291	4.6	40	3.5
Region of origin (n, %)								
Netherlands	3,638	60.2	2,560	48.3	3,936	61.4	763	66.6
W-Europe/N-America/Australia	681	11.3	379	7.2	403	6.3	55	4.8
Caribbean/S-America	579	9.6	669	12.6	712	11.1	112	9.8
Sub-Saharan Africa	766	12.7	1,241	23.4	767	12.0	94	8.2
Other	383	6.3	447	8.4	590	9.2	121	10.6

	Year of starting cART							
	1995–2001		2002–2007		2008–2012		2013	
Socio-economic status (SES)****								
1	288	4.8	247	4.7	336	5.2	64	5.6
2	1,265	20.9	1,056	19.9	1,449	22.6	232	20.3
3	1,474	24.4	1,505	28.4	1,805	28.2	374	32.7
4	1,456	24.1	1,294	24.4	1,553	24.2	255	22.3
5	966	16.0	1,040	19.6	1,136	17.7	193	16.9
Missing	598	9.9	154	2.9	129	2.0	27	2.4
CLINICAL CHARACTERISTICS								
CD4 cell count at start cART, cells/mm^3 (median, IQR)	200	80–340	190	90–280	280	170–370	370	250–500
HIV RNA at start cART, $\log_{10}$ cps/ml (median, IQR)	4.82	4.15–5.31	5.00	4.47–5.34	4.93	4.39–5.36	4.84	4.29–5.31
AIDS diagnosis at the start of cART (n, %)	1,952	32.3	1,403	26.5	1,047	16.3	158	13.8
CD4 cell count <200 or AIDS at start of cART (n, %)	3,260	59.0	2,849	57.5	2,046	33.7	259	23.9
CD4 cell count ≥200 without AIDS at start of cART (n, %)	2,261	41.0	2,110	42.5	4,030	66.3	825	76.1
CD4 cell count <350 or AIDS at start of cART (n, %)	4,377	79.3	4,337	87.5	4,416	72.7	514	47.4
CD4 cell count ≥350 without AIDS at start of cART (n, %)	1,144	20.7	622	12.5	1,660	27.3	570	52.6
CD4 cell count <500 or AIDS at start of cART (n, %)	5,038	91.3	4,574	94.2	5,548	91.3	819	75.6
CD4 cell count ≥500 without AIDS at start of cART (n, %)	1,009	8.7	722	5.8	806	8.7	326	24.4
HCV status at start cART (n, %)								
Negative	4,833	79.9	4,635	87.5	5,862	91.5	1,029	89.9
HCV RNA positive	107	1.8	157	3.0	219	3.4	36	3.1
HCV Ab positive	332	5.5	100	1.9	23	0.4	7	0.6
Unknown	775	12.8	404	7.6	304	4.7	73	6.4
HBV status at start cART*** (n, %)								
Negative	5,207	86.1	4,737	89.4	5,856	91.4	1,026	89.6
Positive	419	6.9	352	6.6	332	5.2	42	3.7
Unknown	421	7.0	207	3.9	220	3.4	77	6.7

	Year of starting cART							
	1995–2001		2002–2007		2008–2012		2013	
TREATMENT CHARACTERISTICS								
ART-naive at start cART	3,807	63.0	5,051	95.4	6,307	98.4	1,133	99.0
Other drug class in addition to NRTI in initial cART (n, %)								
NNRTI	1,138	18.8	2,977	56.2	4,314	67.3	703	61.4
PI	4,662	77.1	1,924	36.3	1,670	26.1	367	32.1
NNRTI+INSTI			2	0.0	56	0.9	7	0.6
PI+INSTI			2	0.0	47	0.7	10	0.9
INSTI					113	1.8	47	4.1
Other	247	4.1	391	7.4	208	3.2	11	1.0
Daily frequency of initial cART intake (n, %)								
Once	87	1.4	2,129	40.2	5,200	81.2	1,029	89.9
Twice	3,098	51.2	3,060	57.8	1,186	18.5	115	10.0
Three times	2,706	44.7	84	1.6	8	0.1	1	0.1
Four or more times	122	2.0	12	0.2	5	0.1		
Unknown	34	0.6	11	0.2	9	0.1		
cART started during pregnancy	137	2.3	390	7.4	197	3.1	25	2.2
cART started during primary infection**	97	1.6	204	3.9	444	6.9	140	12.2
OTHER CHARACTERISTICS								
Smoker*								
No	2,403	39.7	2,356	44.5	3,196	49.9	548	47.9
Yes	2,432	40.2	1,662	31.4	2,523	39.4	466	40.7
Unknown	1,212	20.1	1,278	24.1	689	10.8	131	11.5

** Based on information obtained once during follow-up, for most patients at entry into care.*

*** cART started within 6 months of estimated date of seroconversion (midpoint between last negative and first positive HIV test or, in case of laboratory evidence of acute infection, the date of HIV diagnosis).*

**** by hepatitis B surface antigen.*

***** Socio-economic status: a combined measure based on income, employment, and level of education obtained by interviewing one household in each six-position postal code and aggregated into a single score for each four-position postal code using principal component analysis. Scores were classified in five groups such that they contained approximately 7%, 24%, 38%, 24%, and 7% of all postal codes; 1 indicates high SES and 5 indicates low SES[49].*

***Legend:** cART= combination antiretroviral therapy; MSM=men who have sex with men; IDU=injecting drug use; W-Europe=Western Europe; N-America=North America; S-America=South America; CDC-C=Centers for Disease Control category C; HCV=hepatitis C virus; HBV=hepatitis B virus; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor; IQR=interquartile range.*

Of the 18,896 patients who had ever started cART, 3738 were women (20%) of whom 27% were born in the Netherlands. Of the 1,145 patients who started cART in 2013, 810 (71%) were MSM, which is a slightly higher percentage than in 2012 (67%). Among the 112 patients of Caribbean or South American origin who started cART in 2013, 37 originally came from the former Netherlands Antilles (33%), 31 from Surinam (28%), 15 from Brazil (14%) and 7 from Jamaica (6%). The 121 individuals from other regions of origin who started in 2013 were from Central and Eastern Europe (n=52), Southeast Asia (n=42), North Africa and the Middle East (n=23), Oceania and the Pacific (n=3), and the region of origin was unknown for 1 individual.

CD4 cell count at the start of cART

The CD4 cell count threshold below which the US Department of Health and Human Services (DHHS) guidelines (generally followed by the NVHB) recommend starting cART increased to 350 cells/mm^3 in 2007 and to 500 cells/mm^3 in 2009. More recently, these guidelines have recommended cART for all HIV-infected patients, regardless of CD4 count[9,50]. The median CD4 cell count at the start of cART increased from 210 cells/mm^3 in 2007 to 330 cells/mm^3 in 2012 and 370[1] cells/mm^3 in 2013 (Cuzick test for trend p<0.0001). The percentage of individuals starting cART without an AIDS diagnosis and a CD4 count of 350 cells/mm^3 or more was significantly higher (p<0.0001) in 2013 (53%) than during the period 2008-2012 (27%). *Figure 2.1* shows the percentage of men and women who started cART without AIDS and with a CD4 cell count of ≥200, ≥350, and ≥500 cells/mm^3. The percentage of male patients without AIDS and with ≥350 CD4 cells/mm^3 at the start increased over time from 10% in 1996 to 54% in 2013, and 60% when restricted to MSM in 2013. Among women, this increase was less pronounced: from 14% in 1996 to 42% in 2013.
Among women, the median CD4 cell count at the start of cART increased from 210 cells/mm^3 in 2007 to 260 cells/mm^3 in 2012, and it sharply increased to 330 cells/mm^3 in 2013 (*Figure 2.2*). Median counts among men increased from 210 cells/mm^3 in 2007 to 370 cells/mm^3 in 2013. The increase was less pronounced among men from Sub-Saharan Africa (from 190 cells/mm^3 in 2007 to 260 cells/mm^3 in 2013). *Web Appendix Table 2.1* gives an overview of the number of men and women contributing to the trends shown in *Figures 2.1* and *2.2*. *Chapter 1* gives more information on trends in time between HIV diagnosis and the start of cART over time. The percentage of patients with an AIDS diagnosis at the start of cART declined over time (test for trend p<0.0001). More than 12% of patients starting cART in 2013 did so during primary infection, compared to 10% in 2012. Starting cART during primary infection has been shown to result in a lower viral load set point (associated with a slower rate of disease progression), a longer total time off therapy, and a longer time to reaching CD4 cell counts of 350 cells/mm^3 or lower[51-53].

[1] *This figure differs slightly (by 10 cells/mm^3) from that presented in Chapter 1 for the median CD4 cell count at the start of cART in 2013. This is due to a larger window of selecting CD4 cell count measurements prior to starting cART in this chapter:24 weeks compared to 12 weeks in Chapter 1.*

Figure 2.1: Percentage of patients starting combination antiretroviral therapy (cART) without AIDS and with a CD4 cell count of ≥200, ≥350, and ≥500 cells/mm³ in men (left) and women (right).

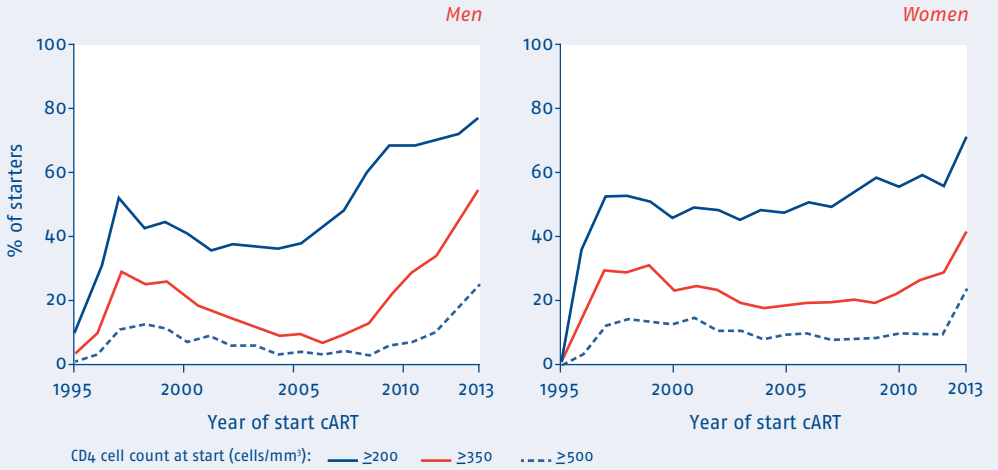
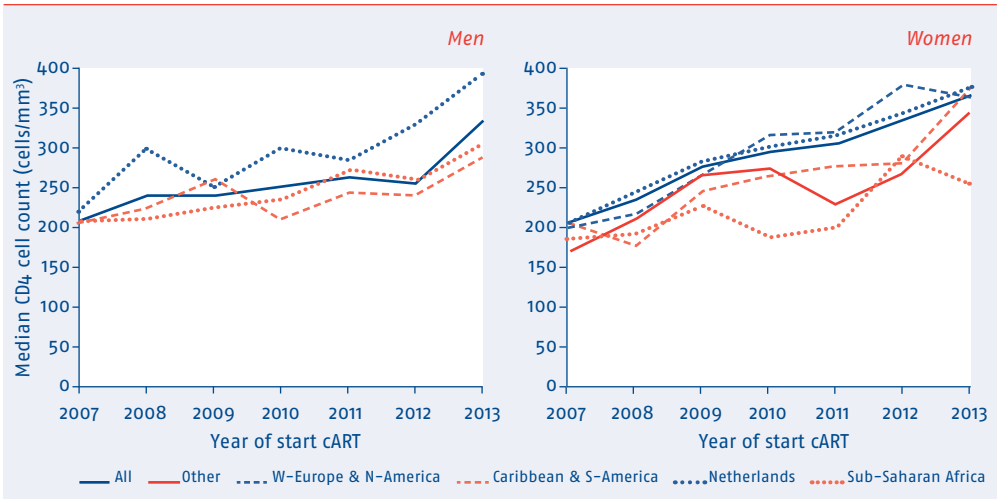


Figure 2.2: Median CD4 cell count at the start of cART according to region of origin (2007-2013) for men (left) and women (right).



Legend: cART=combination antiretroviral therapy; W-Europe=Western Europe; N-America=North America; S-America=South America.

In a logistic regression analysis of 1,064 individuals who started cART in 2013 with a known CD4 cell count, we adjusted for the demographic characteristics listed in *Table 2.1*, as well as whether therapy was started during pregnancy and whether a previously negative HIV test was available. In line with a previous study showing that repeated testing for HIV may lead to diagnosis at a less advanced stage, thus making a timely start of cART possible[54], individuals repeatedly tested (defined as having a documented negative HIV test 1.5 years or less prior to HIV diagnosis) had higher odds of starting cART at ≥350 cells/mm^3, (odds ratio [OR] 2.90 (2.13-3.95, p<0.0001)). Repeated testing for HIV is less frequent in the heterosexual population compared to the homosexual population (*Chapter 1*). However, independent of repeated testing, the probability of starting cART at a CD4 cell count of 350 cells/mm^3 or more was lower among heterosexually infected individuals than among MSM (OR 0.53, 95% CI 0.35-0.80, p=0.003). Furthermore, the probability of starting at 350 cells/mm^3 or more was also lower among individuals from Sub-Saharan Africa (OR 0.50, 95% CI 0.28-0.89, p=0.02) when compared to individuals from Western Europe or North America. With older patient age, the start of cART at ≥350 cells/mm^3 became less likely (OR per 10-year increase in age at the start of cART 0.83, 95% CI 0.74-0.93, p=0.001).

Initial regimens at initiation of cART

The percentage of patients starting a first-line boosted protease inhibitor (PI)-containing regimen increased slightly from 30% in 2012 to 32% in 2013. The percentage of patients starting on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen remained similar (63% and 62%, respectively).

Table 2.2: Most frequently used initial cART regimens in 2009–2013. Combinations shown only if used by at least 10 individuals in at least one calendar year.

	2009		2010		2011		2012		2013	
	n	%	n	%	n	%	n	%	n	%
Number of individuals initiating cART	1,334	100.0	1,358	100.0	1,221	100.0	1,230	100.0	1,145	100.0
TDF/FTC/EFV	742	55.6	739	54.4	583	47.7	428	34.8	346	30.2
TDF/FTC/DRV/r	19	1.4	120	8.8	178	14.6	183	14.9	226	19.7
TDF/FTC/RPV	4	0.3					139	11.3	218	19.0
TDF/FTC/NVP	138	10.3	137	10.1	119	9.7	172	14.0	108	9.4
TDF/FTC/ATV/r	99	7.4	118	8.7	134	11.0	115	9.3	81	7.1
TDF/FTC/RAL	28	2.1	14	1.0	31	2.5	28	2.3	31	2.7
AZT/3TC/LOP/r	53	4.0	44	3.2	39	3.2	33	2.7	22	1.9
TDF/FTC/LOP/r	73	5.5	30	2.2	18	1.5	16	1.3	16	1.4
ABC/3TC/NVP	5	0.4	9	0.7	8	0.7	9	0.7	12	1.0
TDF/FTC/EVG/cobi									10	0.9
AZT/3TC/NVP	19	1.4	24	1.8	10	0.8	14	1.1	9	0.8
ABC/3TC/EFV	11	0.8	6	0.4	4	0.3	5	0.4	5	0.4
TDF/FTC/EFV/RAL	4	0.3	15	1.1	10	0.8	5	0.4	4	0.3
TDF/FTC/EFV/LOP/r	43	3.2	24	1.8	19	1.6	3	0.2		
AZT/3TC/EFV	12	0.9	7	0.5	3	0.2				
Other	84	6.4	71	5.3	65	5.4	80	6.6	57	5.2

***Legend:** cART=combination antiretroviral therapy; TDF=tenofovir; FTC=emtricitabine; EFV=efavirenz; DRV/r=boosted darunavir; RPV=rilpivirine; NVP=nevirapine; ATV/r=ritonavir boosted atazanavir; RAL=raltegravir; 3TC=lamivudine; LOP/r=ritonavir boosted lopinavir; ABC=abacavir; EVG/cobi=cobicistat boosted elvitegravir; AZT=zidovudine.*

The fixed-dose combination of tenofovir and emtricitabine was used in 92% of all starting regimens in 2013. The five most frequently used starting regimens in 2013 were tenofovir plus emtricitabine, combined with efavirenz (30%), darunavir/ritonavir (20%), rilpivirine (19%), nevirapine (9%), or atazanavir/ritonavir (7%). Patterns in the type of initial cART over time in the Netherlands have been shown to follow treatment guidelines[55]. Over the last five years, the combination tenofovir plus emtricitabine plus efavirenz was the most frequently used initial regimen, but during the last 2 years rilpivirine has increasingly been chosen instead of efavirenz as the addition to tenofovir and emtricitabine (as part of a fixed-dose single-tablet regimen). The fixed-dose combination of abacavir and lamivudine, which according to current guidelines may be considered as a starting regimen in patients with <100,000 HIV RNA copies, without active hepatitis B virus co-infection, and with low cardiovascular risk, and at a lower cost, was used in only 3% of starting regimens in 2013.
Over time, initial regimens have increasingly shifted from requiring doses three times daily to once daily (90% of individuals starting cART in 2013). All recommended first-line regimens

(efavirenz/tenofovir/emtricitabine [NNRTI-based], ritonavir-boosted atazanavir/tenofovir/emtricitabine or ritonavir-boosted darunavir/ tenofovir/emtricitabine [both PI-based]) are once-daily regimens[50]. A meta-analysis of randomised controlled trials found that lower pill burden is associated with significantly better adherence and higher rates of virological suppression. Once-daily regimens have also been associated with modestly better adherence, although virological suppression rates were similar to those with twice-daily regimens[56]. Finally, the integrase inhibitor raltegravir, not recommended in starting regimens because it needs to be taken as part of a twice-daily regimen, has only been used in 4% of starting regimens since 2009.

Virological response to cART

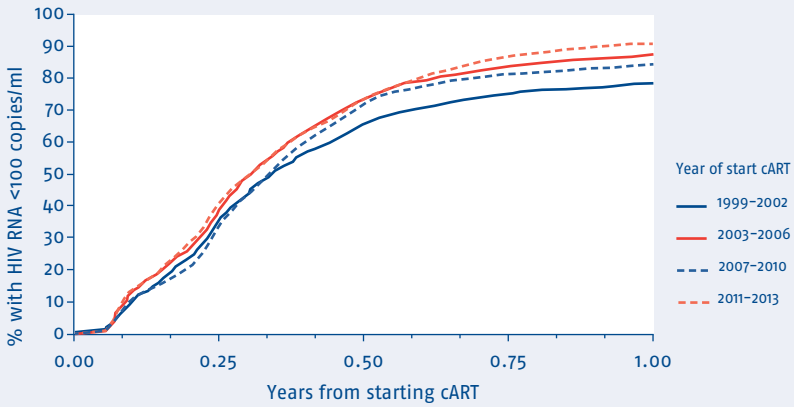
A total of 18,896 patients have started cART since 1995. The key goal of cART is to achieve and maintain durable viral suppression. The definition of viral suppression has changed over the years with the introduction of more sensitive viral load assays, and nowadays a cut-off of 40 or 50 copies/ml is most often used. In this report, we will focus on the 12,112 ART-naïve patients starting cART whose first two available plasma viral loads after the start were measured with an assay with a lower detection limit of 50 copies/ml or less that has been introduced gradually into routine clinical monitoring of HIV RNA since 1999. Results in this paragraph on the virological response to cART are restricted to these 12,112 patients.

Short-term virological response

The short-term virological response to cART is an important marker for longer-term clinical outcome. We therefore monitor the time to virological suppression to below 100 copies/ml during the first year after the start of cART. The cut-off of 100 copies/ml was chosen, rather than the more conventional 50 copies/ml, because plasma samples tested with the Roche COBAS AmpliPrep COBAS TaqMan HIV-1 assay, version 2.0 (CAP/CTM v2.0) are known to give higher results of plasma viral load when the load is at levels close to the lower limit of detection[57,58].

Overall, the Kaplan–Meier estimate of the percentage of patients with initial virological suppression to below 100 copies/ml (first of 2 consecutive measurements <100 copies/ml) increased from 72% (95% CI 71-73%) at 6 months to 83% (82-83%) at 9 months and 86% (85-87%) at 12 months. The percentage of patients with a plasma viral load below 100 copies/ml 9 months after starting cART was 75% (95% CI 73-77%) between 1999 and 2002, 82% (80-83%) between 2003 and 2006, 84% (95% CI 83-85%) between 2007 and 2010, and 87% (95% CI 86-88%) between 2011 and 2013 (*Figure 2.3*). Although the percentage of patients with a plasma viral load <100 copies/ml at 9 months was higher when cART was started between 2011 and 2013, compared to between 2007 and 2010, it was lower between 1-6 months after the start of cART. Changes in the frequency of HIV RNA monitoring over time might contribute to the lower percentage of patients with virological suppression between 1-6 months among those started between 2011 and 2013. Differences in time to initial suppression across the four periods for the start of cART were small but significant (overall log rank test $p<0.0001$).

Figure 2.3: Kaplan–Meier estimates of the percentage of patients with initial suppression to <100 copies/ml during the first year after starting combination antiretroviral therapy (cART).



Legend: cART=combination antiretroviral therapy

To study factors associated with a shorter time to initial suppression to HIV RNA <100 copies, we performed Cox regression using demographic and clinical data from the 12,112 patients, as well as data on the frequency of daily ART intake (once, twice, three times daily, or more often) and type of initial regimen (NNRTI-based, PI-based, ritonavir-boosted PI [PI/r]-based, triple-NRTI, and other), whether an integrase inhibitor was used (yes/no), and type of viral load assay (CAP/CTM v2.0 vs. other assays). In adjusted analyses, female gender, a lower plasma viral load at the start of cART, and having positive hepatitis C virus (HVC) RNA at the start were independently associated with a shorter time to viral suppression (*Table 2.3*). On the other hand, having been born in the Caribbean/South America or Sub-Saharan Africa (compared to the Netherlands), and being younger than 30 years of age when starting cART were associated with a longer time to initial viral suppression. Socio-economic status was not significantly associated (p=0.95) with time to initial viral suppression. Starting a regimen that included an integrase inhibitor was significantly associated with a shorter time to suppression. Changes in the baseline characteristics over time explained some, but not all variation in time to suppression between the four periods of starting cART. In adjusted analyses, differences between the four periods of starting cART were smaller than in unadjusted analyses, but still significant (p=0.01).

Table 2.3: Unadjusted and adjusted hazard ratios (95% confidence intervals) of time from combination antiretroviral therapy initiation to a confirmed HIV RNA <100 copies/ml by Cox proportional hazard regression analysis. Time to a confirmed HIV RNA <100 copies/ml is shorter compared to the reference group when the hazard ratio is higher than 1.00.

		Unadjusted		Adjusted
	HR (95% CI)	(overall) p-value	HR (95% CI)	(overall) p-value
Gender				
Male	1.00		1.00	
Female	1.01 (0.96-1.06)	0.72	1.11 (1.03-1.19)	0.004
Transmission risk group		(<0.0001)		(<0.0001)
MSM	1.00		1.00	
Heterosexual	0.91 (0.88-0.95)	<0.00001	0.90 (0.85-0.96)	0.002
IDU	0.68 (0.59-0.78)	<0.0001	0.59 (0.49-0.71)	<0.0001
Region of origin		(<0.0001)		(0.01)
Netherlands	1.00		1.00	
Caribbean & S-America	0.84 (0.79-0.89)	<0.0001	0.92 (0.86-0.99)	0.02
Sub-Saharan Africa	0.86 (0.81-0.90)	<0.0001	0.92 (0.85-0.99)	0.02
Western Europe / North America	0.71 (0.66-0.77)	<0.0001	0.89 (0.82-0.98)	0.01
Socio-Economic Status		(0.71)		
1	1.05 (0.95-1.15)	0.33		
2	1.01 (0.96-1.07)	0.71		
3	1.00			
4	1.01 (0.96-1.06)	0.78		
5	0.98 (0.93-1.04)	0.50		
Age (years)		(<0.0001)		(0.001)
16-29	0.90 (0.86-0.95)	0.0002	0.90 (0.85-0.96)	0.001
30-39	1.00		1.00	
40-49	1.07 (1.03-1.13)	0.003	1.02 (0.97-1.08)	0.38
≥50	1.04 (0.99-1.10)	0.14	1.00 (0.94-1.06)	0.98
CD4 cell count (cells/mm^3)		(<0.0001)		(<0.0001)
<50	0.84 (0.78-0.90)	<0.0001	1.06 (0.97-1.15)	0.18
50-200	0.90 (0.85-0.96)	0.001	1.03 (0.96-1.10)	0.42
200-350	1.05 (0.99-1.11)	0.10	1.08 (1.01-1.14)	0.02
350-500	1.00		1.00	
>500	0.91 (0.84-0.99)	0.02	0.99 (0.91-1.08)	0.85
HIV RNA ($\log_{10}$ copies/ml)		(<0.0001)		
<4	1.30 (1.22-1.38)	<0.0001	1.49 (1.39-1.59)	<0.0001
4-5	1.00		1.00	
≥5	0.67 (0.64-0.70)	<0.0001	0.63 (0.61-0.67)	<0.0001

		Unadjusted		Adjusted
	HR (95% CI)	(overall) p-value	HR (95% CI)	(overall) p-value
Year of starting		(<0.0001)		(0.01)
1999–2002	0.74 (0.70–0.78)	<0.0001	0.96 (0.88–1.03)	0.27
2003–2006	0.92 (0.87–0.96)	0.0004	1.06 (1.00–1.12)	0.04
2007–2010	1.00		1.00	
2011–2013	0.97 (0.92–1.02)	0.18	0.98 (0.92–1.04)	0.43
HBV co-infection				
–	1.00			
+	1.05 (0.97–1.14)	0.23		
HCV co-infection				(0.007)
–	1.00		1.00	
RNA +	1.13 (1.02–1.26)	0.03	1.17 (1.04–1.32)	0.009
Ab +	0.95 (0.79–1.13)	0.53	1.10 (0.89–1.35)	0.38
Integrase inhibitor included in regimen	1.33 (1.15–1.53)	0.0001	1.61 (1.36–1.90)	<0.0001
Daily frequency of initial cART intake		(<0.0001)		(0.0002)
Once	1.00		1.00	
Twice	0.82 (0.79–0.86)	<0.0001	0.95 (0.89–1.01)	0.08
Three times	0.42 (0.33–0.54)	<0.0001	0.59 (0.42–0.82)	0.002
Four or more times	0.48 (0.21–1.06)	0.07	0.45 (0.14–1.40)	0.17
Start during primary infection	0.87 (0.80–0.94)	0.0007	0.90 (0.82–0.99)	0.04
Start during pregnancy	1.17 (1.08–1.28)	0.0003	1.09 (0.97–1.24)	0.14
HIV RNA assay				
CAP/CTM v2.0	1.05 (1.00–1.10)	0.05		
Other assay	1.00			

Legend: *CI=confidence interval; HR=hazard ratio; MSM=men who have sex with men; IDU=injecting drug users: Socio-economic status (see Table 2.1); HBV=hepatitis B virus; HCV=hepatitis C virus; cART=combination antiretroviral therapy; CAP/CTM v2.0=COBAS AmpliPrep COBAS TaqMan HIV-1 assay, version 2.0.*

We also found a significant interaction between the CD4 cell count at the start of cART and the year of starting cART (p=0.001). Starting at 500 CD4 cells or higher, which occurred in only 1,030 out of 12,112 patients (9%), was associated with a significantly longer time to viral suppression compared to starting at 200-350 cells/mm^3 when cART was started between 1999 and 2006, but not when cART was started in or after 2007 (*Table 2.4*). This association remained when individuals who started cART during primary infection were excluded from the analysis. There also appeared to be a change over calendar time in the time to virological success between individuals born in the Netherlands and those born elsewhere. Time to suppression was significantly shorter in individuals of Dutch origin when cART was started in or before 2006, but shorter in individuals of other origin when cART was started in or after 2010. A possible explanation for both these observations may be that adherence to cART was reduced in patients starting with CD4 cell counts ≥500 cells/mm^3 before 2007

because of a lower perceived necessity for therapy and a reduced quality of life due to the more toxic effects of antiretroviral drugs used at the time; this effect was possibly more pronounced in patients of non-Dutch origin.

Table 2.4: *Selected hazard ratios (95% confidence intervals) of time from cART initiation to a confirmed HIV RNA <100 copies/ml by Cox proportional hazard regression analysis, after including interaction terms between year of starting cART and CD4 cell count at the start of cART, age, and region of origin. Time to a confirmed HIV RNA <100 copies/ml is shorter compared to the reference group when the hazard ratio is higher than 1.00.*

			Year of starting cART	
	1999–2002	**2003–2006**	**2007–2010**	**2011–2013**
CD4 cell count at start of cART (cells/mm³)				
<200	1.03 (0.90–1.18)	1.01 (0.92–1.11)	0.89 (0.82–0.96)	0.91 (0.82–1.02)
200–350	1.00	1.00	1.00	1.00
350–500	0.78 (0.64–0.95)	0.92 (0.78–1.09)	0.94 (0.85–1.03)	0.99 (0.90–1.10)
≥500	0.79 (0.63–0.98)	0.79 (0.64–0.96)	0.96 (0.83–1.12)	1.05 (0.93–1.19)
Age at start of cART (years)				
16–29	0.95 (0.81–1.11)	0.81 (0.71–0.91)	0.87 (0.78–0.96)	1.09 (0.97–1.23)
30–39	1.00	1.00	1.00	1.00
40–49	1.16 (1.01–1.33)	0.99 (0.89–1.10)	1.04 (0.96–1.13)	0.96 (0.87–1.07)
≥50	1.04 (0.87–1.24)	1.06 (0.93–1.20)	0.98 (0.88–1.08)	0.95 (0.85–1.07)
Region of origin				
Netherlands	1.00	1.00	1.00	1.00
Other	0.84 (0.74–0.94)	0.86 (0.79–0.95)	0.98 (0.91–1.06)	1.10 (1.01–1.20)

Legend: *cART=combination antiretroviral therapy.*

We subsequently further restricted the dataset to individuals starting in or after 2009 with one of the following four regimens: tenofovir plus emtricitabine and either efavirenz, rilpivirine, darunavir/ritonavir or atazanavir/ritonavir (all currently recommended as initial regimen). Time to initial suppression was significantly longer when rilpivirine, darunavir/ritonavir or atazanavir/ritonavir was the third drug used with tenofovir and emtricitabine as compared to efavirenz (*Table 2.5*). However, this was due to a higher rate of early virological success, since the rate at 12 months was similar. Changes in the frequency of HIV RNA monitoring after cART initiation over calendar time might also have a role, as well as other unmeasured confounders.

Table 2.5: Adjusted hazard ratios (95% confidence intervals) of time from cART initiation to a confirmed HIV RNA <100 copies/ml by Cox proportional hazard regression analysis in a subgroup of patients starting cART from 2009 onwards on one of the currently recommended regimens. Time to a confirmed HIV RNA <100 copies/ml is longer compared to the reference group when the hazard ratio is lower than 1.00. The analysis has been adjusted for all variables listed in Table 2.3.

	HIV RNA at start of cART (copies/ml)					
	<100,000 (n=1,926)			≥100,000 (n=1,475)		
Third drug alongside tenofovir and emtricitabine	HR (95% CI)	p value	% 1 yr. virological success*	HR (95% CI)	p value	% 1 yr. virological success*
efavirenz	1.00		97	1.00		91
rilpivirine	0.79 (0.67–0.93)	0.006	97	Not recommended		
darunavir/ritonavir	0.78 (0.67–0.92)	0.002	96	0.79 (0.68–0.92)	0.003	84
atazanavir/ritonavir	0.76 (0.65–0.88)	0.0004	93	0.84 (0.71–1.00)	0.04	88

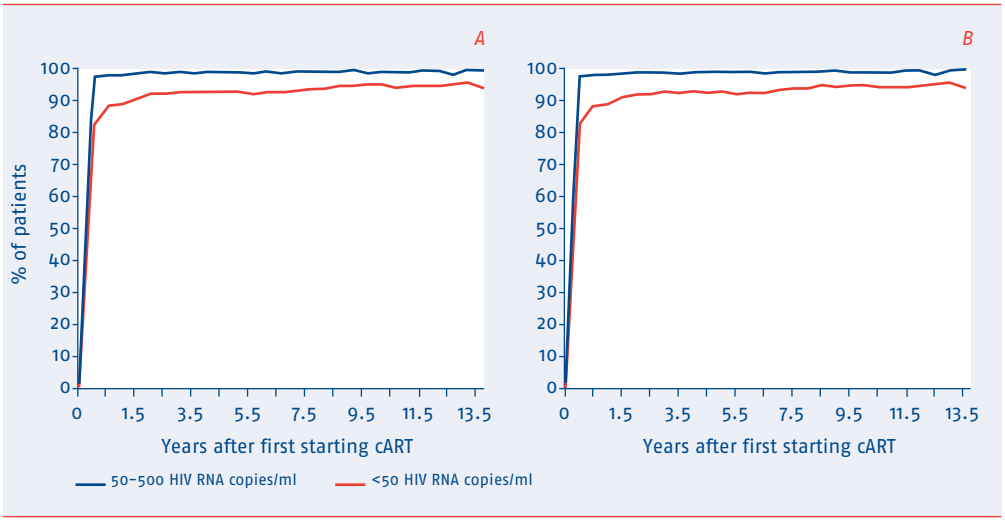
** Estimated by the Kaplan–Meier method.*

***Legend:** cART=combination antiretroviral therapy; HR=hazard ratio; CI=confidence interval.*

Long-term virological response

Figure 2.4 shows that the percentage of patients with a viral load <50 copies/ml increased from 82% at 1 year to 94% at 13.5 years and, likewise, increased from 88% to 94% for those continuously on cART. The increasing percentages with increasing time after starting cART probably reflect the selection of patients who do well and remain in follow-up.

Figure 2.4: The percentage of patients with a plasma HIV RNA concentration <50 (red line) and <500 copies/ml (blue line) at months 9, 12, 18, and at every 6 months of follow-up thereafter. Only plasma samples measured with assays with a lower detection limit of ≤50 copies are included. Plot A shows results from all patients after first starting combination antiretroviral therapy (cART), and plot B shows a subgroup of patients who remained on cART continuously, allowing for a therapy interruption of <2 weeks. A total of 12,112 treatment-naïve patients starting cART were included, but this number diminished over time due to differences in length of follow-up.



As these plots do not show the total percentage of patients with virological failure over time, we also analysed time to virological failure using Cox proportional hazard models. Virological failure is further described in *Chapter 3* on virological failure and resistance.

Immunologic response

After initiation of cART, most individuals suppress HIV viral load to levels below the detection limit of HIV RNA assays, and this is accompanied by an increase in CD4 cell count. Failure to suppress viraemia is associated with poorer CD4 cell count recovery to levels seen in the general population[59,60], approximately 800 cells/mm^3. In the general population, CD4 cell count is dependent on age, ethnicity, gender, and smoking status among other factors. Incomplete immunological recovery may also occur when plasma viral load is sustained to levels below the limit of detection and is associated with progression to AIDS and non-AIDS diseases[61]. Whereas CD4 cell count is considered the key prognostic factor, recent evidence has emerged suggesting that other immunological measures such as the CD4/CD8 ratio may also independently predict time to death and non-AIDS-defining endpoints[62-65]. In the general population, a low CD4/CD8 ratio has been associated with immunosenescence and all-cause mortality[66-68].

As the clinical benefit of cART is strongly related to the level of recovery of the immune status, in particular CD4 cell count (*Chapter 4*)[69-73], we report on the immune status of the 18,896 individuals who started cART from 1995 onwards, describing long-term CD4 cell count and CD4/CD8 ratio responses after the start of cART, including a description of patients with incomplete immunological recovery 3 years after having started cART.

Immune status in the treated population by calendar year

Figure 2.5 shows the immune status of patients in each calendar year after the start of cART. After starting cART, the percentage of patients with counts <350 cells/mm^3 (a level that puts them at higher risk of both AIDS and non-AIDS co-morbidity) dropped from 74% in 1996 to 13% in 2013. Likewise, the number of patients with CD4 cell counts <350 cells/mm^3 at the end of each calendar year decreased from 2,427 in 2008 to 1,748 in 2013 (numbers for 2013 may increase slightly because data collection is not yet complete). The trend of starting cART at higher CD4 cell counts, which has been observed since 2007, partly explains the drop in absolute number of patients with low CD4 cell counts at the end of each calendar year.

Figure 2.5: Last available CD4 cell count (cells/mm³) in each calendar year after the start of combination antiretroviral therapy (cART), shown as percentage (A) and absolute number (B) of patients. The last available CD4 cell count in each year and after the start of cART was selected for each patient.

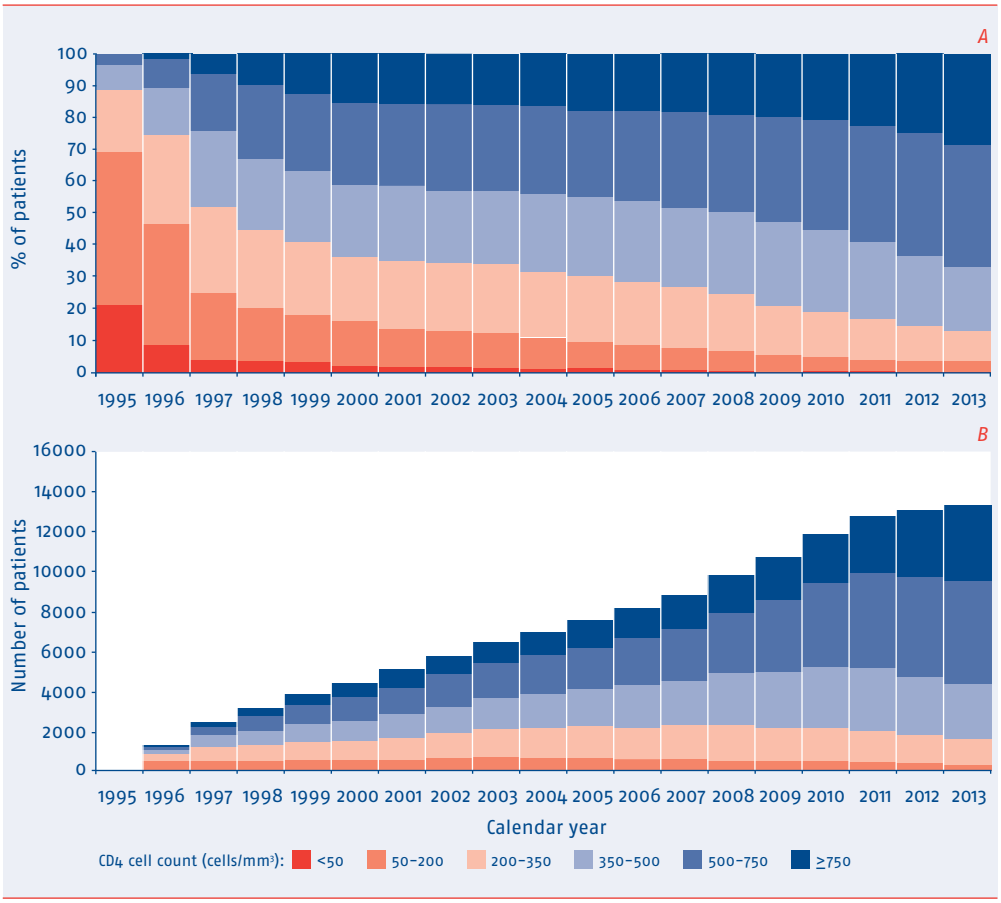
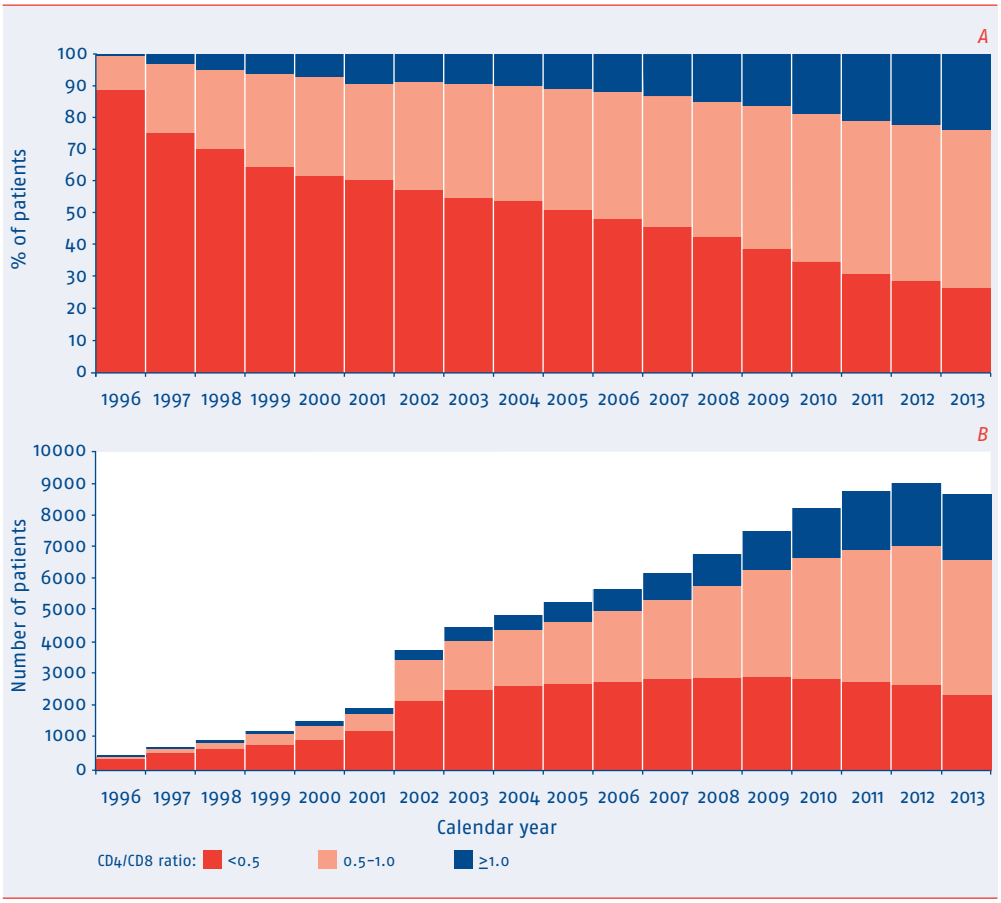


Figure 2.6 shows that the percentage of patients with a CD4/CD8 ratio of 1 or higher increased from 1% in 1996 to 24% in 2013.

Figure 2.6: *Last available CD4/CD8 ratio in each calendar year after the start of cART. The percentage (top plot) and the absolute number (lower plot) of patients with CD4/CD8 ratios are shown. The last available CD4/CD8 ratio in each year and after the start of cART was selected for each patient. Ratios are not available for all centres.*

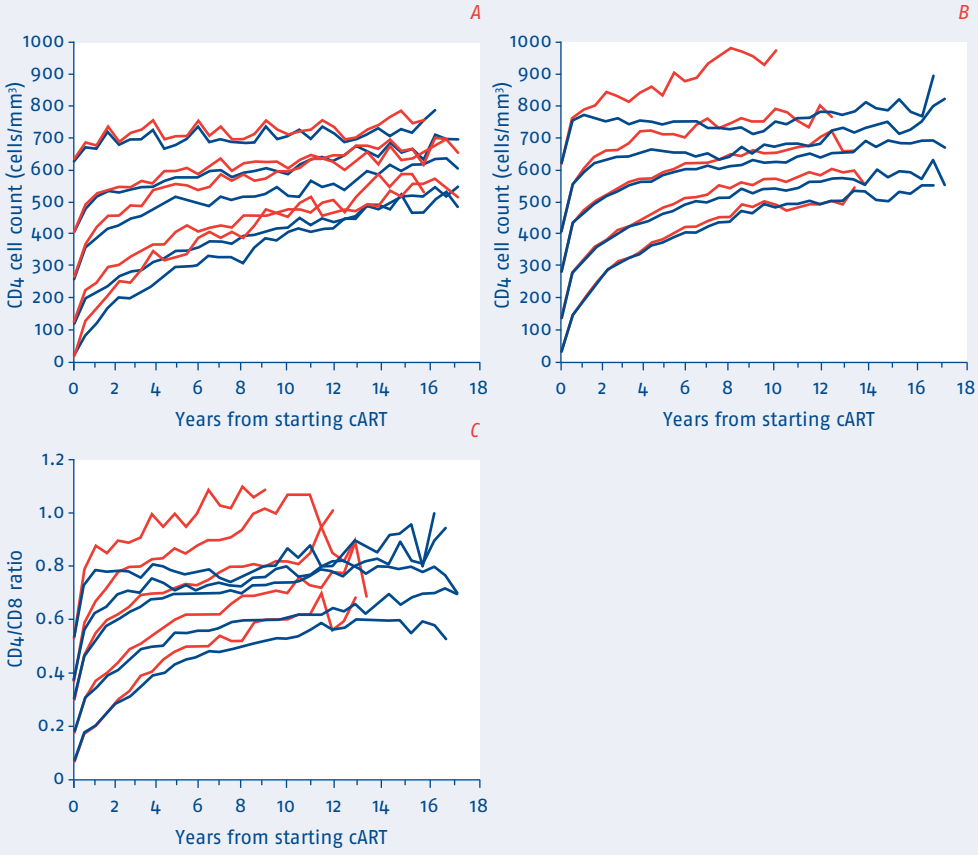


Longitudinal CD4 cell count changes after starting cART

Of the 18,896 patients (including both ART-naïve and ART-experienced patients) who first started cART, a CD4 cell count at the start of therapy or thereafter was available for 17,184 (91%) patients; these patients were included in further analyses. In this group, we studied CD4 cell count changes after starting cART, irrespective of whether patients had experienced one or more therapy interruptions or had been on cART continuously. In patients who had received antiretroviral monotherapy or dual therapy before starting cART, median CD4 cell counts increased from 200 cells/mm^3 (IQR, 80-340) at the start to 320 CD4 cells/mm^3 (IQR, 180-500) at 1 year, 450 (IQR, 280-640) at 5 years, 510 (IQR, 330-730) at 10 years, and 590 (IQR, 410-800) at 17 years.

The median CD4 cell count at the start of cART in ART-naïve patients was slightly higher compared to ART-experienced patients, with a median of 240 cells/mm^3 (IQR, 120-350) and greater increase: to 390 (IQR, 240-530) at 1 year, 530 (IQR, 380-700) at 5 years, 580 (IQR, 420-780) at 10 years, and 650 (IQR, 480-850) at 17 years. *Figure 2.7* shows the median CD4 cell count after the start of cART stratified by the CD4 cell count at the start of cART. In the ART-experienced group (*Figure 2.7.A*), median CD4 cell counts for patients starting cART with <50 and 50-200 cells/mm^3 seemed to converge after 12 years. In the group of patients who started with low CD4 cell counts, this may be partly due to patients with a poor immunological response dying after starting treatment and to survivors doing well and remaining in follow-up.

Figure 2.7A–C: Median CD4 count according to the count at the start of combination antiretroviral therapy (cART) in ART-experienced patients (A) and ART-naïve patients (B), and CD4/CD8 ratio in ART-naïve patients (C), all stratified by CD4 cell count at the start of cART (<50, 50–200, 200–350, 350–500 and ≥500 cells/mm³). Blue lines show the median CD4 cell counts (in plot A and B) and CD4/CD8 ratio (in plot C) in all patients after starting cART, including patients on cART and those who experienced a therapy interruption. Red lines in plot A, B and C show the median CD4 cell counts and CD4/CD8 ratio for the subgroup of patients with an initial suppression to <500 (plot A) and <50 (plot B and C) copies/ml within nine months after starting cART and with suppressed levels of plasma HIV RNA concentration thereafter (<500 copies/ml in plot A and <200 in plots B and C). In this subgroup, CD4 cell counts and CD4/CD8 ratio were censored at the first of two consecutive measurements of HIV RNA >500 (plot A) or >200 (plot B) copies/ml after the initial suppression. Because plot A includes treatment-experienced individuals who started cART during calendar years when less sensitive viral load assays were used in routine clinical practice, different cut-offs were used in plot A compared to plots B and C. Trend lines stopped when the number of patients in a subgroup dropped to below 40 patients.



Legend: cART=combination antiretroviral therapy.

To study the maximum capacity of cART to restore CD4 cell counts, we performed an additional analysis that was restricted to therapy-naïve patients who experienced sustained viral suppression (<200 copies/ml) on cART. Only patients were included who had reached HIV RNA levels of <50 copies/ml within nine months after the start of cART. Patients were censored after virological failure (defined as two consecutive viral load measurements >200 copies/ml), after a therapy interruption of 2 weeks or more, or after the start of immunosuppressive therapy (chemotherapy, interferon). There was no restriction on the duration of time that patients' viral loads were undetectable after initial suppression. This group, therefore, represents a highly selected group of patients whose CD4 cell count changes show the best possible response to cART. Median CD4 counts at 10 years were 490 cells/mm^3 for patients starting with <50 cells/mm^3, 570 cells/mm^3 for those starting between 50 and 200 cells/mm^3, 660 cells/mm^3 for those starting between 200 and 350 cells/mm^3, 780 cells/mm^3 for those starting between 350-500 cells/mm^3, and 910 cells/mm^3 for those starting with 500 cells/mm^3 or higher (*Figure 2.7 B*, red lines). Although median CD4 cell counts fluctuated over time and did occasionally decrease, the trend over time was an increase in median CD4 cell counts in patients remaining virologically suppressed on cART. Median CD4 cell counts for subgroups of patients within each of the five CD4 cell count categories at the start of cART did not converge. For all patients starting cART with <50 CD4 cells/mm^3, the median CD4 cell counts (blue lines) did not differ greatly from the median CD4 cell counts for the restricted populations with suppressed viral load (red lines). The difference in median CD4 cell counts over time between all patients and those with a sustained suppressed viral load became more pronounced as the CD4 cell count at the start of cART was higher. This may be because a substantial proportion of patients starting cART within the highest CD4 cell count strata either interrupted therapy or did not maintain a viral load <50 copies/ml whilst on therapy, as shown earlier.

Similar to the CD4 cell count response, median CD4/CD8 ratios during sustained virological suppression on cART (*Figure 2.7C*, red lines) in the five baseline CD4 cell count strata did not seem to converge. Importantly, the ability to achieve a CD4/CD8 ratio of 1 or higher seemed to be strongly related to the CD4 cell count at the start of cART. Median CD4/CD8 ratio reached levels higher than 1 after 3.5 years of suppressive cART when counts at the start were ≥500 cells/mm^3, and after 8 years when counts were 350-500 cells/mm^3. Median CD4/CD8 ratio levels of 1 or higher were only reached within 10 years of virologically suppressive cART when cART was started with ≥350 CD4 cells/mm^3. Although lower CD4/CD8 ratios have been suggested to be associated with increased immune activation markers during sustained viral suppression [74], non-AIDS events [65], and subclinical atherosclerosis [62], the clinical significance of these findings remains to be further investigated in larger cohorts.

Incomplete immunological recovery

Despite long-term successfully suppressed viral load during cART, compared to a continued CD4 cell count recovery, incomplete CD4 cell count recovery is associated with an increased risk of mortality, AIDS, and non-AIDS diseases[61,75,76]. We investigated the CD4 cell count response in patients who started cART with ≤350 cells/mm^3, had not received prior monotherapy or dual therapy, had been continuously on cART at 2 and 3 years (allowing for therapy interruptions of less than 2 weeks), and were virologically successfully treated at 2 and 3 years (defined as having supressed viral load of ≤100 copies/ml within 9 months from starting cART and not having had a confirmed viral load of >200 copies/ml after initial suppression; single blips between 200 and 500 copies/ml were allowed). The CD4 cell counts between 1.5 and 2 years (closest to 2 years), and between 2.5 and 3 years (closest to 3 years) were selected. Median CD4 cell count at 2 years was 440 cells/mm^3 (IQR 330-570) and at 3 years 480 (360-610). *Table 2.6* shows the distribution of CD4 cell counts in patients at 2 and 3 years after starting cART, according to whether counts at start of cART were <200 or 350 cells/mm^3.

***Table 2.6:** Number and percentage of patients with <200 and <350 CD4 cells/mm^3 at the start of cART and their CD4 cell count at 2 and 3 years.*

		CD4 cell count at start of cART (cells/mm^3)		
		<200		<350
CD4 cell count at 2 / 3 years	2 years	3 years	2 years	3 years
<200	301 (13%)	134 (7%)	313 (7%)	142 (4%)
200-350	813 (36%)	576 (30%)	1,025 (22%)	709 (19%)
350-500	687 (30%)	611 (32%)	1,482 (32%)	1,115 (30%)
500-750	397 (17%)	458 (24%)	1,509 (32%)	1,366 (37%)
≥750	92 (4%)	114 (6%)	330 (7%)	381 (10%)
Total	2,290	1,893	4,659	3,713

***Legend:** cART=combination antiretroviral therapy.*

At three years, 37% of patients who started cART at <200 CD4 cells/mm^3 and 23% who started with <350 CD4 cells/mm^3 still had values <350 cells/mm^3, and thus they remained at an increased risk for an AIDS or non-AIDS defining event.

Independent risk factors significantly associated with still having <200 CD4 cells/mm^3 after three years of virologically suppressive cART when cART was started at <200 cells/mm^3 were: older age, lower CD4 cell count at the start of cART, an HIV RNA <100,000 copies/ml at the start, and infection through intravenous drug use (*Table 2.7*). Compared with the start of cART during 2007-2010, there was a trend for the start between 1999 and 2002 to be associated with an increased risk of incomplete immunological recovery. There was no significant difference in the risk of incomplete recovery between starting with a boosted PI and an NNRTI-based regimen.

Table 2.7: *Adjusted* odds ratios of the risk of maintaining a CD4 cell count <200 cells/mm³ after three years of virologically successful combination antiretroviral therapy in patients starting treatment at <200 CD4 cells/mm³.*

	OR (95% CI)	(Overall) p value
Gender		
Male	1.00	
Female	0.74 (0.42–1.31)	0.30
Age (per 10 years older)	1.39 (1.14–1.68)	0.0009
CD4 cell count at the start of cART (per 50 cells/mm³ increase)	0.47 (0.39–0.58)	<0.0001
Region of origin		(0.41)
Netherlands	1.00	
Caribbean & South America	0.83 (0.44–1.58)	0.58
Sub-Saharan Africa	1.12 (0.60–2.10)	0.71
Western Europe / North America	0.95 (0.46–1.96)	0.88
Other	0.45 (0.19–1.09)	0.08
HIV RNA at the start of cART (log_{10} copies/ml)		(0.02)
<4	1.36 (0.61–3.01)	0.45
4–5	1.00	
≥5	0.57 (0.37–0.86)	0.008
Initial regimen		(0.25)
NNRTI	1.00	
PI	1.12 (0.47–2.66)	0.80
PI/r	0.93 (0.62–1.42)	0.75
3 NRTI	1.80 (0.51–6.34)	0.36
Other	2.04 (1.00–4.15)	0.05
Transmission risk group		(0.01)
Homosexual	1.00	
Heterosexual	0.99 (0.60–1.64)	0.97
IDU	3.55 (1.36–9.24)	0.01
Socio-economic status**		(0.32)
1–2	1.22 (0.70–2.13)	0.48
3	1.00	
4–5	1.50 (0.95–2.38)	0.08

** In addition to all variables listed, year of starting cART and co-infection with HBV and HCV were also considered for adjusted analyses.*

*** See Table 2.1.*

Legend: *cART=combination antiretroviral therapy; OR=odds ratio; CI=confidence interval; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; IDU=injecting drug user; HBV=hepatitis B virus; HCV=hepatitis C virus.*

The Antiretroviral Therapy Cohort Collaboration (ART-CC) and Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

Risk factors for failure to achieve CD4 counts of ≥200 cells/mm^3 after three years of sustained viral suppression were identified in patients with <200 CD4 cells/mm^3 at the start of the suppressed period. These factors were: older age, lower initial CD4 cell count, male heterosexual and injecting drug user transmission, cART initiation after 1998, and longer time from initiation of cART to the suppressed period. Individuals with <200 CD4 cells/mm^3 after three years of viral suppression had a significantly increased mortality (adjusted hazard ratio, 2.60; 95% confidence interval, 1.86-3.61) compared to those with 200 CD4 cells/mm^3 [77].

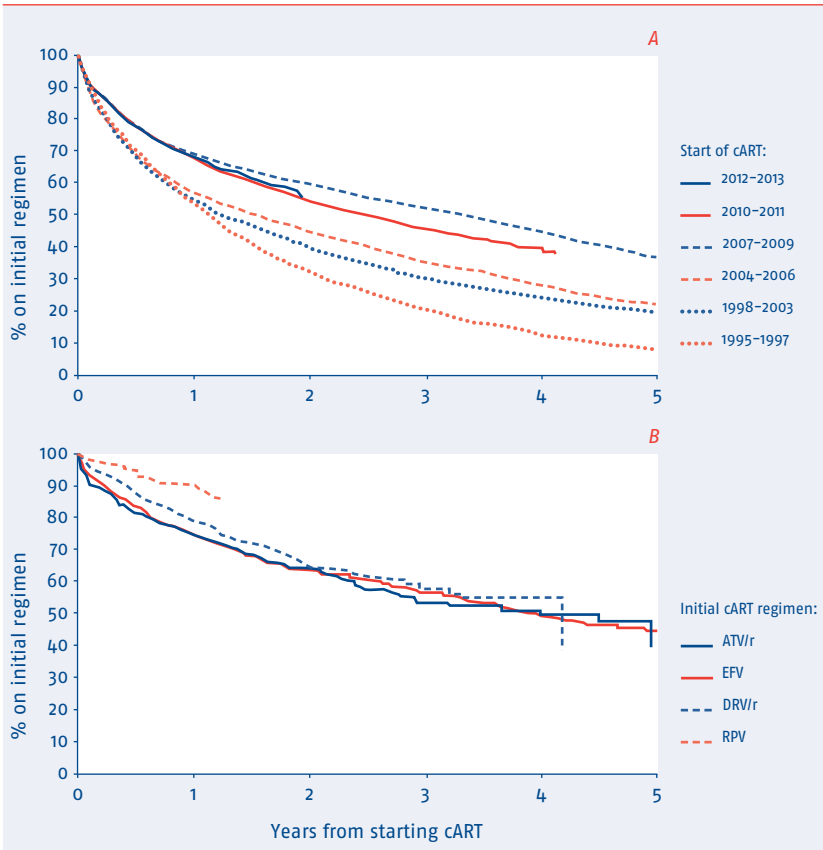
Therapy switches and incidence of toxicity-driven regimen change during the first three years after start of cART

Antiretroviral therapy may be associated with adverse clinical events and laboratory toxicities. This may lead to reduced adherence and treatment discontinuation, which are major reasons for treatment failure and emergence of antiretroviral drug resistance [78-80]. In this section we report on trends over time in treatment switches and especially treatment-limiting toxicities during the first three years after the start of cART.

Discontinuation of the initial regimen

Of the 18,896 patients who had started cART, 14,024 discontinued the initial regimen. A trend over time towards a longer interval before discontinuation of the initial cART regimen is shown in *Figure 2.8*. However, a lower percentage of patients starting cART between 2010 and 2011 were still on the initial regimen three years after starting cART, compared to those who started cART between 2007 and 2009. The percentage of patients still on the initial cART regimen three years after starting was 21% (95% CI, 19-22%) for those starting during 1995-1997, 31% (95% CI, 30-32%) during 1998-2003, 36% (95% CI, 34-38%) during 2004-2006, 52% (95% CI, 51-54%) during 2007-2009, and 46% (95% CI, 44-48%) for those starting in 2010 or 2011. A study from the Antiretroviral Therapy Cohort Collaboration (ART-CC), which includes data from SHM, found that rates of modification and interruption were particularly high in the first year of ART. In adjusted analyses, rates of interruption were higher for patients starting ART with CD4 cell count >350 cells/mm^3 than for other patients. Decreased rates of substitutions or switches to nonstandard regimens in recent years may be linked to greater use of well tolerated once-daily drugs [81].

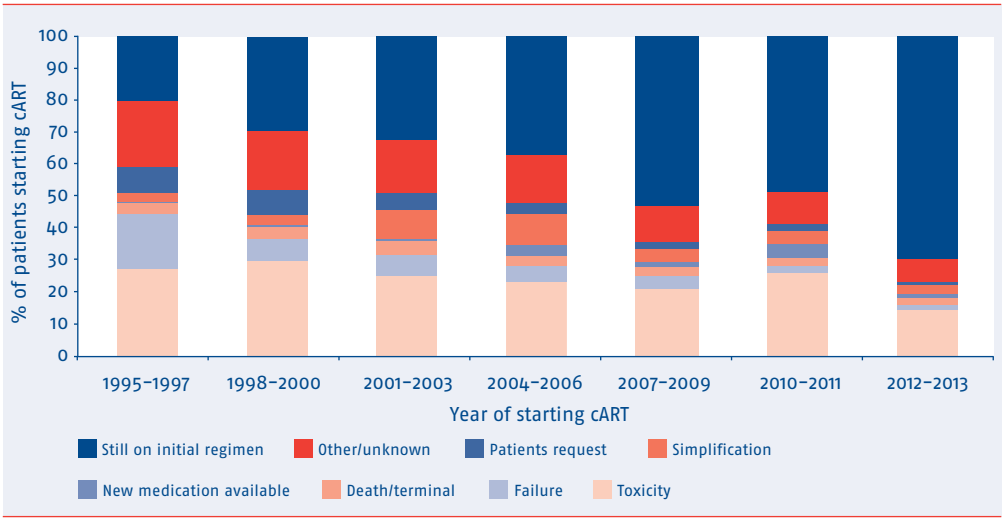
Figure 2.8: Kaplan–Meier estimates of the percentage of patients remaining on their initial combination antiretroviral therapy (cART) regimen by period of initiation (A) and by cART regimen (B) in a subset of patients starting in or after 2009 on tenofovir and emtricitabine plus a third drug (one of the four currently recommended starting regimens). Planned switches according to study protocol (in trial participants) and same drug changes from individual components to part of fixed-dose co-formulations were not counted as a regimen change.



***Legend:** ATV/r=atazanavir plus ritonavir; DRV/r=darunavir plus ritonavir; EFV=efavirenz; RPV=rilpivirine.*

In the subset of patients starting cART in or after 2009 on one of the four currently recommended initial regimens, a significantly higher proportion of individuals starting on tenofovir emtricitabine plus rilpivirine continued on the regimen compared to those whose regimen included efavirenz, darunavir/ritonavir or atazanavir/ritonavir (all p<0.0001). As rilpivirine has only been available in the Netherlands since 2012, follow-up for this regimen is shorter compared to the other 3 regimens. Time to discontinuation was not significantly different between regimens containing efavirenz, darunavir/ritonavir and atazanavir/ritonavir.

Figure 2.9: Relative distribution of reasons for stopping or switching at least one of the drugs in the regimen within three years of combination antiretroviral therapy (cART) initiation according to starting year of cART. (Failure includes virological, immunological and clinical failure; other reasons for stopping include new medication available, pharmacokinetic reasons, precautionary reasons [such as a high cardiovascular risk profile], problems with adherence and unknown reasons).



***Legend:** cART=combination antiretroviral therapy.*

Overall, 10,983 patients discontinued the initial regimen within three years. The most common reasons for discontinuing were toxicity (41%), treatment failure (11%), simplification (8%), and patient request (7%), which are similar to results reported by others [81, 82]. *Figure 2.9* shows trends in reasons for stopping over time. An increasing proportion of patients were still on the initial regimen at three years. Results for patients starting in 2012 and 2013, and to a lesser extent, 2011, should be interpreted with caution as most of these patients have not yet had three years of follow-up. Of those who discontinued cART within three years of initiating cART (cART started between 1995 and 1997), 22% were due to failure, compared to 4% of all discontinuations in 2010 or 2011. Finally, over time, toxicity has remained the major reason for discontinuing the initial regimen.

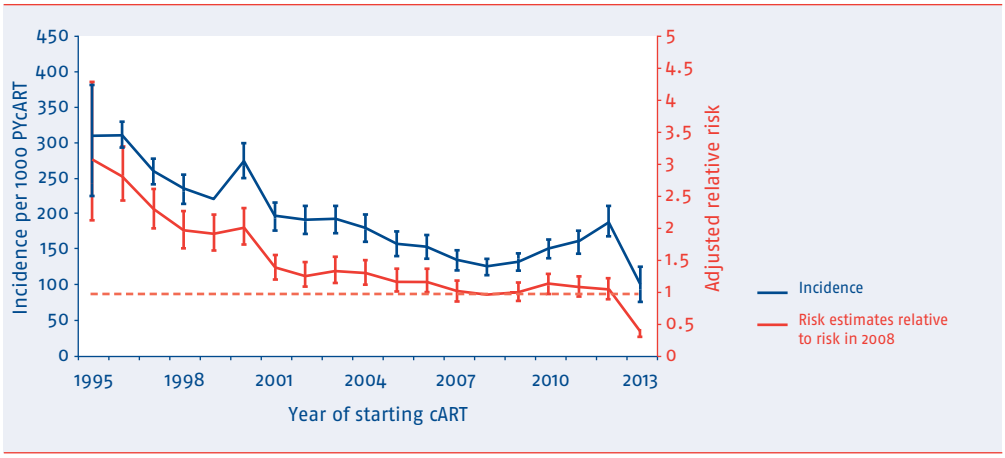
Toxicity was also the major reason for stopping in those patients who discontinued one of the four currently recommended initial cART regimens within one year (71%, 58%, 51% and 36% of individuals discontinuing an initial regimen containing tenofovir and emtricitabine and either efavirenz, rilpivirine, atazanavir/ritonavir or darunavir/ritonavir, respectively). Simplification was another reason for stopping one or more drugs in a high percentage of patients on tenofovir and emtricitabine and darunavir/ritonavir (58% of discontinuations within 1 year from the start of cART), mostly followed by fixed-dose single-tablet regimens tenofovir/emtricitabine/rilpivirine (43% of discontinuations due to simplification) and tenofovir/emtricitabine/efavirenz (20%).

Toxicity-driven therapy changes

As toxicity is the most common reason for discontinuing not only the first regimen but also subsequent regimens, we will focus further on trends over time in toxicity-driven therapy changes during the first three years of cART. Of note, these changes are importantly influenced by the extent to which, over time, less toxic alternatives have become available to replace regimen components associated with particular toxicities.

During the first three years after the start of cART, patients were followed for a total of 45,608 person years (PY), of which 44,622 person years (97.8%) on cART (PYcART). The overall incidence of toxicity-driven regimen changes was 193 (95% CI 189-198) per 1000 PYcART. Patients could change the regimen more than once. During follow-up, 13,147 of the 18,896 patients (70.0%) did not change the regimen because of toxicity. The maximum number of changes due to toxicity in a single patient was 14.

Figure 2.10: Toxicity-driven changes in therapy during the first three years after the start of combination antiretroviral therapy (cART). The incidence per 1000 PY cART for each starting year of cART (blue line, vertical lines are 95% Poisson confidence intervals [CI]) and adjusted risk estimates (red line, reference year is 2008, vertical lines are 95% CI) obtained with logistic regression models including: age, gender, region of origin, transmission risk group, weight, time after starting cART (0-6, 6-12, 12-24 and 24-36 months), HCV co-infection status, CD4 cell count and HIV RNA at the start of cART, initial regimen, and whether cART was started during primary infection.



Legend: cART=combination antiretroviral therapy; PYcART=person years on cART during the first 3 years following the start of cART; CI=confidence interval; HCV=hepatitis C virus.

The incidence was highest (491 per 1000 PYcART) during the first three months after the start of cART; it declined to 215 per 1000 PYcART between three and six months, 176 per 1000 PYcART between 6 and 12 months, 149 per 1000 PYcART between 12 and 24 months, and 125 per 1000 PYcART between 24 and 36 months ($p<0.0001$). The incidence of toxicity-driven

therapy changes during the first three years following cART initiation declined from 2000 to 2008 (*Figure 2.10*). The increase thereafter, from 2009 onwards, can be largely attributed to confounders and patients not yet having three years of follow-up after starting cART, although in analyses adjusted for time after start of cART and other confounders, the likelihood of a toxicity-driven therapy change remained slightly elevated when cART was initiated in 2010 (relative risk [RR] compared to 2008 1.16, 95% CI 1.01-1.32, p=0.03), but not when cART was started in 2011 or 2012 (*Figure 2.10*). Therefore other factors, such as introduction of new medication associated with less toxicity, are likely to play a role as well.

The likelihood of a toxicity-driven therapy change was 42% higher in women than in men, independent of weight at the start of cART (p<0.0001). In MSM, the likelihood of a toxicity driven therapy change was 15% (95% CI 5-27, p=0.002) higher when the CD4 cell count at the start was ≥500 cells/mm^3, compared to 200-500 cells/mm^3. However, no such association was found in those with heterosexually acquired HIV (≥500 compared to 200-500 cells/mm^3 RR 0.72, 95% CI 0.42-1.22, p=0.22). There was no evidence that the association between high CD4 cell counts in MSM starting cART and the risk of a toxicity-driven therapy change had changed over time (test for interaction, p=0.17).
Independent of CD4 cell count at the start, starting cART during primary infection was also associated with an increased risk, mainly when it was started in or before 2006 (hazard ratio [HR] 1.54, 95% CI 1.34-1.76, p<0.0001) and less so in or after 2007 (HR 1.16, 95% CI 1.01-1.35, p=0.04.

In another adjusted Cox regression analysis of time to a toxicity-driven therapy change, restricted to individuals starting cART in or after 2009 on a combination of tenofovir and emtricitabine with either efavirenz, rilpivirine, atazanavir/ritonavir or darunavir/ritonavir, the hazard of a toxicity-driven regimen change was lower when cART included rilpivirine (HR) compared to efavirenz 0.30, 95% CI 0.18-0.49, p<0.0001), darunavir/ritonavir (HR 0.47, 95% CI 0.37-0.68, p<0.0001) or atazanavir/ritonavir (HR 0.74, 95% CI 0.61-0.90, p=0.002).

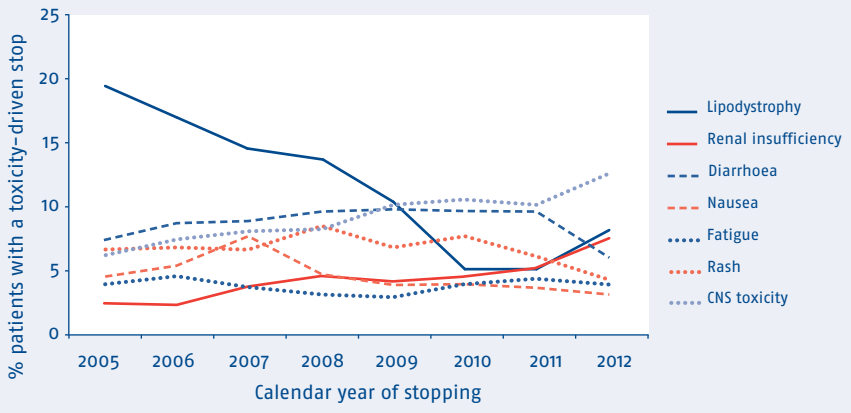
We have shown that although the incidence of toxicity-driven therapy changes declined up to 2008, toxicity does remain the major reason for regimen change. In the next paragraph we give an overview of patterns in the most frequently recorded adverse events associated with these therapy changes.

Adverse events associated with a toxicity-driven therapy change

An overview of adverse events associated with a toxicity-driven therapy change is given in *Table 2.2* in the Web Appendix. Whilst the absolute number of patients with at least one toxicity-driven therapy change was stable between 2008 and 2011, it increased to 1,338 in 2012 and 1,112 in 2013 (likely to increase further due to the lag in data entry). In addition to an increasing number of patients on cART over time, the availability of new drugs associated with less toxicity has probably driven the increase during the last 2 years.
Figure 2.11 shows the change in distribution of the seven most frequently-registered adverse events associated with a regimen change over time. The most interesting change was the

absolute and relative decline in treatment-limiting toxicity due to lipodystrophy (both peripheral fat loss and central fat accumulation): down from 153 patients in 2006 (17% of all toxicity-driven therapy changes in 2005) to 37 (3%) in 2013. In most of these cases of therapy change due to lipodystrophy, patients discontinued using lamivudine/zidovudine (36%), followed by lamivudine/zidovudine/abacavir (18%) and stavudine (13%). These were replaced by tenofovir/emtricitabine (in 57% of the therapy changes that were followed by a new cART regimen), abacavir/lamivudine (19%), or tenofovir/lamivudine (11%).
The percentage of patients who stopped because of central nervous system (CNS) toxicity increased from 81 out of 889 patients with a toxicity-driven therapy stop in 2006 (9%) to 216 out of 1,112 patients in 2013 (19%). Among those 216, efavirenz was stopped due to CNS toxicity in 203 patients (94%). Of the 195 patients (96%) who subsequently switched to another cART regimen, 58% switched to rilpivirine, 20% switched to nevirapine, 10% to ritonavir-boosted darunavir, and 5% to ritonavir-boosted atazanavir.
The percentage of changes because of renal insufficiency (both acute and chronic combined) was lowest (3%) in 2006 and increased thereafter (8%) in 2013. Most of the discontinuations in 2012 and 2013 involved tenofovir (73% of cases, either as a single drug or as part of fixed-dose combinations) or lamivudine (20% of cases). The new regimen was most likely to contain abacavir/lamivudine (73% of cases).
The percentage of therapy changes because of nausea and diarrhoea was relatively stable between 2006 and 2013. The percentage of changes because of rash was highest in 2008, at 9% of toxicity-driven therapy changes, and declined thereafter to 5% in 2013.

Figure 2.11: *Relative distribution over time of the seven most frequently recorded adverse events associated with a toxicity-driven therapy change of at least one of the drugs in the combination antiretroviral therapy (cART) regimen. For every toxicity-driven therapy change, one to three adverse events can be recorded; therefore, percentages do not add up to 100%. Central nervous system (CNS) toxicity includes the following adverse events in the database: dizziness, sleeplessness, nightmares, mood changes, concentration disorders, and confusion.*



Legend: *CNS=central nervous system.*

Summary and Conclusion

CD4 cell count at the start of cART

In summary, CD4 cell counts at which cART is initiated have continued to increase since 2007 and reached a median of 330 cells/mm^3 in 2012 and 370 cells/mm^3 in 2013. Counts at the start of cART in 2013 were similar in men from Dutch and Caribbean or South American origin, but remained lower in men from Sub-Saharan Africa. In women, CD4 cell counts at the start were also lower in those from Sub-Saharan Africa, the Caribbean, and South America. cART is currently recommended for all HIV-infected patients. If the goal of antiretroviral therapy is to restore CD4 cell counts to levels seen in uninfected patients, it is important to start cART at ≥350 CD4 cells/mm^3, as normal cell counts with virologically successful cART are approached only after eight years of continuous therapy. Although patients currently start cART at higher CD4 cell counts than ever before, a considerable proportion (58% of women and 46% of men) continue to be late-starters, having either AIDS or <350 CD4 cells/mm^3 at the time they start cART. The five most frequent starting regimens in 2013 were tenofovir plus emtricitabine, combined with efavirenz (30%), darunavir/ritonavir (20%), rilpivirine (19%), nevirapine, (9%), or atazanavir/ritonavir (9%). The fixed-dose combination of tenofovir and emtricitabine was used in 92% of all starting regimens in 2013.

Virological response

Within nine months, 87% of patients who started cART between 2011 and 2013 reached initial virological success (a confirmed HIV RNA <100 copies/ml). Ensuring rapid suppression of plasma viral load and maintaining suppression is important as high-level viraemia or longer periods of low-level viraemia are associated with smaller CD4 cell count increases, higher probability of treatment failure, and emergence of drug resistance. Although time from the start of cART to virological success when cART was started in or before 2006 was significantly longer in younger individuals (<30 years of age) compared to older individuals, in individuals born in the Netherlands compared to those born elsewhere, and when cART was initiated at high CD4 cell counts (≥500 cells/mm^3) compared to lower counts, these differences were no longer present in individuals starting between 2011 and 2013. Virological suppression rates one year after the start of cART on one of the four currently recommended 'third' drugs (efavirenz, rilpivirine, atazanavir/ritonavir or darunavir/ritonavir, in addition to tenofovir and emtricitabine) were 96% and 89% when cART was started at <100,000 and ≥100,000 HIV RNA copies/ml, respectively.

Immunological response

A timely start of cART is important because CD4 cell counts approach those seen in the general population after eight years of virologically suppressive cART only if cART is started at ≥350 CD4 cells/mm^3. Despite virologically successful cART, 37% of patients starting cART at CD4 cell counts <200 cells/mm^3 and 23% of patients starting at counts <350 cells/mm^3 still had counts <350 cells/mm^3 at three years of treatment and thus remained at an increased risk of AIDS and non-AIDS morbidity.

Similar to CD4 cell count changes, normalisation of the CD4/CD8 ratio towards 1 or above seems to be strongly related to the CD4 cell count at the start of cART. Median CD4/CD8 ratio exceeded 1 after 3.5 years of suppressive cART if CD4 cell counts were ≥500 cells/mm^3, and after 8 years if counts at the start were between 350 and 500 cells/mm^3. However, patients starting at lower CD4 cell counts did not reach median levels higher than 1 during follow-up. Although lower CD4/CD8 ratios have been suggested to be associated with increased immune activation markers during sustained viral suppression and with subclinical atherosclerosis, the clinical significance of these findings remains to be investigated further.

Durability and toxicity

Lifelong use of ART requires tolerable and durable regimens. Approximately 50% of patients currently starting cART are able to remain on their first-line regimen for more than three years. Toxicity remains the main reason for changing treatment, although the incidence of therapy changes driven by toxicity has dramatically declined since the introduction of cART. MSM have a higher likelihood of a toxicity-driven therapy change compared to heterosexual men, as do women and older patients. Among MSM, the risk was higher when cART was started at CD4 cell counts ≥500 cells/mm^3. Among those patients changing therapy due to toxicity, the most frequently recorded adverse event in 2013 was CNS toxicity, which led to substitution of efavirenz with rilpivirine in many patients and likely explains the observed increasing rate of first-line cART discontinuation in the last four years. There remains a need for better tolerated drugs, such as rilpivirine, and more individualised strategies for patient management to continuously improve the durability of cART regimens.

3. Virological failure and resistance

Ard van Sighem, Luuk Gras, Anne Wensing, Jan Prins, Kees Brinkman and Peter Reiss

Introduction

Treatment with combination antiretroviral therapy (cART) generally results in sustained suppression of HIV viral load to levels below the threshold of quantification. It is generally believed that viral replication has been halted in individuals on cART, although some studies of treatment intensification suggest that active replication persists in some infected individuals[83]. Moreover, patients may have difficulty maintaining optimal adherence to the treatment regimen because of, for example, drug-related toxicities resulting in drug concentrations that may be too low to completely halt the replication of HIV. Monitoring of longer-term virological response is, therefore, of importance as high-level viraemia has been associated with a poorer clinical outcome and smaller increases in CD4 cell count[59,84-87]. In addition, frequent or persistent periods of low-level viraemia have been reported to be associated with the emergence of drug resistance and treatment failure[88,89].

Here we report on the long-term virological response in the 12,112 antiretroviral therapy-naïve patients starting cART from 1999 onwards whose short-term response was described in the preceding chapter. We also look at the presence of resistance in the total treated HIV-infected population followed by Stichting HIV Monitoring (SHM) and the extent to which resistant virus strains are transmitted to uninfected individuals.

Virological failure

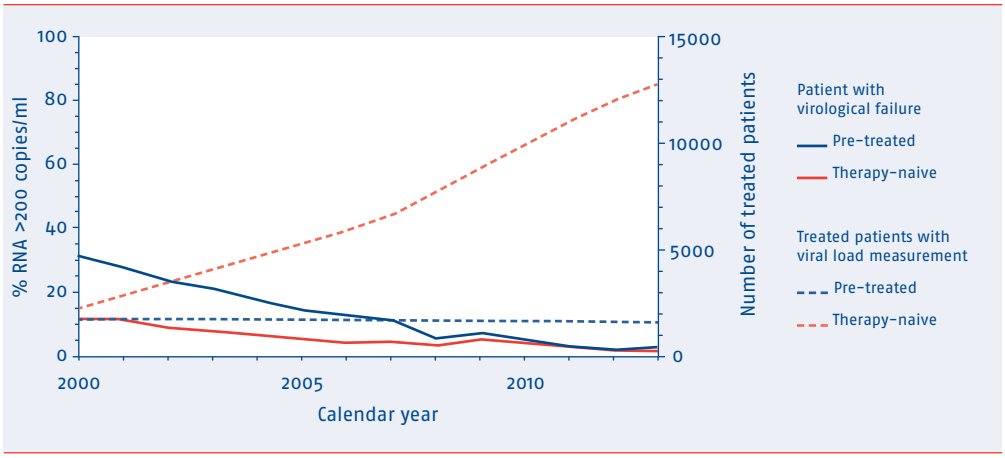
Low-level viraemia

After having achieved initial virological suppression, more than 30% of patients on cART experience episodes of viraemia[84]. Often, these episodes are limited to a single measurement above the quantification limit of the viral load assay, so-called blips[90,91]. However, the clinical significance of infrequent low-level viraemia remains less clear. Short-term low-level viraemia is not associated with AIDS, non-AIDS events, death, or CD4 cell count response[84,92-95]. Although short-term low-level viraemia is assay-dependent[96] and became more frequently detected when new assays with a lower limit of detection were introduced[97,98], resistance-associated mutations have also been found in patients with plasma viral load levels below 50 copies/ml[89,99]. In addition, even at plasma viral load levels below 50 copies/ml, patients with low, but detectable, plasma viral load levels had a lower probability of sustained viral suppression than patients with completely undetectable viral loads[100].

Less virological failure

To minimise the effect of blips and the new quantification assay, we used a viral-load threshold of 200 copies/ml as a marker of virological failure[9]. Since 2000, the annual proportion of patients with a viral load above 200 copies/ml has decreased to approximately 3%. During the same time, the difference between patients pre-treated with monotherapy or dual therapy and those starting cART whilst antiretroviral therapy-naïve has disappeared (*Figure 3.1.; Web Appendix Figure 3.1*). From 2008 onwards, approximately equal proportions of patients in these two groups experienced a viral load above 200 copies/ml, coinciding with the introduction of new antiretroviral drugs. These drugs are able to suppress viral load, even in patients who have had multiple episodes of virological failure and harbour virus strains that are resistant to many of the older drugs.

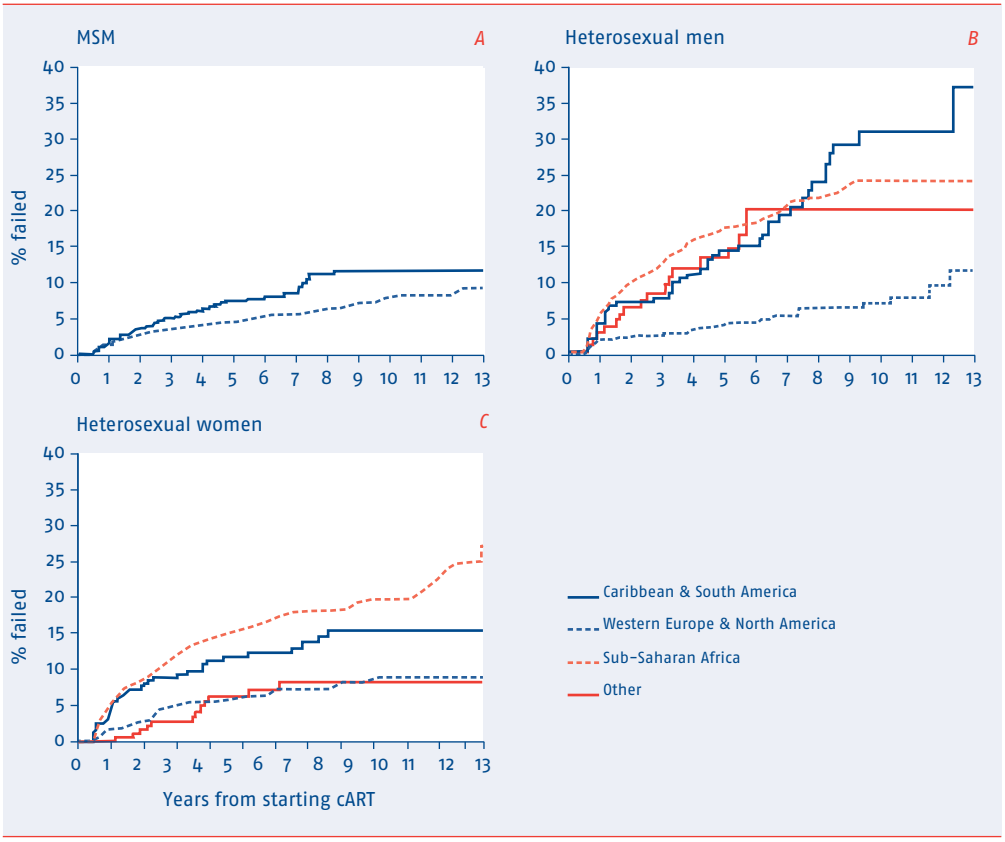
Figure 3.1: *Annual number of treated patients with a viral load measurement whilst on treatment (dashed lines), and the proportion of patients with virological failure (solid lines) (i.e., a viral load above 200 copies/ml whilst on treatment and measured at least four months after start of cART or four months after resuming treatment following a treatment interruption). Among approximately 1,700 pre-treated patients, the proportion with failure by a threshold of 200 copies/ml decreased from 32% in 2000 to 3% in 2013. Among previously therapy-naïve patients, failure was less common and decreased from 11% to 2% during the same period, whilst the number of such patients increased from approximately 2,375 to 12,800.*



Virological failure was defined as time to the first of two consecutive plasma viral HIV RNA levels more than 200 copies/ml after 24 weeks on antiretroviral therapy, as defined in the US Department of Health and Human Services (DHHS) guidelines[9]. cART interruptions shorter than two weeks did not count as interruptions. In total, 859 (7.5%) out of 12,112 treatment-naïve patients who started cART from 1999 onwards met the definition of virological failure.

The Kaplan–Meier estimate of the percentage of patients with virological failure within 12 years after first starting cART was 13% (95% confidence intervals [CI] 12-14%). Men who have sex with men (MSM) from Western Europe (including the Netherlands) and North America were significantly less likely to experience virological failure compared to those from the Caribbean/South America (*Figure 3.2A*, overall log rank p=0.005). Among heterosexuals, differences in the risk of failure were more pronounced. The risk was higher among heterosexual men from Sub-Saharan Africa and the Caribbean/South America compared to those from Western Europe/North America (middle plot in *Figure 2.5*, overall log rank p<0.0001). Although less pronounced than in heterosexual men, the risk was also higher in women from Sub-Saharan Africa, the Caribbean/South-America compared to those from Western Europe/North America (overall log rank p<0.0001).

Figure 3.2: *Kaplan–Meier estimates of the percentage and 95% confidence intervals of patients with virological failure according to transmission risk group (A: men who have sex with men [MSM], B: heterosexual men, and C: heterosexual women) and region of origin. No lines are shown for the subgroups of MSM from Sub-Saharan Africa and other regions of origin because of limited numbers of individuals.*



Legend: *MSM=men who have sex with men; cART=combination antiretroviral therapy.*

In adjusted analyses, the risk of failure decreased with later calendar years of starting cART (*Table 3.1*). This is likely to be a reflection of changes in HIV care and cART regimens over time. The risk of virological failure decreased with older age at the start of cART. Those with higher viral load at the start and those starting with CD4 cell counts below 200 cells/mm^3 compared to those with higher CD4 cell counts had an increased risk of failure. There was no significant difference in risk between starting at 350-500 CD4 cells/mm^3 and at 500 CD4 cells/mm^3 or more (p=0.67). There was no evidence that virological failure was more likely when cART was started during primary infection (p=0.56) or pregnancy (p=0.24); however, it should be noted that time was censored when individuals interrupted cART for longer than two weeks. Socio-economic status was not significantly associated with time to virological failure (p=0.89). Finally, there was insufficient statistical power to compare time to virological failure between currently recommended initial cART regimens.

Table 3.1: *Adjusted* hazard ratios (95% confidence intervals) of time to virological failure. Time to virological failure is shorter compared to the reference group when the hazard ratio is higher than 1.00.*

	HR (95% CI)	(Overall) P value
Risk group		(0.001)
MSM	1.00	
Heterosexual men	1.32 (1.07–1.62)	0.008
Heterosexual women	1.30 (1.05–1.61)	0.01
Region of origin		(<0.0001)
Netherlands /Western Europe / North America	1.00	
Caribbean/South America	1.89 (1.55–2.31)	<0.0001
Sub-Saharan Africa	2.30 (1.88–2.81)	<0.0001
Age at the start (years)		(<0.0001)
16–29	1.49 (1.25–1.77)	<0.0001
30–39	1.00	
40–49	0.90 (0.75–1.08)	0.24
≥50	0.96 (0.77–1.21)	0.75
CD4 cell count at the start (cells/mm^3)		(<0.0001)
<50	1.93 (1.39–2.68)	<0.0001
50–200	1.75 (1.29–2.37)	0.0003
200–350	1.16 (0.85–1.58)	0.35
350–500	1.00	
>500	1.10 (0.70–1.72)	0.67
Start during primary infection	0.88 (0.58–1.34)	0.56
HIV RNA at the start (log_{10} copies/ml)		(<0.0001)
<4	0.53 (0.38–0.75)	0.0003
4–5	1.00	
≥5	1.47 (1.25–1.74)	<0.0001

	HR (95% CI)	(Overall) P value
Year of starting		(<0.0001)
1999–2002	2.18 (1.81–2.63)	<0.0001
2003–2006	1.39 (1.16–1.67)	0.0004
2007–2009	1.00	
2011–2013	0.68 (0.48–0.95)	0.02
Started during pregnancy	0.80 (0.55–1.16)	0.24

**In addition to the variables listed, other variables considered for the adjusted analysis include socio-economic status, co-infection with hepatitis C virus and hepatitis B virus, and having an AIDS diagnosis at the start of cART.*
***Legend:** HR=hazard ratio; CI=confidence interval; MSM=men who have sex with men.*

Resistance during treatment

Scanning for drug resistance

In patients who experienced virological failure, resistance to antiretroviral drugs was ascertained by scanning genotypic sequences (obtained at the time of failure) of the reverse transcriptase (RT) and protease genes for specific mutations known to be associated with resistance to the three originally most commonly used classes of drugs, including lamivudine and emtricitabine, other nucleoside RT inhibitors (NRTI), non-nucleoside RT inhibitors (NNRTI), and protease inhibitors (PI)[101]. In recent years, new drug classes have also been introduced, including integrase and entry inhibitors, and genotypic sequences of the relevant genes are increasingly being obtained during routine clinical care. However, only approximately 30 sequences of the integrase gene were available in the SHM database and were therefore not considered for further analysis. A genotypic resistance interpretation algorithm by Stanford University (version 7.0) was used to infer a drug susceptibility score for each sequence according to a five-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance[102].

International collaborations

The HIV Resistance Response Database Initiative (RDI) was established in 2002 with the aim of exploring the relationship between the HIV genotype, as well as other clinical and laboratory factors and response to antiretroviral therapy. RDI develops computational models to help physicians and their patients select the best individualised combination of drugs. In a recent publication, 5,752 episodes of a treatment change were selected to train the models[103]. The performance of the models was assessed via cross-validation and an independent set of 50 treatment change episodes. The models achieved a consistently high level of accuracy in predicting the probability of virological response to a new regimen, which was superior to that of genotypic sensitivity scores from rules-based genotype interpretation systems like the Stanford algorithm.

Sequences

In total, 4,267 sequences were obtained from 2,678 patients after the start of cART in 1996 or later. Pre-treated patients were disproportionally represented with 1,633 sequences (38%). From 2008 onwards, however, only 16% of the sequences were from pre-treated patients, whilst 10% of all treated patients in clinical care had been pre-treated. All together, 3,468 sequences (81%) were obtained whilst patients were receiving treatment. High-level resistance to at least one antiretroviral drug was found in 73% of these 3,468 sequences, including in 89% of the sequences obtained from pre-treated patients and in 63% of those from patients who started cART whilst being antiretroviral therapy-naïve. It is interesting to note that 8% of the sequences from pre-treated patients and 24% of those from previously therapy-naïve patients were susceptible to all antiretroviral drugs, likely indicating that the patients did not take their prescribed medication at the time the blood sample was obtained.

Less resistance

All together, the proportion of sequences with high-level resistance at the time of virological failure decreased from 91% in 2000 to 48% in 2013 (*Web Appendix Figure 3.2*). Generally, patients who were pre-treated with monotherapy or dual therapy had higher levels of resistance at the time of failure compared to previously therapy-naïve patients. Differences in proportions with resistance were most apparent for PIs and NRTIs, whereas the proportions with resistance to lamivudine and emtricitabine and to NNRTIs were comparable between pre-treated and previously therapy-naïve patients (*Figure 3.3*; *Web Appendix Figure 3.3 and 3.4*). From 2008 onwards, the proportion of sequences with resistance showed a sharp decrease for pre-treated patients, which was concomitant with the decrease in the proportion with virological failure.

Figure 3.3: Annual proportion of available sequences with high-level resistance to (A) lamivudine (3TC) and emtricitabine (FTC), (B) other nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), (C) non-nucleoside reverse transcriptase inhibitors (NNRTI), and (D) protease inhibitors (PI). In total, 3,468 sequences were obtained from patients whilst they were on treatment, with a distinction made between patients who started combination antiretroviral therapy (cART) whilst being antiretroviral therapy-naïve and those who were pre-treated with non-cART regimens. High-level resistance was found in 2,542 (73%) sequences, including 1,252 (89%) sequences from pre-treated patients and 1,290 (63%) sequences from previously therapy-naïve patients. Note that in recent years the number of sequences from pre-treated patients is very small.

Legend: 3TC=lamivudine; FTC=emtricitabine; NRTI=nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI=non-nucleoside reverse transcriptase inhibitors; PI= protease inhibitors.

Type of regimen

In total, 277 sequences were obtained from previously antiretroviral therapy-naïve patients who started cART from 2000 onwards and were still on their first-line regimen at the time the sequence was obtained. The proportion of sequences with high-level resistance to at least one antiretroviral drug was similar for patients on NNRTI-based regimens (63%) and for patients on PI-based regimens (54%). In 62% of the patients on an NNRTI-based regimen, high-level resistance to an NNRTI was found, whilst 35% were fully susceptible to all NNRTIs. In contrast, only 18% of the patients on a PI-based regimen were resistant to a protease inhibitor, and 61% were fully susceptible to all PIs. Resistance to lamivudine and emtricitabine was found in 49% of patients on a PI-based regimen and in 46% of those on NNRTI-based regimens, whilst resistance to other NRTIs was observed in 5% and 21%, respectively.

Overall prevalence of resistance

All together, as of June 2014, resistance-associated mutations had been found in 2,094 (12%) of the 17,750 HIV-infected patients who were still in clinical care[101]. For 1,570 patients (9%), including 606 patients who had been pre-treated with non-cART regimens, these mutations resulted in high-level resistance to at least one antiretroviral drug. Since resistance tests were available for only 25% of patients with virological failure in or after 2002, the true prevalence of resistance is probably higher. A crude estimate would put the true prevalence at approximately 40%, which would be more in line with findings in other European countries[104,105].

Of the 1,570 patients with evidence of high-level resistance, 71% had resistance to lamivudine and emtricitabine, whilst 50% had resistance to at least one other NRTI. Resistance to at least one PI was found in 31% of cases and to at least one NNRTI in 62% of cases. High-level resistance to drugs from one drug class was observed in 39% of patients, resistance to two classes in 46%, and resistance to all three original drug classes in 15%. Predicted levels of resistance for each antiretroviral drug are shown in *Web Appendix Tables 3.1 and 3.2*.

Transmission of drug resistance

Limited treatment options

Treatment options may be more limited when patients become infected with a strain of HIV that is already resistant to one or more of the currently available antiretroviral drugs. In such patients, standard treatment combinations may not be the most efficacious, and as a result, patients may experience delayed viral suppression or have an increased risk of virological failure. It is, therefore, important to screen patients for the possible presence of drug resistance so that the initial treatment regimen can be optimised[106,107].

Back mutation

Although a resistant virus strain may evolve to a drug-susceptible virus (a process sometimes referred to as back mutation), tiny concentrations of resistant variants will remain dormant in resting CD4 cells and other reservoirs, awaiting more favourable conditions for replicating after treatment has started. The presence of transmitted resistance, therefore, needs to be established as close to the moment of infection as possible[108-110]. In particular, the M184V mutation in reverse transcriptase (RT), which is associated with high-level resistance to lamivudine and emtricitabine, can disappear relatively quickly after transmission. Other mutations disappear at a much slower rate or do not disappear at all, depending on the extent to which the virus becomes capable of replicating or whether its evolution is constrained by fixation through compensatory mutations[111].

Screening for resistance

In 2003, screening for resistance at the time of entry into care was incorporated in the Dutch treatment guidelines. Since then, SHM has collected pre-treatment sequences for 4,854 patients who have been screened for transmitted drug resistance, which comprise 38% of all 12,663 patients diagnosed with HIV during that period, but only 26% of patients diagnosed in 2011 or later. To reduce a possible effect of back mutation on observed levels of resistance, only patients who had a genotypic sequence within 1 year of diagnosis and who had not started antiretroviral treatment were included in this total number. In addition, patients were divided into two complementary groups, one including patients with a recent infection (32%) and another including those with non-recent infection (68%). An infection was considered recent when the time between the last negative HIV test, if available, and the first positive test was 1.5 years at most. Patients without a previously negative test or with a negative test more than 1.5 years before the first positive test were considered non-recent infections. These two groups differed markedly regarding patient characteristics. Dutch homosexual men represented 68% of the recently infected group, but only 42% of the group of long-standing infections. In contrast, patients of Sub-Saharan African origin accounted for 17% of those with long-standing infections, but only 3% of those with recent infections.

Transmitted drug resistance

Overall, at least one resistance-associated mutation was found in 11% of the 4,854 patients with a genotypic sequence within one year of diagnosis, including 4% with NRTI mutations, 5% with NNRTI mutations, and 2% with mutations in the protease gene[101]. Between 2003 and 2013, there were no significant changes in these proportions, nor were there changes in specific mutations.

In total, 96 patients had high-level resistance to drugs from 1 class, 13 patients had high-level resistance to drugs from 2 classes, and 4 patients had high-level resistance to drugs from 3 classes. It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. All classes include drugs with

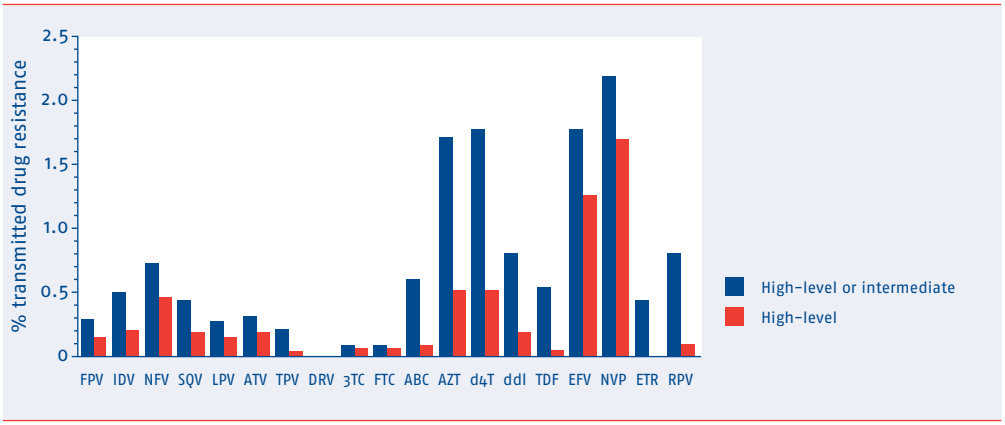
little cross-resistance between them. Moreover, other classes of drugs have become available in recent years. As a result, even for patients with resistance to all three classes, there may still be fully efficacious cART combinations [112].

High-level resistance to at least one antiretroviral drug was found in 2.3% of the 4,854 patients, whilst 2.1% had intermediate levels of resistance (*Table 3.2*). The proportion of patients with resistance and a recent infection was similar to the proportion with resistance and a long-standing infection, although resistance to NNRTIs appeared to be somewhat more common among those with long-standing infection. Overall, intermediate or high-level resistance to zidovudine and stavudine were most frequently observed, but both drugs are no longer commonly used (*Figure 3.4*). In addition, 1.3% of the patients had high-level resistance to efavirenz, whilst 1.7% were resistant to nevirapine. In recent years, no changes were observed in the proportion of patients with predicted high-level resistance.

Table 3.2: *Number of diagnosed patients with intermediate or high-level resistance to any drug, protease inhibitors (PI), lamivudine (3TC) and emtricitabine (FTC), other nucleoside reverse transcriptase inhibitors (NRTI), or non-nucleoside reverse transcriptase inhibitors (NNRTI), according to the Stanford genotypic interpretation algorithm [102]. Only patients diagnosed in 2003 or later are included. A diagnosed infection was considered to be recent if the time between the last negative HIV test and the first positive test was, at most, 1.5 years.*

	Recent infection, n=1,569		Non-recent infection, n=3,285		All diagnoses, n=4,854	
	n	%	n	%	n	%
Any drug						
Intermediate	33	2.1	71	2.2	104	2.1
High-level	33	2.1	80	2.4	113	2.3
PI						
Intermediate	5	0.3	10	0.3	15	0.3
High-level	8	0.5	14	0.4	22	0.5
3TC and FTC						
Intermediate	1	0.1	0	0.0	1	0.0
High-level	2	0.1	1	0.0	3	0.1
NRTI						
Intermediate	21	1.3	47	1.4	68	1.4
High-level	7	0.4	19	0.6	26	0.5
NNRTI						
Intermediate	10	0.6	20	0.6	30	0.6
High-level	20	1.3	64	1.9	84	1.7

Figure 3.4: The predicted proportion of patients with high or intermediate levels of transmitted drug resistance, according to the Stanford interpretation algorithm, was 1.7% for AZT and 1.8% for d4T (two drugs that are no longer commonly used) and 2.2% for NVP and 1.8% for EFV[102]. High-level or intermediate resistance to other drugs was observed in less than 1% of new infections. Only patients with an HIV diagnosis in 2003 or later were included.



Legend: *FPV=fosamprenavir; IDV=indinavir; NFV=nelfinavir; SQV=saquinavir; LPV=lopinavir; ATV=atazanavir; TPV=tipranavir; DRV=darunavir; 3TC=lamivudine; FTC=emtricitabine; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine; TDF=tenofovir; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; RPV=rilpivirine.*

Gender and viral subtype

The proportion of HIV infections with evidence of intermediate or high-level resistance was similar between men and women. However, transmission of virus strains with predicted full susceptibility to all NRTIs was less frequent among men (91%) than among women (97%). In contrast, virus strains susceptible to all PIs were observed in 90% of men, but in only 64% of women.

These differences between the sexes can largely be explained by the HIV-1 subtype with which patients were infected. Overall, 84% of men, but only 34% of women, were infected with a subtype B virus. Intermediate or high-level resistance to NRTIs was seen in 2.4% of subtype B viruses, compared with only 0.3% of non-B viruses. These higher levels of resistance to NRTIs were largely due to subtype B strains with revertant mutations in RT such as 215S or 215D, which have established themselves as sub-epidemics[113]. Revertant mutations at position 215 in RT were found in 210 (6%) subtype B infections, but in only 4 out of 1,147 non-B infections. Over time, there has been a clear increase in the proportion of patients infected with a virus strain with a 215S mutation in the absence of any resistance-associated mutations. Between 2011 and 2013, 5% of all sequences had this specific mutation compared to 1% before that time. However, due to a backlog in data collection, it is not possible to determine if this increase was a regional phenomenon or occurred on a national level.

Full susceptibility to all protease inhibitors was found in 96% of subtype B sequences, but only 52% of non-B viruses. This difference is likely due to naturally occurring polymorphisms at minor resistance-associated positions in the protease gene that are not considered clinically relevant[101].

Conclusions

In terms of percentages, virological failure is less common nowadays than it was in 2000, due to improvements in combination treatment itself and the availability of more treatment options. This appears to hold true even for patients pre-treated with monotherapy or dual therapy, who now have the same rates of virological failure as previously therapy-naïve patients. Nevertheless, due to a growing volume of treated HIV-infected patients, approximately 300 to 400 patients per year still experience virological failure. The risk of virological failure remains higher in younger individuals (<30 years), individuals with low CD4 cell counts (<200 cells/mm^3) or high viral load (>100,000 copies/ml) at the start of cART, men and women heterosexually infected as compared to MSM, and patients from Sub-Saharan Africa, the Caribbean, and South America.

Resistance patterns in sequences obtained at approximately the time of failure seem to indicate that in one-quarter of previously therapy-naïve patients, virological failure is the result of patients failing to take their prescribed medication, which could be due to drug-related toxicity. In patients with a sequence obtained whilst failing on a PI-based or an NNRTI-based first-line regimen, overall levels of drug resistance are similar. However, PIs appear to be more resilient to the development of drug resistance than NNRTIs, most likely because of the larger number of mutations necessary to render the virus fully resistant[114]. In patients on a PI-based regimen, resistance to lamivudine and emtricitabine is most commonly observed, whereas in patients on NNRTI-based regimens, resistance to NNRTIs and, to a lesser extent, to lamivudine and emtricitabine is most frequent.

Unfortunately, sequences are available to SHM for only approximately 25% of the patients with virological failure. Without a thorough understanding of the conditions under which sequences are made available in the SHM database, it is difficult to draw firm conclusions on the prevalence of resistance in the entire HIV-infected population in care in the Netherlands. Furthermore, for some patients, virological failure may be caused by resistance to integrase or entry inhibitors, but sequences of the genes involved in this type of resistance are not yet routinely available in all treatment centres.

Even though the true prevalence of resistance may be as high as 40% in the entire population in care, only 11% of patients have become infected with a virus that harbours any resistance-associated mutations. This proportion is most likely relatively low because the majority of patients on antiretroviral treatment have well suppressed viral loads, even in the presence of resistance-associated mutations. This implies that transmission takes place mainly via HIV-infected individuals who are not yet treated[15,16]. The transmitted

mutations give rise to intermediate or high-level resistance to at least one antiretroviral drug in only 4% of the patients, such that a suitable first-line treatment regimen will be available for most patients.

Recommendations

Until now, data collectors in HIV treatment centres have not routinely collected protease and RT sequences, mainly due to the complex infrastructure and data management processes. This is one of the reasons why sequences are available for such a low proportion of patients with virological failure. 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 coming months.

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.

Further, obtaining a sequence at the time of diagnosis or entry into care needs to be continued as a standard procedure. Clearly, without information on resistance before the start of treatment, patients could start with a partially active cART regimen that might lead to virological failure. Moreover, even though no resistance-associated mutations are currently found in many patients, there is no guarantee that this situation will not change. Monitoring these changes will be nearly impossible without pre-treatment resistance profiles. A concomitant advantage of having genetic information of HIV sequences is that it allows identification of transmission networks (see *Chapter 8* as well), which will help formulate tailor-made intervention strategies to reduce HIV incidence.

4. HIV-related and non-HIV-related morbidity and mortality

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Introduction

Of the 21,417 adult patients ever registered in the Dutch national HIV registration and monitoring database, 89% are currently on combination antiretroviral therapy (cART). The life expectancy of HIV-infected patients has markedly improved since the introduction of cART, and, in a subgroup of recently-diagnosed, effectively-treated patients, has been shown to be similar to that of the general population in the Netherlands [115].

Although the incidence of AIDS-defining infections and malignancies has markedly decreased [116], morbidity and/or mortality associated with non-AIDS-related diseases such as renal and liver disease, diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies, has increased amongst HIV-1 infected patients during the cART era [73,117-123].

Various reports suggest that the risk of non-AIDS morbidity may be higher amongst HIV-infected individuals treated with ART than amongst uninfected individuals of comparable age [124,125,126]. For example, pulmonary hypertension [127], bone disease and non-traumatic bone fractures [128-130] have been reported to be more common in HIV-infected patients. There is also a concern that HIV-related neurocognitive impairment may persist or even progress, despite otherwise effective long-term cART [131-133]. Traditional risk factors (e.g., tobacco use [134], alcohol abuse and viral hepatitis co-infection [135]) are likely to also importantly contribute to the increased risk of certain non-AIDS co-morbidities in HIV, similar to uninfected individuals.

Importantly, one of the most prevalent co-morbidities in HIV is cardiovascular disease (CVD). In addition to traditional risk factors such as smoking, probable additional risk factors amongst HIV-infected patients are metabolic abnormalities, including dyslipidaemia, insulin resistance, hypertension, diabetes, and changes in body fat distribution (lipodystrophy), which may partly be driven by use of cART, as well as sustained HIV-associated immune activation and inflammation [119,136].

In this chapter, we report on rates of mortality and causes of death for HIV-1-infected patients on cART based on updated Stichting HIV Monitoring (SHM) data. In addition, we report on the incidence of AIDS and non-AIDS co-morbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in HIV-1 infected patients on cART. Incidence rates and risk factors are presented.

Definitions applied in analyses

AIDS is defined as the presence of any Centers for Disease Control (CDC) category C condition, including the presence of any AIDS-defining malignancy (Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer [137]). A CD4 count less than 200 cells/mm^3 in the absence of an AIDS-defining condition does not qualify as AIDS in these analyses.

Diabetes mellitus was defined according to criteria established by the Data Collection on Adverse Events of anti-HIV drugs (D:A:D) study *(http://www.cphiv.dk/DAD/studydocuments/tabid/112/default.aspx)*.

Cardiovascular disease including myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting and carotid endarterectomy were defined according to criteria established by the D:A:D study (http://www.cphiv.dk/DAD/studydocuments/tabid/112/default.aspx).

Non-AIDS-defining malignancies, excluding precancerous stages of anal and cervical cancer, basal-cell carcinoma, and squamous-cell carcinoma of the skin, were defined according to criteria established by the D:A:D study (http://www.cphiv.dk/DAD/studydocuments/tabid/112/default.aspx), with the only exception that Castleman's disease was also defined as a non-AIDS-defining malignancy. Histological confirmation of malignancies is part of standard clinical practice in the Netherlands, and therefore, pathology reports have been used as much as possible for the purpose of establishing the presence of any malignancy.

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min (estimated with the Cockcroft-Gault equation), confirmed with a consecutive abnormal measurement after 3 months or longer. Creatinine levels have been routinely collected in the SHM from January 2007 onwards. For that reason we report on CKD from 2007 onwards.

Methods

For the analyses of incidence per calendar year and period, we consider all events after an individual was diagnosed with HIV-1 and after the start of routine collection of data on the condition of interest, whichever occurred most recently. For instance, data on CKD were analysed from 2007 onwards because that was the time point where laboratory data became available electronically for entry into the database. In the analyses presented, we also excluded patients who experienced the event of interest before they started cART or before routine data collection on the event of interest was started.

Mortality and AIDS

When constructing Cox proportional hazard models to estimate the time to AIDS and death, we used the baseline parameters described and categorised in *Web Appendix Table 4.1* as covariates.

Non-AIDS defining events

We investigated risk factors for each of the non-AIDS events and a combined endpoint (first of cardiovascular disease, diabetes mellitus, or non-AIDS malignancy). CKD was not included as creatinine was not part of routine data collection before 2007). Baseline for treated and untreated HIV-1-infected individuals was defined as the date of HIV-1 diagnosis, or June 2000, whichever came last. Subsequent follow-up time was divided into 3-monthly periods. Individuals with a particular endpoint prior to baseline were excluded from that particular analysis. Logistic regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for most recent CD4 cell count, body mass index, gender, region of birth, most likely HIV-1 transmission route, current age, known time with <200 CD4 cells/mm^3, known time with HIV RNA >1000 copies/ml, prior diagnosis of AIDS and presence of chronic active hepatitis B and C virus infection.

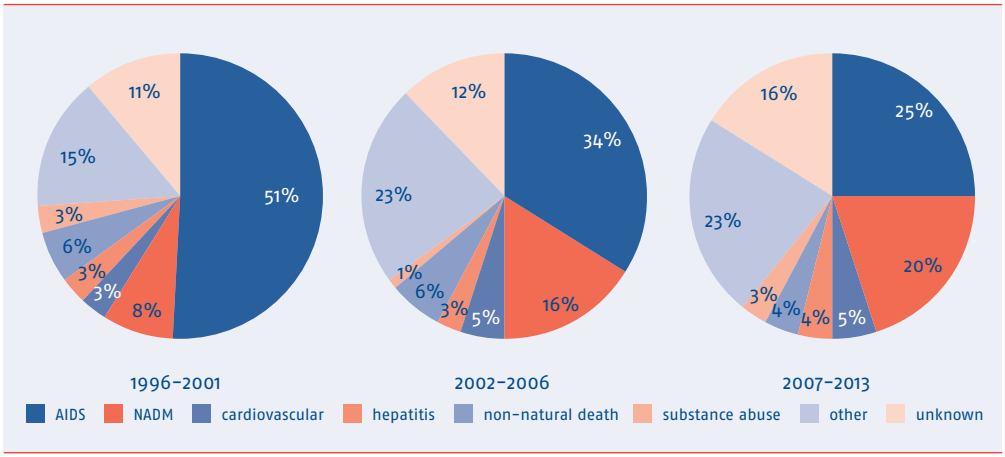
Mortality and AIDS

From 1996 onwards, the overall mortality rate in all 21,928 HIV-1-infected adults and children ever recorded in the SHM database and with a recorded date of HIV diagnosis was 11.6 (95% confidence interval [CI] 11.1-12.1) per 1,000 person years and declined over time to 8.2 (6.9-9.8) per 1,000 person years in 2013 (*Web Appendix Figure 4.1A; Web Appendix Table 4.2*). Although the mortality rate has improved over time, it remains well above the rate that would be expected for the general population in the Netherlands when taking into account gender and age. The excess mortality rate may be partly explained by patients who already had AIDS at the time of their HIV diagnosis. When these patients are excluded, the mortality rate is 10.0 per 1,000 person years overall and 7.0 (5.7-8.6) per 1,000 person years in 2013. The overall mortality rate is even lower, 9.2 per 1,000 person years, in patients who were diagnosed with HIV in 1996 or later. Generally, these patients quickly and durably suppressed HIV replication after they received a potent cART regimen as their first treatment regimen, instead of first having been treated with mono- or dual NRTI therapy in the period before cART first became available. In the same group of 21,928 patients, the incidence of AIDS has decreased sharply to approximately 10 cases per 1,000 patients per year in recent years (*Web Appendix Figure 4.1B*).

Likewise, the mortality rate after the start of cART has substantially decreased over calendar time to 8.8 (7.4-10.5) per 1,000 person years in 2013 (*Web Appendix Figure 4.1C*). This decrease should, however, be interpreted with caution since it is, in part, due to a survival effect. Similarly, the incidence of AIDS after the start of cART has decreased dramatically and was 5.6 (4.4-7.0) per 1,000 person years in 2013 (*Web Appendix Figure 4.1D*). The incidence of AIDS after starting cART was lower with higher latest CD4 cell counts, also at high CD4 cell counts, and was 427.1 (95% CI 359.3-504.0) per 1000 person years of follow-up, 62.4 (54.9-70.7), 17.0 (14.7-19.4), 7.9 (6.7-9.2), 4.2 (3.5-5.0), and 3.6 (2.8-4.5) when latest CD4 cell counts were <50, 50-200, 200-350, 350-500, 500-750, and ≥750 cells/mm^3, respectively.

Observed underlying causes of death are presented in *Web Appendix Table 4.3*. Although the proportion of patients who die of AIDS has decreased significantly since the advent of cART, it still remains substantial. This is likely to be largely driven by the high number of patients who still present late for care and already have advanced immune deficiency. Patients who died of AIDS had lower CD4 counts (median 100 cell/mm^3 (IQR 30-300)) when entering care compared to patients who die from another cause (median 350 cells/mm^3 (IQR 160-541). The time between entry into care and death was significantly shorter in patients who died of AIDS (median 3 years (IQR 0.7-8)) compared to patients who died of a non-AIDS cause (median 7 years (IQR 3-12)) (p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 4.1*), which is likely the consequence of AIDS-related mortality becoming a less important competing cause of death.

Figure 4.1: *Relative changes in causes of death in HIV-infected patients in different periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands.*



Legend: *NADM=non-AIDS-defining malignancy.*

We examined factors associated with death in patients from the start of cART using Cox regression analysis. After correction for all of the variables listed in *Web Appendix Table 4.1*, the hazard ratios for the individual categories of the covariates are presented in *Web Appendix Table 4.4*. In general, the time to death was shorter for men than for women. Patients survived for a shorter duration after starting cART if they were older, had been HIV-1-positive for longer before they started cART or had a CD4 cell count less than 200 cells/mm^3 at the start of cART, were underweight or had tested positive for chronic hepatitis B or C infection at time of cART initiation. Lower mortality rates were observed in patients born in Sub-Saharan Africa; this is likely due to the larger proportion of Sub-Saharan Africans being lost to follow-up[115,138].

The incidence of the first occurrence of any AIDS-defining event was 30 events per 1000 person years of follow-up. The most common AIDS events occurring between 2007 and 2014 were oesophageal candidiasis (18% of all events), Kaposi's sarcoma (11%), tuberculosis (9%), cytomegalovirus-associated end organ disease (5%) and AIDS dementia complex/HIV encephalopathy (4%). Risk factors for AIDS-defining events are shown in *Web Appendix Table 4.4*. In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of cART, excluding events occurring within the first 3 months. The results of these analyses show that patients were more likely to experience their first AIDS-defining event after the start of cART if they had become HIV-1-positive due to blood contact or injecting drug use, were underweight, had been diagnosed with HIV-1 less than one year before the start of cART, had more than 10,000 HIV RNA copies/ml or had a CD4 count less than 200 cells/mm^3 at cART initiation.

Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D:) Study

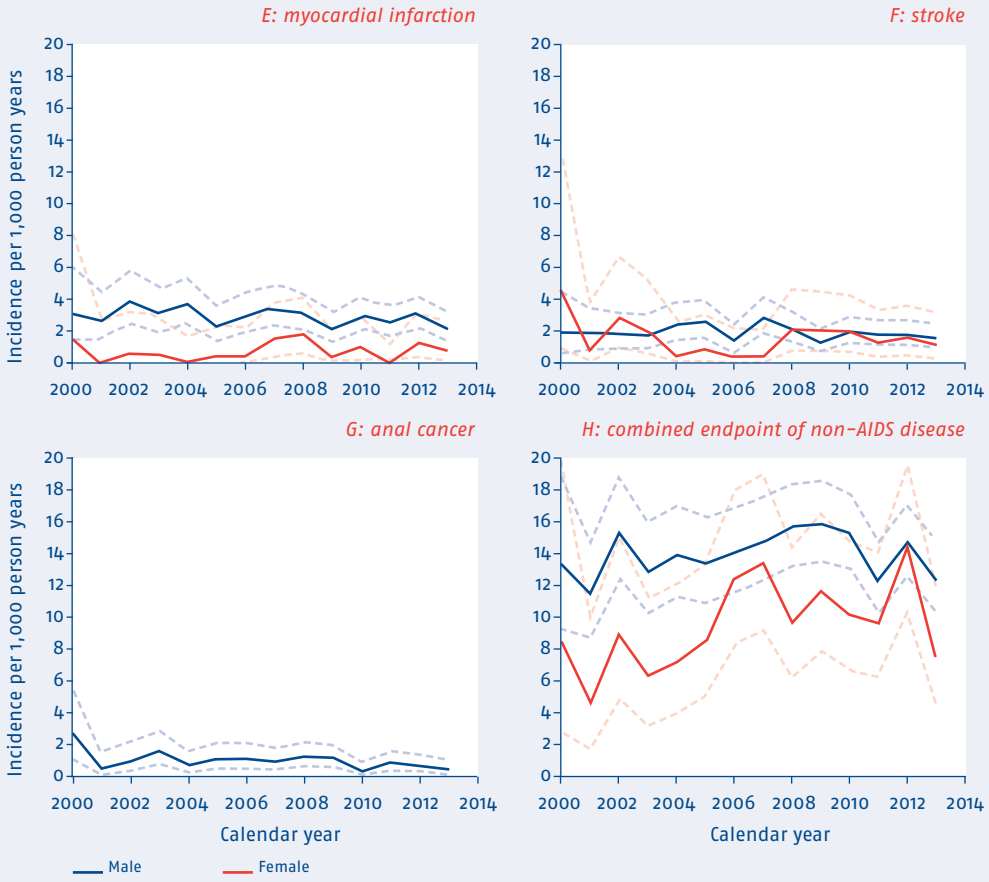
The D:A:D: Study, which includes data from individuals living with HIV in the Netherlands, investigated trends over time in all-cause mortality and for specific causes of death in people with HIV from 1999 to 2011. Of the 49,731 study participants, 3,909 died during the 308,719 person years of follow-up (12.7 per 1,000 person years). Leading underlying causes of death were AIDS-related (29%), non-AIDS-defining cancers (15%), liver disease (13%) and cardiovascular disease (11%). All-cause mortality was higher during the period 1999-2000 (17.5 per 1,000 person years in 1999-2000) compared to 2009-2011 (9.1), and also higher for AIDS-related deaths (5.9 to 2.0), liver-related death (2.7 to 0.9), and death due to cardiovascular disease (1.8 to 0.9). Incidence of death due to non-AIDS defining cancer increased slightly from 1.6 per 1,000 person years in 1999 to 2.1 in the period 2009-2011 (p=0.58). After adjustment for time-updated CD4 cell count, no decreases in AIDS-related death rates, suggesting improvements in death rates over time, are likely due to continued improvement in CD4 cell count. However, after adjusting for CD4 cell count as well, all-cause mortality, and rates of death due to liver disease, and cardiovascular disease still decreased in later years. The investigators hypothesise that these reductions can be explained by improved use of non-HIV-specific preventive interventions. Non-AIDS cancer is now the leading non-AIDS cause of death and without any evidence of improvement.

The Antiretroviral Therapy Cohort Collaboration (ART-CC) also studied trends of cause-specific mortality after the start of cART. Rates of AIDS-related death decreased with time since starting cART, but mortality from non-AIDS malignancy increased (4% per year longer on cART). Higher mortality in men than in women during the first year of ART was mostly due to non-AIDS malignancy and liver-related deaths. Associations with age were strongest for cardiovascular disease, heart/vascular-related deaths, and malignancy-related deaths. CD4 count at baseline and at 12 months played a persistent role in predicting AIDS, non-AIDS infection, and non-AIDS malignancy deaths. Lack of suppression on ART was associated with AIDS, non-AIDS infection, and other causes of death [139,140].

Non-AIDS-defining events

We present the incidence per 1,000 person years of observation of diabetes mellitus, cardiovascular diseases (and separately for myocardial infarction and stroke), non-AIDS malignancies (and separately for anal cancer) and CKD. We also present the incidence of the first occurrence of either diabetes mellitus, cardiovascular diseases and non-AIDS malignancies as a combined non-AIDS disease endpoint (*Figure 4.2)*.

Figure 4.2: *Crude incidence rates per 1,000 person years of follow-up and 95% confidence intervals (dotted lines) of diabetes mellitus (A), cardiovascular disease (B), chronic kidney disease (C), non-AIDS defining malignancies (D), myocardial infarction (E), stroke (F), anal cancer (G), and combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease and non-AIDS defining malignancies) (H) by gender, with exception of the incidence of anal cancer which is presented for males only.*



We present the incidence of diabetes mellitus, cardiovascular disease, CKD, and non-AIDS malignancy according to age and gender in *Web Appendix Table 4.5* and the results of the risk factor analysis in *Web Appendix Table 4.6.*

Diabetes mellitus

Overall, 677 of the 21,417 patients were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 4.2.A*) and in 2013 was 4.0 (95% CI 3.3-6.8) per 1,000 person years of follow-up in men and 3.4 (95% CI 1.5-6.4) per 1,000 person years in women. In both men and women, the incidence increased with older age (*Web Appendix Table 4.5.a*). As the HIV-population has aged over time, we also estimated an incidence rate for the period 2007-2013, standardised according to the distribution of age during the period 2000-2006. In men, the age-standardised incidence was significantly

lower in 2007-2013 compared to 2000-2006, as illustrated by a standardised incidence ratio significantly lower than 1.00. In women, the age-standardised incidence ratio was not significantly different than 1.00. An improvement in diabetes risk management over time may have contributed to the lower age-standardised incidence in men.

Table 4.1: Crude and age-standardised incidence of diabetes mellitus per 1,000 years of follow-up during 2000-2006 and 2007-2013, and age-standardised incidence ratio and 95% confidence intervals.

	Men	Women
Crude incidence 2000-2006	4.4 (3.8-5.1)	4.5 (3.4-5.9)
Crude incidence 2007-2013	4.3 (3.9-4.8)	5.3 (4.3-6.5)
Age-standardised incidence 2007-2013*	3.5 (3.1-4.0)	4.6 (3.7-5.8)
Standardised incidence ratio*	0.81 (0.72-0.90)	0.99 (0.82-1.21)

**Standardised according to the observed age distribution between 2000-2006.*

Demographic and clinical factors independently associated with increased risk of new-onset diabetes were male gender, being of non-Dutch origin, older age, having a BMI greater than 25 kg/m^2, BMI less than 18 kg/m^2, hypertension, acquisition of HIV through heterosexual or contaminated blood contact or injecting drug use, having a latest CD4 cell count <200 cells/mm^3, longer time on didanosine, zidovudine and stavudine, and an AIDS diagnosis (*Web Appendix Table 4.6*).

The effect of cumulative exposure to specific antiretrovirals on the onset of diabetes mellitus was investigated in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) prospective observational cohort study of over 33,000 HIV-infected patients, to which SHM contributes significantly (with approximately 20% of these patients). The strongest relationship with diabetes was exposure to stavudine, although exposure to zidovudine and didanosine was also associated with an increased risk[141].

Another study by D:A:D shows that the risk of a myocardial infarction is more than doubled amongst HIV-infected patients with diabetes. Insulin resistance amongst treated HIV-infected patients is multifactorial: in addition to the common contributors to insulin resistance (e.g., obesity, genetic influences, and physical inactivity), antiretroviral drugs and lipodystrophy, which may be a consequence of treatment, particularly with thymidine analogues, are involved[29].

Cardiovascular disease

From 2000 onwards, 721 individuals had a cardiovascular disease diagnosis (377 myocardial infarction, 288 stroke, 58 individuals underwent coronary artery bypass grafting, 266 coronary angioplasty or stenting, and 6 carotid endarterectomy). The crude incidence over time remained stable and was lower in women than in men (*Figure 4.2.B*). The incidence in both men and women increased with older age (*Web Appendix Table 4.5.b*). As the

HIV-population as a whole has aged over the period 2000-2014, we estimated the incidence rate for the period 2007-2013, standardised according to the observed age distribution during the period 2000-2006 (Table 4.2). The standardised incidence ratio was significantly lower than 1.00 in men and close to 1.00 for women.

Table 4.2: Crude and age-standardised cardiovascular disease incidence per 1,000 years of follow-up during 2000-2006 and 2007-2013, and age-standardised incidence ratio and 95% confidence intervals.

	Men	Women
Crude incidence 2000-2006	5.2 (4.6-6.0)	1.8 (1.1-2.7)
Crude incidence 2007-2013	5.4 (4.9-5.9)	2.6 (1.9-3.4)
Age-standardised incidence 2007-2013*	4.0 (3.6-4.5)	2.0 (1.4-2.7)
Standardised incidence ratio*	0.76 (0.69-0.83)	1.04 (0.79-1.38)

**Standardised according to the observed age distribution between 2000-2006.*

Increasing awareness of and improvement in cardiovascular risk management with time may have contributed to the declining age-standardised incidence trend. In the risk factor analysis, factors associated with cardiovascular disease were male gender, being of Dutch origin, older age, infection through intravenous drug use, having a latest CD4 cell count <200 cells/mm^3, having a prior AIDS diagnosis, longer exposure to indinavir, current use or use of abacavir in the last 6 months, being a current smoker, and hypertension (*Web Appendix Table 4.6*).

Two other studies using data from D:A:D found that indinavir, lopinavir-ritonavir, didanosine and abacavir were associated with a significantly increased risk of myocardial infarction[28]. The increased relative risk of myocardial infarction with protease inhibitor use was partially attenuated by controlling for dyslipidaemia, diabetes and hypertension, suggesting that the effects of antiretroviral therapies on traditional cardiac risk factors might contribute in part to the increased rate of myocardial infarction[30].

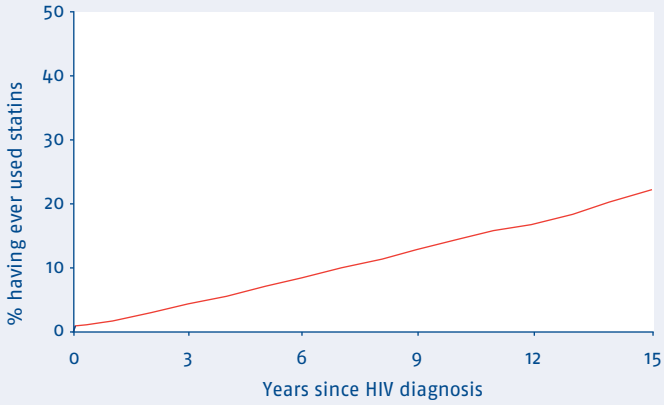
Use of statins in the cART-treated population

Early in the course of HIV infection, both high-density cholesterol (HDL-c) and low-density lipoprotein (LDL) cholesterol levels decrease, and during more advanced stages of infection triglyceride levels increase[142]. After starting ART, dyslipidaemia is typically manifested as a further increase in triglyceride levels, while HDL-c levels remain low and LDL cholesterol levels increase, usually to levels higher than before HIV infection, depending on the drugs used in the regimen[143]. These changes may place HIV patients at an increased risk of cardiovascular disease. Therapy with hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) in HIV-infected patients is well established in treating hyperlipidaemia, but has not been formally proven to prevent cardiovascular disease. In addition, whether the anti-inflammatory properties of statins might also contribute to lowering the risk of age-associated non-AIDS morbidity and mortality, including due to cardiovascular disease, remains to be proven[144,145].

Currently it is unknown whether the use of statins in HIV infection is associated with an increased risk of diabetes, as has been described in the general population. Furthermore, results from observational studies in non-HIV settings suggest there may be an increased risk of several adverse events, including musculoskeletal disease, with the use of statins [146,147]. Analyses of all of these issues are hampered by the observational nature of the available data. In this paragraph we report on the use of statins after starting cART, as an indirect marker of clinically relevant hyperlipidaemia, and look at the clinical and demographic characteristics of patients at the start of statin use.

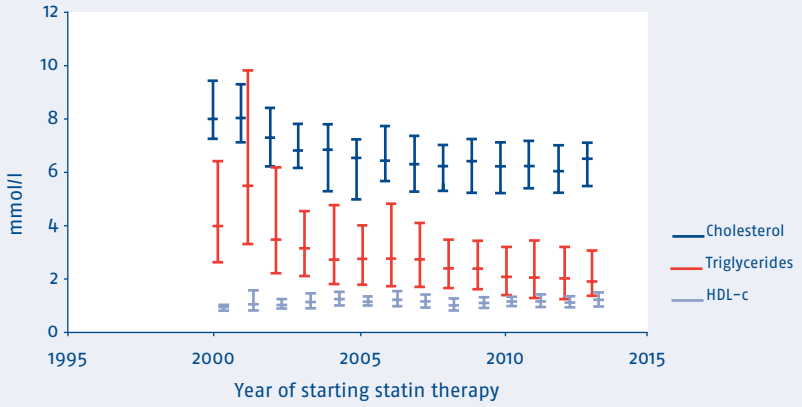
Out of 21,417 individuals older than 16 years at HIV-1 diagnosis, 18,371 were diagnosed in or after 1995 and have been included in this paragraph on cardiovascular risk factors. Of these 18,371, 2,156 had started statins therapy during follow-up. We excluded 136 patients (6%) from the analysis, as the date of start of statin use was unknown. The estimated proportion of patients ever having used a statin within 1, 3, 5, 10 and 15 years from HIV diagnosis among the remaining 18,235 individuals was 2%, 4%, 7%, 15%, and 22%, respectively (*Figure 4.3*).

Figure 4.3: Kaplan–Meier estimates of the percentage of patients who started therapy with statins.



The median age at which therapy with statins was started increased from 49.0 years (IQR 39.1-55.9) in 1997 and 1998 to 51.9 (45.6-59.1) between 2013 and 2014. Moreover, median CD4 cell counts at which patients started statin therapy also increased from 394 cells/mm^3 (254-580) in 1997 and 1998 to 560 cells/mm^3 (410-745) in 2013-2014. Twelve percent of patients starting statin therapy had a previous diabetes mellitus diagnosis.

Figure 4.4: Median and interquartile range of lipid levels at the start of statin therapy according to year of start. Information on whether levels were obtained during fasting was not available.



Legend: HDL-c = high-density lipoprotein cholesterol.

Over time, there was a decrease in triglyceride and total cholesterol levels at which therapy with statins was initiated, and an increase in HDL-c levels (see *Figure 4.4*). The proportion of patients with hypertension (either using anti-hypertensive therapy, with a latest recorded systolic blood pressure of >140 mmHg, or hypertension reported in the patient's medical file in the year prior to the start of statins) was 18.5% in the period 2013-2014. At the start of statin therapy in 2013-2014, 14% of individuals had a previous diabetes diagnosis and 13% had had a previous myocardial infarction. In the D:A:D: Study, abnormal triglycerides, total and HDL cholesterol all were independently associated with an earlier start of lipid-lowering medication. Furthermore, a higher BMI, previous diabetes mellitus diagnosis, previous cardiovascular event or a family history of cardiovascular disease were also independently associated with an earlier start [148].

Trends in cardiovascular risk factors

The percentage of patients with a cholesterol level of 6.2 mmol/l or higher has decreased over time from 24% of patients with a measurement available in 2000 (regardless whether statins were used) to 13% in 2013 (*Figure 4.5*).

Figure 4.5: Distribution of the cholesterol (mmol/l) at the end of each calendar year in absolute numbers (A) and as a percentage of the total number of individuals with a known cholesterol available (B). For each patient, the last available measurement in each year was selected.

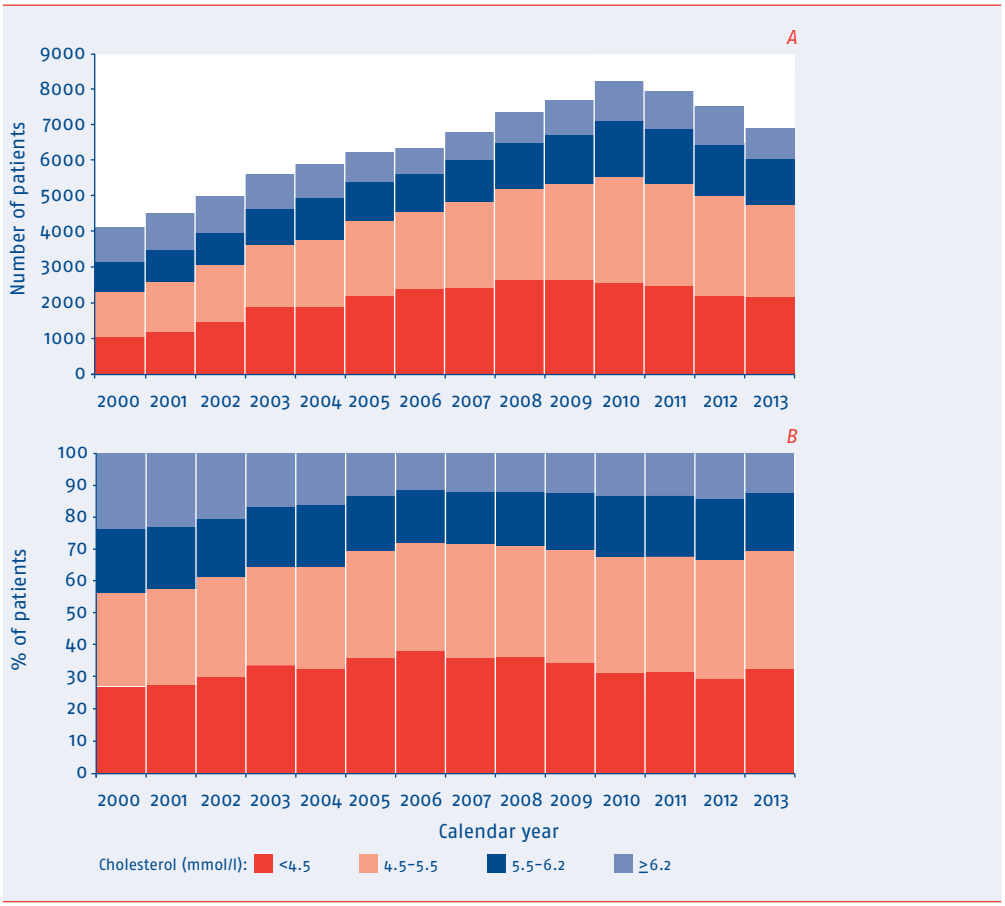
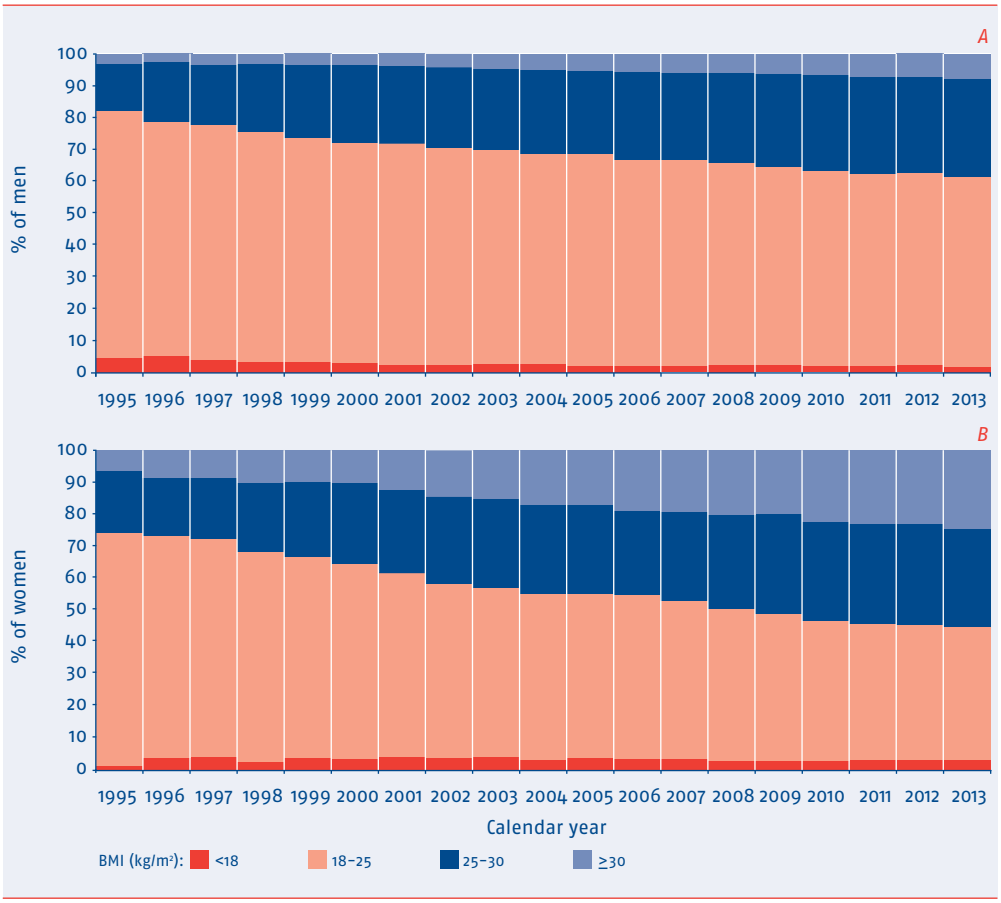


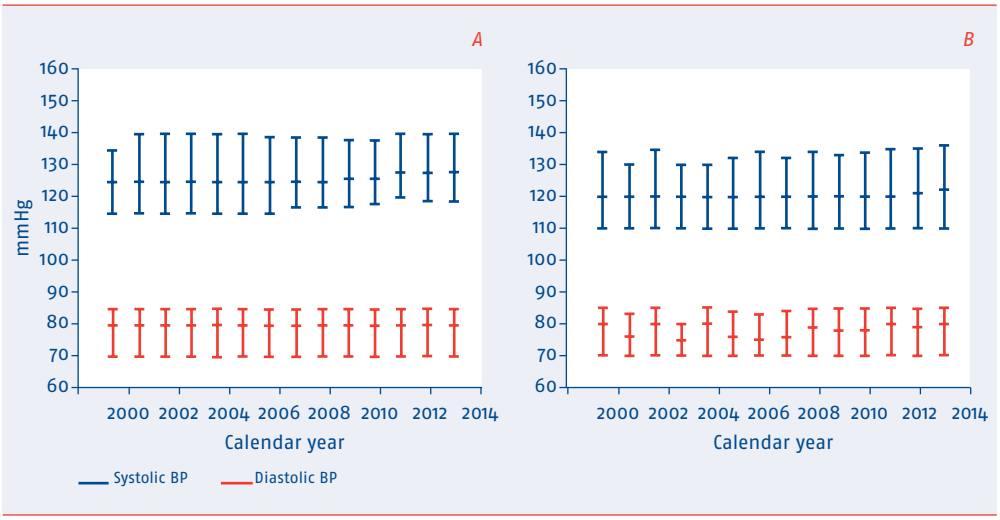
Figure 4.6 presents the distribution of body mass index (BMI) in the HIV-1-infected population over time. The body mass index in men and women increased over time. The percentage of overweight (25-30 kg/m^2) and obese (≥30 kg/m^2) individuals in 2013 among men with a BMI measurement was 30% and 7%, respectively. In women these percentages were 31% and 24%, respectively. *Web Appendix Figure 4.2* gives an overview of the absolute numbers of individuals in each BMI category. Using mixed effects modelling, we checked whether the increase in BMI over time could be explained by ageing of the HIV-infected population. However, adjusting for age did not explain the increase in BMI over time in women, and only partially explained it in men.

Figure 4.6: Distribution of the body mass index (BMI) at the end of each calendar year in men (A) and women (B) as a percentage of the total number of men and women with a known BMI in each year. For each patient, the last available weight measurement in each year was selected.



Legend: BMI=body mass index.

Figure 4.7: Median (interquartile range, IQR) of systolic and diastolic blood pressure at the end of each calendar year in men (A) and women (B). For each patient the last available blood pressure measurement in each year was selected, regardless of whether anti-hypertensive therapy was used.



Legend: BP=blood pressure.

In both men and women, median diastolic and systolic blood pressures remained stable over time *(Figure 4.7)*. Blood pressure was higher in older individuals: in individuals under 50 years of age, median diastolic and systolic blood pressure in 2013 was 78 and 124 mmHg, respectively, whilst in those aged 50 years or more it was 80 and 130 mmHg, respectively.
As the patient population with HIV ages further in the years to come, cardiovascular disease risk management, including the use of statins when appropriate according to general guidelines, will become increasingly important.

Figure 4.8: Estimated 5-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study[149]. Calculation of the risk involves, amongst other variables, total cholesterol, high density lipoprotein cholesterol (HDL-c) and systolic blood pressure. Values for these variables were estimated on the basis of a 'last observation carried forward' approach. The algorithm as published by the D:A:D: study distinguishes between current and ex-smokers; if this information was not available, a value was imputed. Plot A shows the percentage of patients and plot B shows the number of patients. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL-c measurements were often lacking or absent completely. Especially in younger patients, risk could not be estimated because of missing data. Hence, the reported absolute number of patients is smaller than the number of patients in active follow-up at the end of each calendar year, and older patients are overrepresented.

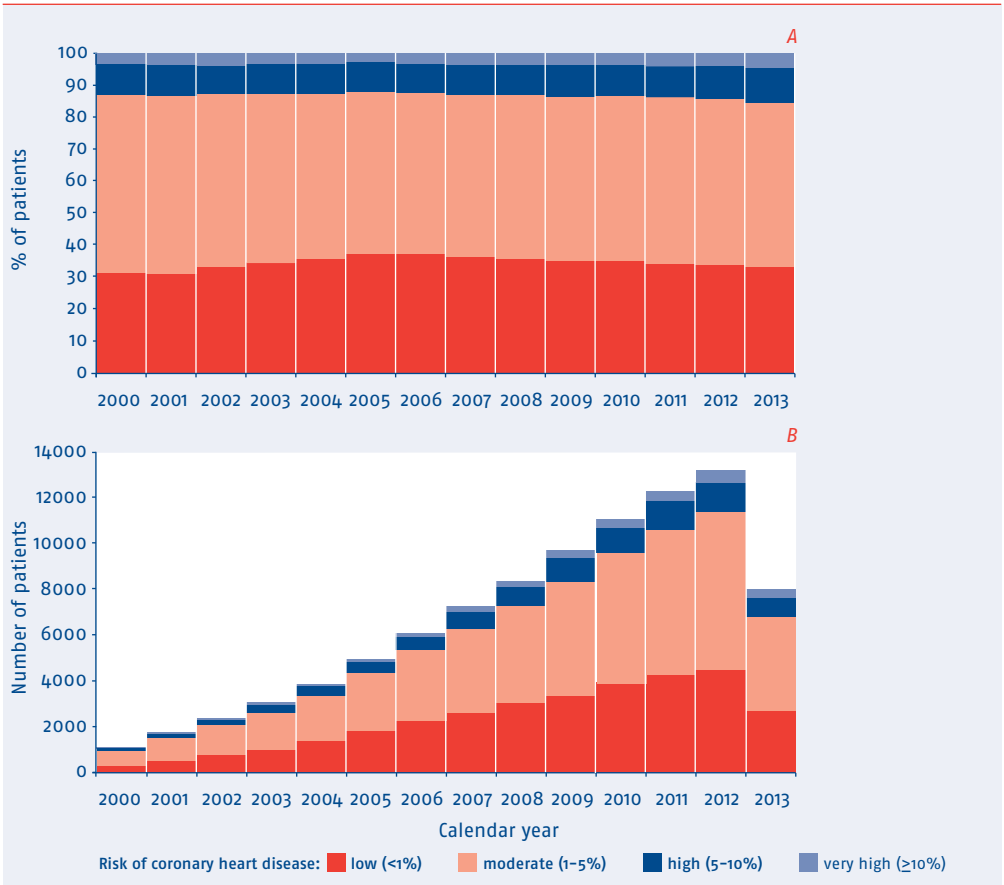
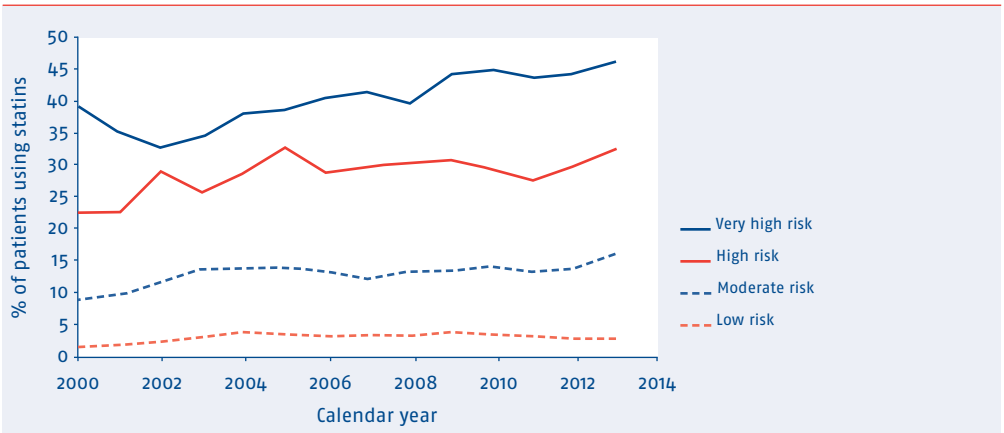


Figure 4.8 gives an overview of the estimated risk of developing coronary heart disease (CHD) in the cART-treated population over time, calculated using the D:A:D: Study algorithm[149]. Over time, the percentage of patients at high (5-10%) or very high risk (≥10%) risk increased slightly from 12.8% in 2007 to 14.9% in 2013. Older age, male gender, current smoking or smoking in the past, current use of abacavir, longer cumulative exposure to indinavir, a family history of cardiovascular disease, a diagnosis of diabetes mellitus, lower HDL cholesterol, a higher total cholesterol and a higher systolic blood pressure all contribute to an increased risk using this algorithm. The ageing of the study population might explain the slight increase in the percentage of patients at high or very high risk. Overall, improved cardiovascular risk management over time, as illustrated by the initiation of statins at less elevated lipid levels, and the preferred use of cART regimens without known cardiovascular risk, may contribute to a lower risk.

Figure 4.9 shows the percentage of patients using statins over time according to the 5-year CHD risk score. Over time, the percentage of patients at high or very high risk of coronary heart disease using statins has increased over time, whereas the percentage in patients at low risk has remained more or less stable. Nevertheless, 65% of patients at high risk and 54% at very high risk in 2013 did not use statins.

Figure 4.9: *Percentage of patients using statin therapy according to estimated 5-year risk of coronary heart disease at the end of each calendar year according to the D:A:D: study algorithm[149].*



Another study from the **Data collection on adverse events of anti-HIV drugs (D:A:D) study** modelled the relative increased risk of cardiovascular disease (CVD) per year of age older, and compared this with the risk in the general population risk equations. Three endpoints were analysed: myocardial infarction (MI), coronary heart disease (CHD) and cardiovascular disease (including coronary heart disease or stroke). Parametric age effects adjusted for known risk factors and antiretroviral therapy use were fitted. The ageing effects from the D:A:D were compared with those from the general population risk equations, the Framingham Heart Study, CUORE and ASSIGN risk scores. A total of 24,323 men were included in the analyses. The crude event rates for MI, CHD, and CVD per 1,000 persons years increased from 2.29, 3.11 and 3.65 in those aged 40-45 years to 6.53, 11.91 and 15.89 in those aged 60-65 years, respectively. The best-fitting models included inverse age for MI and age+age^2 for CHD and CVD. In D:A:D there was a slowly accelerating increased risk of CHD and CVD per year older, which appeared to be only modestly, yet consistently, raised compared with the risk in the general population. The relative risk of MI with age was not significantly different between D:A:D and the general population. There was limited evidence of accelerated increased risk of CVD with age in D:A:D compared with the general population. The absolute risk of CVD associated with HIV infection remains uncertain.[150]

Chronic kidney disease

The glomerular filtration rate (GFR) can be estimated using the Cockcroft Gault, the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[151]. As all equations are based on serum creatinine, equations used to measure the estimated GFR (eGFR) may be importantly affected by rapid changes in muscle mass such as may occur in patients with advanced HIV disease who commence cART. Both the Cockcroft Gault and CKD-EPI equation have been validated in HIV-infected patients[151,152]. Here we have chosen to report eGFR values as estimated by the Cockcroft Gault equation, because this equation takes body weight into account. eGFR typically decreases with increased age in a linear fashion over time *(Web Appendix Figure 4.3)*. The short term change in eGFR has been reported to be strongly related to the risk of end stage renal disease[153]. We calculated the proportional change in eGFR over two years after cART initiation[154]. In 31% of the patients, the eGFR decreased by 10% in the first two years after cART initiation *(Web Appendix Figure 4.4),* in 16% of the patients eGFR decreased between 10 and 20%, and in 9% of the patients eGFR decreased by more than 20%. An international meta-analysis including 1.7 million participants showed that a 30% reduction in eGFR over two years was associated with a 5-fold increased hazard of end-stage renal disease[154]. In total, 6% of the study participants had a greater than 30% decrease in eGFR. The crude incidence of CKD, defined as eGFR <60ml/min/1.73m^2, in patients with an eGFR>60 ml/min/1.73m^2 at inclusion in the analyses and without previously confirmed CKD varied over time *(Figure 4.2 (C))*. From 2007, onwards 615 cases of CKD were identified. The incidence from 2008 onwards declined from 8 to 4.5 cases per 1,000 person years in

men and from 8.7 to 3.4 cases per 1,000 person years in women. Risk factors for CKD were heterosexual HIV transmission risk group, older age, being HCV RNA positive at start of cART and a lower body mass index (*Web Appendix Table 4.6*). A recent study from the D:A:D study showed that tenofovir discontinuation rates increased with decreasing eGFR, which results in a select group of patients still on tenofovir with lower CKD risk. Traditional risk factors and current CD4 cell count were the strongest predictors for CKD [155].

From 2007 onwards, 68 HIV-infected patients underwent dialysis for at least three months and 18 patients received a kidney transplant. The median time between the start of dialysis and kidney transplant was 6 years (IQR: 4-7). Of the 68 patients who were dialysed, 31 died during follow-up (46%); the median time between the start of dialysis and death was 2.5 years (IQR 1-5). Four out of the 18 patients who received a kidney transplant died; the median time to death was 2 years (IQR 1-4) (one patient died within 3 months after kidney transplant).

Data collection on adverse event of anti-HIV drugs (D:A:D) study: within the D:A:D cohort study predictors of chronic kidney disease and end-stage renal disease were assessed amongst HIV-infected patients with at least three glomerular filtration rate (GFR) estimations [155]. D:A:D is a large observational cohort study of more than 30 cohorts of people with HIV in Europe, Australia and the U.S.A. It has provided some of the first evidence of various complications of HIV/AIDS and its treatment. This analysis included 35,192 persons of whom 153 developed chronic kidney disease or end-stage renal disease during 200,119 person years of follow-up with an overall incidence of 0.67 per 1,000 person years. Tenofovir was frequently discontinued as eGFR declined. After adjustment, patients previously exposed to, but currently off, tenofovir had similar rate ratios of chronic kidney disease or end-stage renal disease compared to patients unexposed to tenofovir. Other predictors were diabetes, hypertension, baseline eGFR, smoking and current CD4 cell count. Neither current nor recent antiretroviral drug use predicted advanced chronic kidney disease or end-stage renal disease. Traditional renal risk factors and current CD4 cell count were the strongest advanced predictors.

Non-AIDS-defining malignancies

Overall, 865 patients in SHM have been recorded as having a non-AIDS malignancy from 2002 onwards. The crude incidence of non-AIDS-defining malignancies from 2002 onwards varied from 6.9 to 5.3 cases per 1,000 person years in men and from 1.7 to 6.0 cases per 1,000 person years in women (*Figure 4.2 (D)*). In men, the age-standardised incidence was significantly lower in the period of 2007-2013 compared to 2000-2006, as illustrated by a standardised incidence ratio significantly lower than 1.00 (*Table 4.3*). In women, the age-standardised incidence ratio did not deviate significantly from 1.00. Changes in risk factors such as smoking over time and a higher proportion of individuals with high CD4 cell counts in later years may have contributed to the lower age-standardised incidence in men.

Table 4.3: Crude and age-standardised non-AIDS malignancy incidence per 1,000 years of follow-up during the periods 2000-2006 and 2007-2013, and age-standardised incidence ratio and 95% confidence intervals.

	Men	Women
Crude incidence 2000-2006	5.6 (5.0-6.4)	2.8 (1.9-3.9)
Crude incidence 2007-2013	6.2 (5.7-6.8)	3.6 (2.8-4.5)
Age-standardised incidence 2007-2013*	5.1 (4.6-5.6)	2.6 (2.0-3.5)
Standardised incidence ratio*	0.87 (0.80-0.96)	0.98 (0.77-1.24)

** Standardised according to the observed age distribution during the period 2000-2006.*

Demographic and clinical factors significantly associated with an increased risk of a first non-AIDS-defining malignancy were older age, having chronic hepatitis B virus co-infection, CD4 counts less than 350 cells/mm^3, being a current smoker, having had an AIDS diagnosis, and a lower BMI (*Web Appendix Table 4.6*).

Among HIV-infected men, 105 cases of anal cancer were identified. Overall, the incidence of anal cancer amongst men was 0.92 cases per 1,000 person years (95% CI 0.75-1.11). The incidence of anal cancer slowly decreased over time from 1.2 cases per 1,000 person years in the period of 2002-2003 to 0.6 cases per 1,000 person years in 2012-2013 *(Figure 4.2 (G)*). A possible explanation for the decreasing trend in incidence of anal cancer might be that the long-term treatment with cART is associated with a lower risk of anal-epithelial neoplasia[156], which might affect the anal cancer incidence. Furthermore, the trend over calendar time of starting cART at higher CD4 counts might lead to a decrease in anal cancer incidence, as low nadir CD4 cell count and lower current CD4 cell count are associated with an increased risk of anal cancer[157].

Other collaborations

The AGE$_h$iV Cohort Study

Co-morbidity in HIV-infected persons compared to HIV-uninfected individuals

The AGE$_h$iV Cohort Study, a study in which the HIV outpatient clinic of the Academic Medical Center (AMC) of the University of Amsterdam, the Public Health Service Amsterdam (PHSA), and SHM closely collaborate, captures a broader spectrum of co-morbid conditions, including at an earlier disease stage, than is currently captured by SHM for the whole of the Netherlands. Importantly, the study also includes an HIV-uninfected control population, which allows careful assessment of the potential contribution of HIV and associated factors to the risk of co-morbidity. This is relevant in view of reports suggesting that the incidence of serious non-AIDS-defining diseases, such as renal and liver disease, diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies, is higher among HIV-infected individuals than among those who are uninfected. As such, the study provides important complementary information to the other findings reported in this chapter.

The proportion of individuals using co-medication for diabetes mellitus, hypertension or lipid lowering medication is shown in *Figure 4.10*. These early analyses show a higher prevalence of co-medication use in HIV-infected individuals.

Prevalence of osteoporosis and osteopenia in HIV-infected (n=581) and HIV-uninfected (n=520) individuals included in the AGE$_h$iV Cohort Study is shown in *Figure 4.11*. Assessments performed within the AGE$_h$iV Cohort Study include bone mineral density (BMD) measurements, using dual X-ray absorptiometry (DXA) scanning of the lumbar spine (L1-L4), femoral neck and total hip. The overall prevalence of osteoporosis (13.3 vs. 6.7%, p<0.001), as well as the prevalence of osteoporosis and osteopenia in each of the three bone locations, was higher in HIV-infected study participants.

Preliminary analysis using multivariable linear regression showed that the association between HIV infection and BMD was attenuated by adjusting for traditional risk factors for low BMD. After adjustment for age, body weight, gender, menopausal status, skin pigmentation and pack years of smoking, the association between HIV infection and BMD was lost. Within the HIV-positive study participants, years spent with a CD4 count below 200 was associated with a statistically significantly lower BMD in femoral neck and total hip. As only a small proportion of HIV-infected patients have/had a nadir CD4 count below 200 cells/mm^3, this risk factor was relatively unimportant for our patient population. Notably, no associations were found between BMD and current or past use of certain types of antiretroviral therapy, specifically tenofovir [158].

Figure 4.10: *Proportion of HIV-infected and uninfected individuals using comedication followed in the AGE$_h$iV study.*

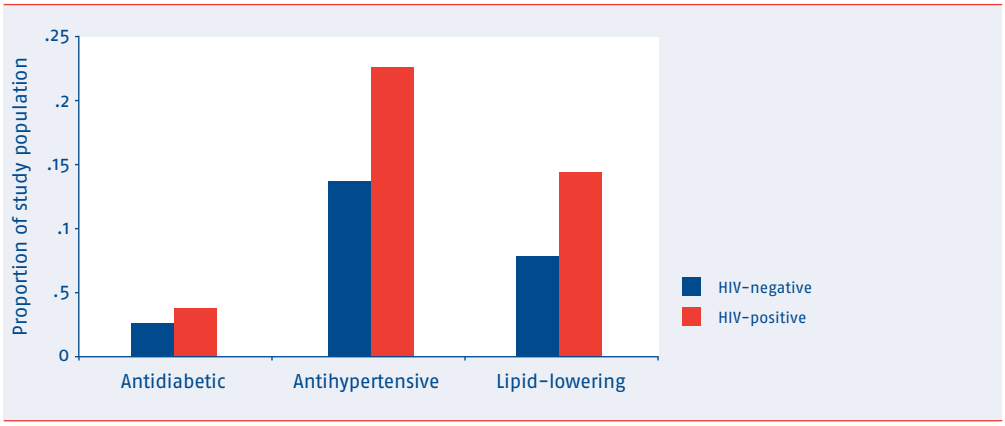
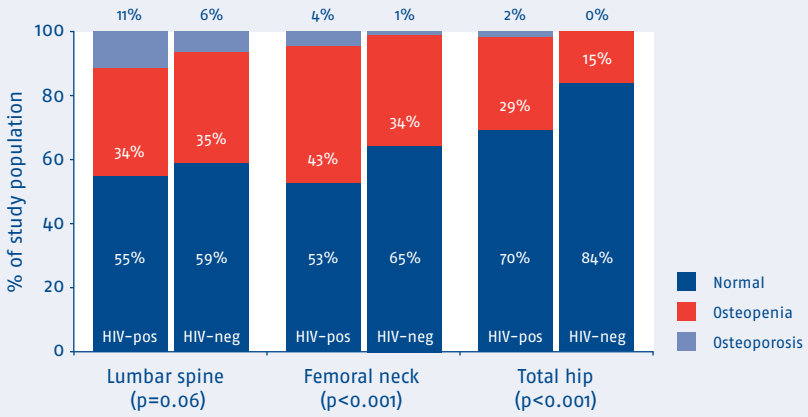


Figure 4.11: Prevalence of osteoporosis in HIV-infected and uninfected individuals followed in the AGE$_h$iV study.



Legend: HIV-pos=HIV-positive; HIV-neg=HIV-negative.

Summary and conclusions

Mortality and AIDS

The rates of AIDS and HIV-related death have decreased dramatically since cART became available in the Netherlands in 1996 and continue to be low, consistent with studies from Spain [159], Denmark [160], the USA [161] and several other European countries [162]. Nonetheless, on average, mortality rates remain higher than in the general population, although they approach rates comparable to those in the general population in the subsets of patients on treatment with a CD4 count more than 500 cells/mm^3. Although an overview of the causes of death among HIV-1 infected patients in the Netherlands indicates a relative decline in the proportion of patients dying of AIDS and a relative increase in non-AIDS causes, the proportion of those dying of AIDS remains substantial. This is a reflection of a high proportion of patients continuing to present late for care who already have advanced immunodeficiency, AIDS or both. Patients who died of AIDS had substantially lower CD4 cell counts at entry into care compared to patients who died from a non-AIDS related cause, and time between entering care and dying was shorter in patients dying of AIDS.

Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and cardiovascular disease in men and women was found to have remained relatively stable, the age-standardised incidence for both diseases declined over time in men.

The decline in age-standardised incidence in men may suggest improved awareness, prevention (including switching away from drugs associated with an increased risk of diabetes mellitus [163] and myocardial infarction [164] towards those that thus far have not been

associated with similar risks), and increased attention to managing traditional risk factors of these conditions. Risk factors were mainly those traditionally known to be associated with these diseases, including age, hypertension, and obesity, similar to those reported in other studies[163,165,166]. Several of these risk factors have been reported to be more prevalent amongst people living with HIV[134].

Cardiovascular risk factors

Despite the increasing age of the HIV-infected population, the proportion at high or very high cardiovascular risk has remained stable during the period 2000-2013. This suggests that cardiovascular risk management may have improved over time, as illustrated by the initiation of statins at less elevated lipid levels, and the preferred use of cART regimens without known cardiovascular risk (*Chapter 2*). Significant room for further improvement remains, however, given that over half of individuals at very high risk of cardiovascular disease in 2013 did not use a statin. Prospective longitudinal monitoring of time-updated lipid levels, smoking status, blood pressure, weight and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing HIV-1 infected population, and to study the impact of interventions such as the use of statins in modifying disease risk.

Renal insufficiency

Older age and those with traditional risk factors such as hypertension were found to be at increased risk for CKD, as were patients with advanced immunodeficiency. Other studies have reported hepatitis B and C virus co-infection[167,168], and the use of tenofovir, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment[169].

Non-AIDS malignancies

The crude incidence of non-AIDS malignancies in the Netherlands has remained stable over time, and we observed a decline in age-standardised incidence of non-AIDS malignancies in men. The most common malignancies are lung, anal, head and neck, as well as Hodgkin's lymphoma. Several cohorts that included a high proportion of men have reported an increased incidence of non-AIDS malignancies[170-172]. Our analyses show that patients diagnosed with non-AIDS malignancies were more likely to be older, infected with hepatitis B, or more likely to have a CD4 count below 350 cells/mm^3. An increase in incidence in non-AIDS-defining malignancies with age has been reported by the Swiss HIV cohort study[173], and the D:A:D study has reported an increase in deaths from non-AIDS-defining malignancies[174]. The effect of immunodeficiency may be stronger for infection-related non-AIDS defining malignancies[175].

Co-morbidity in HIV-infected compared to HIV-uninfected individuals

Results from the AGE$_h$iV Cohort Study demonstrate a higher use of comedication for diabetes, hypertension and dyslipidaemia in HIV-infected participants compared to non-infected participants. The prevalence of osteoporosis and osteopenia in lumbar spine (L1-L4), femoral

neck and total hip was also higher in HIV-infected study participants. Longer time spent with a CD4 count below 200 was associated with a statistically significantly lower BMD in femoral neck and total hip (see section 'Other collaborations' in this chapter).

Recommendations

Although the proportion of patients dying of AIDS in the Netherlands has markedly declined throughout the cART era, it remains unacceptably high. The best hope to achieve a further reduction is to improve the identification of infected individuals at earlier stages of infection, with immediate linkage to care to allow timely initiation of treatment. It is possible that this may also have beneficial impact on the incidence of those co-morbidities, such as non-AIDS malignancies, for which advanced immunodeficiency is a contributing risk factor. In addition, screening for pre-cancerous stages of anal cancer, prevention, identification and appropriate treatment of viral hepatitis co-infections may also contribute to lowering the incidence. Studies such as the AGE$_h$iV Cohort Study are needed to provide further insight into the independent contribution of HIV and HIV-associated factors such as (innate and adaptive) immune and coagulation activation and inflammation, thereby guiding the development of interventions targeted at identified relevant mechanism[124,176]. In addition, prolonged follow-up of participants in such studies will demonstrate the extent to which co-morbidity may occur at a significantly younger age in HIV-infected individuals compared to those who are uninfected, thereby further guiding policy for prevention and management.

It is important to realise that the risk of many, if not each, of the co-morbidities frequently identified in people living with HIV is determined by multiple factors. Apart from immunodeficiency, well-known traditional unmodifiable risk factors such as age and genetic predisposition, modifiable lifestyle-related factors, and known and as yet unknown effects of antiretroviral treatment and co-infection are key additional contributors for consideration. Development of antiretrovirals with improved safety profiles for long-term use should continue to remain a priority, given the association of some of the current generation of drugs with CKD, cardiovascular outcomes, bone loss, and possibly cancer[177].

Ageing, of course, strongly contributes to the risk of the development of co-morbidity, ranging from cardiovascular and chronic kidney disease to diabetes mellitus and non-AIDS malignancies. Given the steadily rising proportion of individuals with HIV in the older age categories, it will be imperative to ensure the continued collection of good quality information regarding comorbidities and their risk factors in our cohort.
Awareness on the part of both physicians and patients in the role of modifiable, lifestyle-related risk factors like smoking, particular in those who are older or otherwise at high a priori risk of certain co-morbidities, and appropriate management of these risk factors offer considerable hope of a lower co-morbidity burden and healthy ageing for persons living with HIV. Although this particularly applies to conditions such as cardiovascular disease and diabetes mellitus, it is also relevant to conditions such as chronic kidney disease, bone density loss and cancer.

5. Viral hepatitis

Colette Smit, Joop Arends, Peter Reiss and Clemens Richter

Background

Infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) are generally uncommon in the Netherlands. It is estimated that 0.1% to 0.4% of the total Dutch population has evidence of ever having been exposed to HCV and 0.2 to 0.4% has ever been exposed to HBV[178]. In contrast, HCV and HBV infections are far more prevalent in HIV-infected individuals due to shared routes of transmission[179].

Individuals with chronic HCV and HBV infection are at risk of developing liver fibrosis, which in time may lead to cirrhosis and can ultimately result in end-stage liver disease and hepatocellular carcinoma (HCC)[180,181]. HBV infection can also directly lead to HCC without cirrhosis. Progression to severe liver disease takes, on average, 20 to 25 years in HCV or HBV mono-infected patients[182,183]. However, in the presence of untreated HIV infection, HCV and HBV infection is associated with more rapid progression of fibrosis[184,185]. In recent years, such long-term complications have led to increased mortality rates in HCV and HBV mono-infected persons, as well as in HIV co-infected individuals[186].

In the era when treatment for HIV infection was either unavailable or insufficiently effective to achieve sustained suppression of viral replication, patients progressed to AIDS and death before the effects of co-infection with HCV or HBV could become clinically manifest as severe chronic liver disease. However, now that the incidence of AIDS and its associated mortality rate have markedly declined with the widespread use of combination antiretroviral therapy (cART), liver disease has become an increasingly frequent cause of morbidity and mortality in persons living with HIV[187].

In view of these developments, Stichting HIV Monitoring (SHM) has markedly increased its efforts to monitor the epidemiology and clinical consequences of HCV and HBV co-infection among patients in care at HIV treatment centres in the Netherlands. This chapter summarises current information regarding the demographic and clinical characteristics, progression to severe chronic liver disease and mortality, and the responses to treatment in this population with HIV and either HCV or HBV co-infection, or both.

A working group on hepatitis, which was set up jointly between the Dutch association of HIV-treating physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) and SHM, has developed a standardised protocol for the collection of data related to liver disease and hepatitis for inclusion in the SHM database. Collection of extensive, additional data according to this protocol was implemented in July 2012. These detailed data span the entire spectrum of both HBV and HCV infection and range from serodiagnostics and treatment responses (including adverse effects) to complications such as severity of liver fibrosis (based on liver elastography [also known as FibroScan®], pathology, radiology, and endoscopy reports). These additional data allow increasingly reliable reporting of the prevalence and incidence of severe liver diseases.

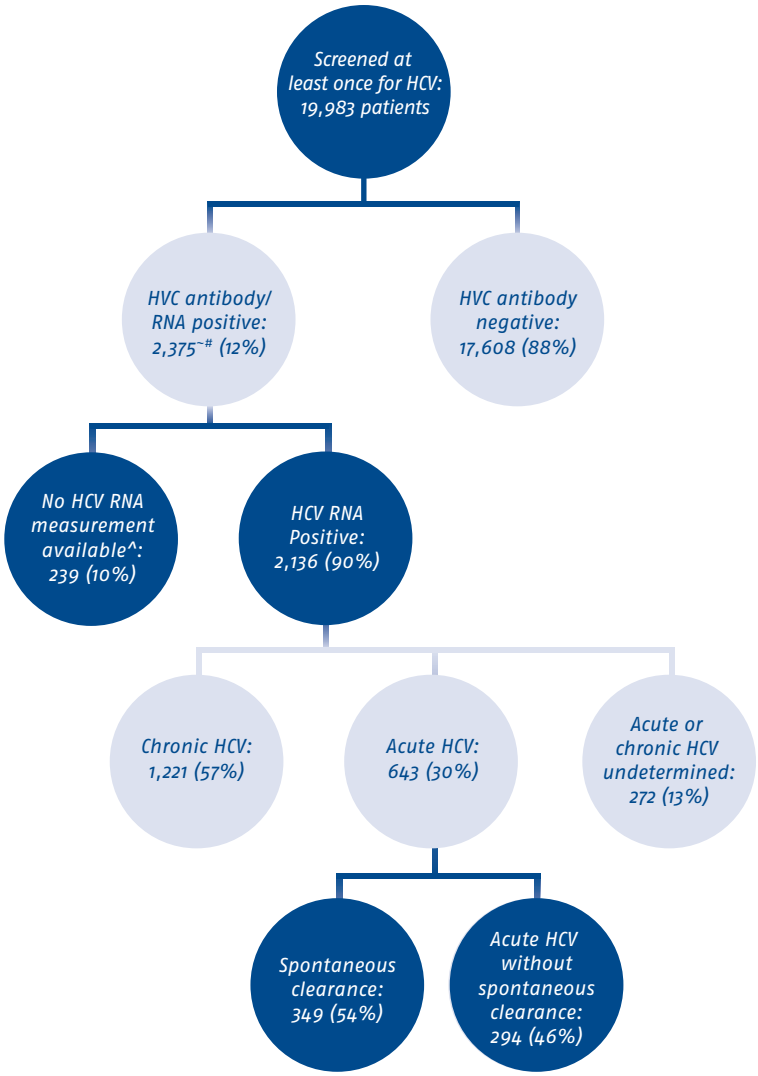
HCV

Demographic and clinical characteristics

In total, 2,375 (12%) of the 19,983 HIV1-infected adults (≥18 years of age at time of HIV-1 diagnosis) in care who were ever screened for HCV co-infection had a positive result with an HCV antibody test or HCV RNA test, confirming a far higher prevalence of HCV in the HIV-infected population compared to estimates for the general population in the Netherlands *(Figure 5.1)*. In 239 of the 2,375 patients (10%), HCV RNA data were not documented. Of the remaining 2,136 patients with available HCV RNA data, 1,221 (57%) were classified as being chronically infected (HCV RNA test result documented to have remained positive for more than six months after the first positive result), and 643 (30%) were diagnosed with acute HCV infection (documented anti-HCV IgG seroconversion or HCV RNA conversion within 12 months). Of these 643 patients with an acute HCV infection, 349 (54%) spontaneously cleared the HCV infection, whereas the remaining 294 patients did not. The remaining 272 patients of the 2,136 patients with available HCV RNA data had one positive test result, but no registered follow-up results. This meant that it was impossible to determine whether the HCV infection was acute or chronic, and, therefore, this group of patients was excluded from further analysis.

The analyses described in the remainder of this section on HCV are limited to patients who could be definitively classified as having either chronic (n=1,221) or acute (n=294) HCV infection without spontaneous clearance.

Figure 5.1: Flowchart of HIV-infected patients tested at least once for HCV.



Legend: ~includingpatients who are HCV RNA poaitive but no known HCV antibody data. #including documented seroconversion. ^excluded from further analyses.

The majority of patients with chronic or acute HCV infection were male (82% and 98%, respectively). Most patients with a chronic or acute HCV infection originated from the Netherlands (chronic 782/1,221 [64%], acute 233/294 [79%]) *(Table 5.1)*. Sixty-one percent of the patients ever registered and infected with HIV through injecting drug use (IDU) or former IDU had chronic HCV infection (424 of the total 700 of IDU/former IDU), while 4% of men who have sex with men (MSM) had chronic HCV infection (537 of the 11,998 MSM) and 2% of MSM had an acute HCV infection (272/11,998). For 1,017 of the 1,221 patients (83%) with a chronic HCV infection, the HCV genotype had been documented. Most of these patients (62%) were infected with HCV genotype 1, 5% with genotype 2, 15% with genotype 3, and 16% with genotype 4. Two percent of the patients were either infected with genotype 5 or 6 or was not typeable. In 265 of the 294 patients (90%) with an acute HCV infection, an HCV genotype was available. In the majority of cases, patients with an acute HCV infection were infected with genotype 1 (70%) or genotype 4 (18%).

Table 5.1: *Demographic characteristics of hepatitis C virus (HCV) co-infected patients registered in the SHM database, 1998–2014.*

	Total	Chronic HCV	Acute HCV
Total number of patients screened for HCV	19,983	1,221	294
Male gender n, (%)*	16,280 (81)	1,006 (82)	238 (98)
Region n, (%)			
Netherlands	11,494 (57)	782 (64)	233 (79)
Europe	1,333 (7)	176 (14)	15 (5)
Sub-Saharan Africa	2,870 (14)	50 (4)	6 (2)
Caribbean/Latin America	2,295 (11)	72 (6)	16 (5)
Southeast Asia	679 (3)	30 (2)	11 (4)
Other	1,312 (7)	111 (9)	13 (4)
HIV transmission route n, (%)			
Men who have sex with men (MSM)	11,998 (60)	537 (44)	272 (93)
Heterosexual	6,012 (30)	127 (10)	11 (4)
Current and former injecting drug users	700 (4)	424 (35)	3 (1)
Other	1,218 (6)	131 (11)	8 (3)
cART n, (%)	17,921 (90)	1,163 (95)	276 (94)

	Total	Chronic HCV	Acute HCV
HCV genotype n, (%*)			
Total determined		1,017	265
1		636 (62)	184 (70)
2		54 (5)	18 (7)
3		158 (15)	5 (2)
4		160 (16)	49 (18)
Other		19 (2)	9 (3)
not determined		204	29
Deaths n, (%)		218 (18)	9 (3)

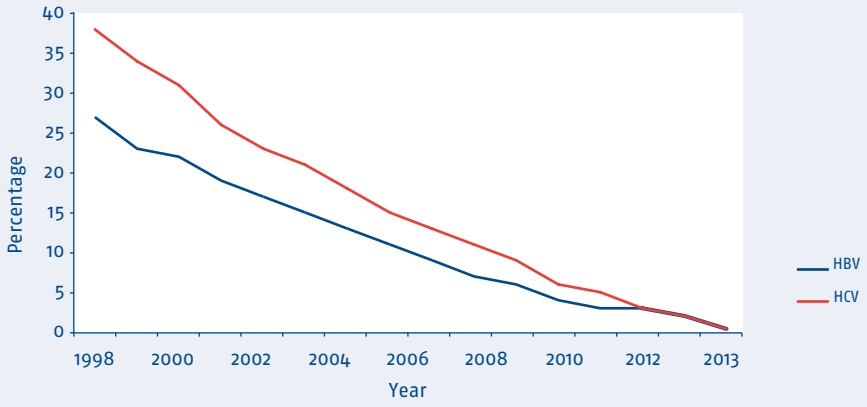
*Legend: n represents the total and (%) represents the percentage of the total for each column; *percentage from total number of patients with an available HCV genotype.*

Changes over time

Testing for HCV over time

Screening for HCV infection among HIV-infected patients in care increased over calendar time. In 1998, 38% of the HIV-infected patients in care had not been screened for the presence of HCV infection in that specific calendar year. However, with time, a strong and steady decrease in the proportion of patients with unknown HCV status has been observed. In 2011, only 3% of the patients in care had not been screened for HCV co-infection, and this total declined further to 0.4% in 2013 (*Figure 5.2*).

Figure 5.2: Percentage of patients in care with an unknown status of HBV or HCV per calendar year of care.

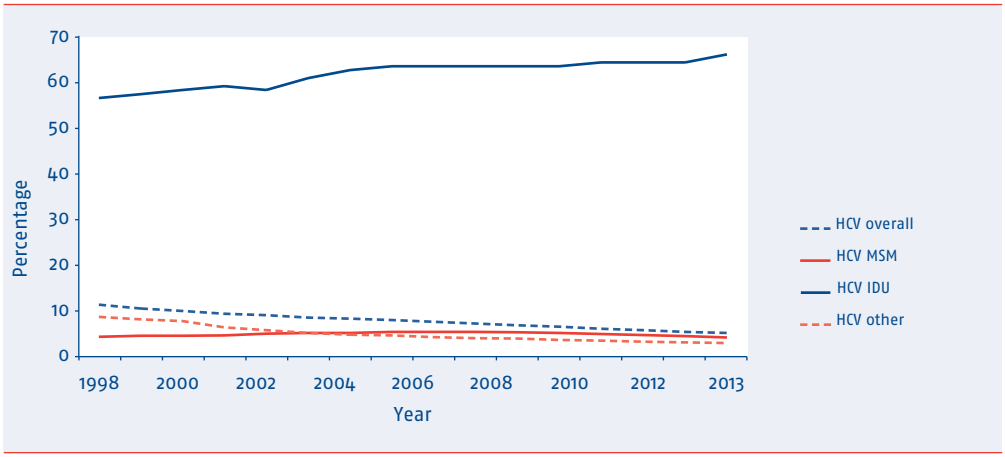


Legend: HBV=hepatitis B virus; HCV=hepatitis C virus.

Prevalence of chronic HCV co-infected patients per calendar year

The overall prevalence of chronic HCV infection (defined as the proportion of patients who tested positive for HCV RNA for at least six months) among patients in care decreased from 13% in 1998 to 6% in 2013, but was not equally distributed among HIV transmission categories. The highest prevalence was found among patients infected with HIV by IDU or former IDU, and this number varied between 65% and 76% (*Figure 5.3*). The prevalence of chronic HCV infection amongst MSM was 5% in 1998; it increased to 6.2% between 2005 and 2006 and dropped to 4.8% in 2013.

Figure 5.3: *Prevalence of chronic HCV co-infection per calendar year.*

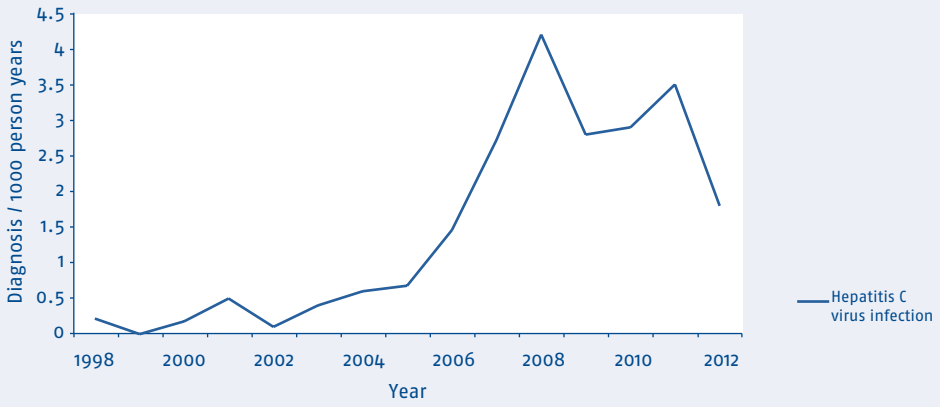


Legend: *HCV=hepatitis C virus; MSM=men who have sex with men; IDU=injecting drug use.*

Incidence of acute HCV infection over time

Figure 5.4 shows the incidence of acute HCV infection over time. The overall rate of acute HCV infection in HIV-infected patients was 1.8 per 1,000 person years (PY) of follow-up (95% confidence interval [CI] 1.7-2.1). This incidence increased from 0 diagnoses per 1,000 PY in 1998 to 3.0 diagnoses per 1,000 PY in 2013. The incidence of acute HCV infection differed importantly between HIV transmission categories. For IDU or former IDU, the overall incidence was low (1.0/1,000 PY, 95% CI 0.2-2.9), probably explained by the already large background prevalence of infection in this group and, therefore, the relatively small number of patients still remaining at risk of newly acquiring HCV infection. Among MSM, however, a steady increase in incidence of acute HCV infection was observed over time, from 0.54 diagnoses per 1,000 PY in 2003 to 5.5 per 1,000 PY in 2011 to 4.2 per 1,000 PY in 2013.

Figure 5.4: Incidence of acute hepatitis C virus infection per calendar year.

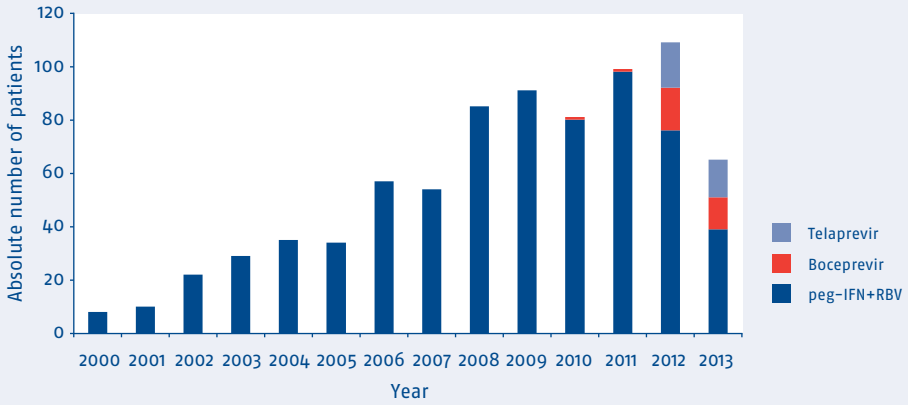


Treatment for HCV infection

The primary aim of treatment for HCV is to achieve a sustained virological response (SVR)[188]. Until recently, treatment consisted of a combination of, originally, unpegylated interferon alpha (IFN-alpha) and subsequently pegylated interferon alpha (peg-IFN alpha) in combination with (weight-based) ribavirin (RBV). The usual duration of treatment was 24 or 48 weeks, depending on HCV genotype. In April 2012, the HCV protease inhibitors (PI) boceprevir and telaprevir, two direct-acting antiviral agents (DAAs) predominantly active against HCV genotype 1, became available in the Netherlands[189]. Triple therapy that includes one of these two agents, together with PEG-IFN alpha and RBV, has since become the treatment of choice for chronic HCV genotype 1 infection. Overall, a total of 789 of the 1,515 patients (52%) with a known chronic or acute HCV infection have been prescribed a combination treatment of PEG-IFN alpha and RBV; 52 of the 789 also received either boceprevir or telaprevir. Since 2013, on the basis of the national Dutch study protocol, boceprevir has also been used for acute HCV genotype 1 infection; 11 patients with an acute HCV infection received treatment with boceprevir or telaprevir with PEG-IFN alpha and RBV.

Figure 5.5 shows the absolute number of patients having started HCV treatment per calendar year. The number of patients starting PEG-IFN alpha and RBV treatment increased from 8 in 2000 to 91 in 2009 followed by a decrease to 39 in 2013. Twenty-three infected patients started with boceprevir between 2010 and 2013, and 29 patients started with telaprevir in the same calendar years. The overall decrease in 2013 is likely due to physicians and patients delaying the start of treatment because superior PEG-IFN-free treatment options with novel DAAs are expected to become available soon.

Figure 5.5: Number of co-infected patients starting hepatitis C virus treatment per calendar year

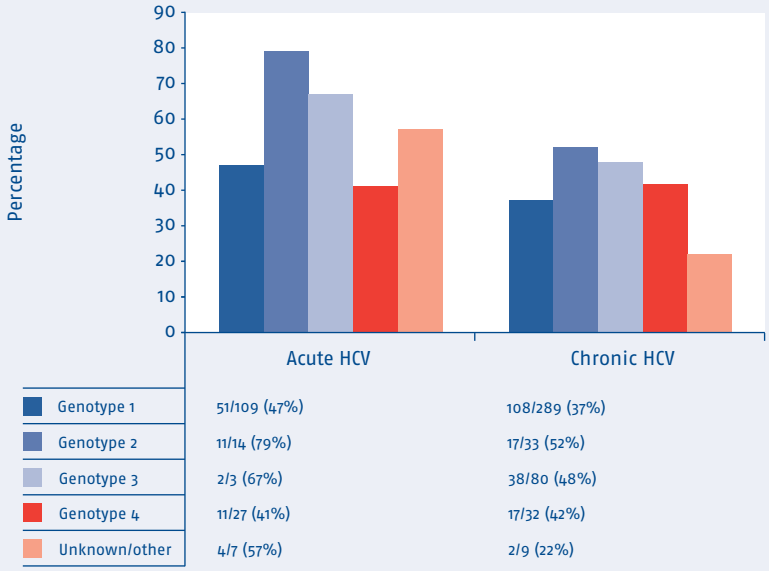


Legend: peg-ifn+RBV = pegylated interferon + ribavirin.

Outcome of treatment for acute HCV infection

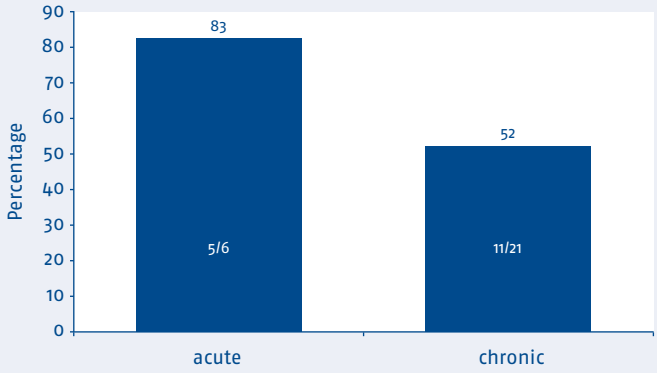
Of the 294 patients with an acute HCV infection, 175 initiated treatment with PEG-IFN alpha and RBV and completed treatment by the time of closure of the database. The median duration of treatment in the 175 patients who completed treatment with PEG-IFN alpha and RBV for acute infection was 24 weeks (interquartile range [IQR] 18-31). SVR rates are shown in *Figure 5.6*, stratified by HCV genotype. SVR rates were as high as 79% in patients with genotype 2, but ranged from only 37% to 42% for genotypes 1, 3, and 4. It should be noted that the number of patients with genotypes 2, 3, and 4 receiving treatment was small, limiting conclusions about treatment response by genotype.

Figure 5.6a: Sustained virological response achieved by hepatitis C virus (HCV) treatment in acute and chronic HCV-infected patients, stratified by HCV genotype.



Legend: HCV=hepatitis C virus.

Figure 5.6b: Sustained virological response 12 weeks after completion of treatment with telaprevir or boceprevir in patients with an acute or chronic hepatitis C infection.



Outcome of treatment for chronic HCV infection

The median duration of treatment in the 517 patients who completed treatment with PEG-IFN alpha and RBV for chronic infection was 25 weeks (IQR 14-48). *Figure 5.6a* shows the SVR rate stratified by HCV genotype. Forty-eight percent of the patients with genotype 3 and 52% with genotype 2 achieved SVR, with lower rates for the other genotypes (i.e., 37% for genotype 1, 42% for genotype 4, and 22% for patients with an unknown or other genotype).

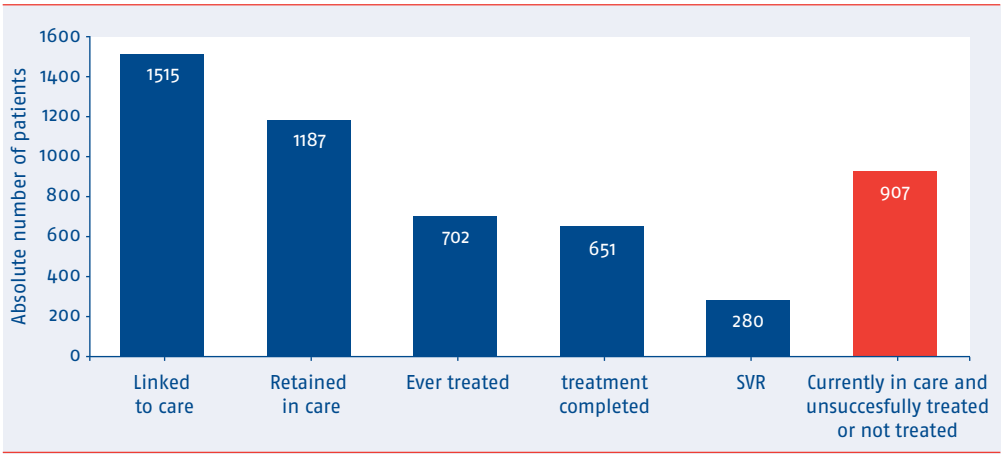
Outcome of treatment with boceprevir or telaprevir

A total of 41 patients with chronic HCV infection started treatment with boceprevir (n=18) or telaprevir (n=23), and 11 patients with an acute HCV infection began treatment with boceprevir (n=5) or telaprevir (n=6). The median duration of treatment with boceprevir was 32 weeks (IQR 12-44 weeks). Patients receiving telaprevir were treated for a shorter duration: the median duration was 12 weeks (IQR 12-13). For 28 patients, HCV RNA follow-up data was available to determine the SVR. SVR was achieved in 83% of patients with an acute HCV infection and in 52% of those with a chronic HCV infection (*Figure 5.6b)*.

HCV treatment cascade

The cascade of treatment for patients with an HCV co-infection is shown in *Figure 5.7*. Out of a total of 1,515 patients linked to HIV care and diagnosed with HCV, (78%) were retained in care as of June 1 2014. Of these 1,187 patients, 702 (59%) had ever received treatment for HCV. Of these 702 treated patients, 651 (93%) had completed HCV treatment and were in care for at least 24 weeks after the end of treatment, with data available to calculate their SVR rate. SVR was achieved in 280 of the 651 (43%) patients. Thus, of the 1,187 HCV/HIV co-infected patients, a total of 907 (76%) remain in need of effective HCV therapy, 485 of whom have never yet received HCV treatment and 422 in whom prior treatment was not successful.

Figure 5.7: HCV cascade of care.



Legend: SVR=sustained virological response.

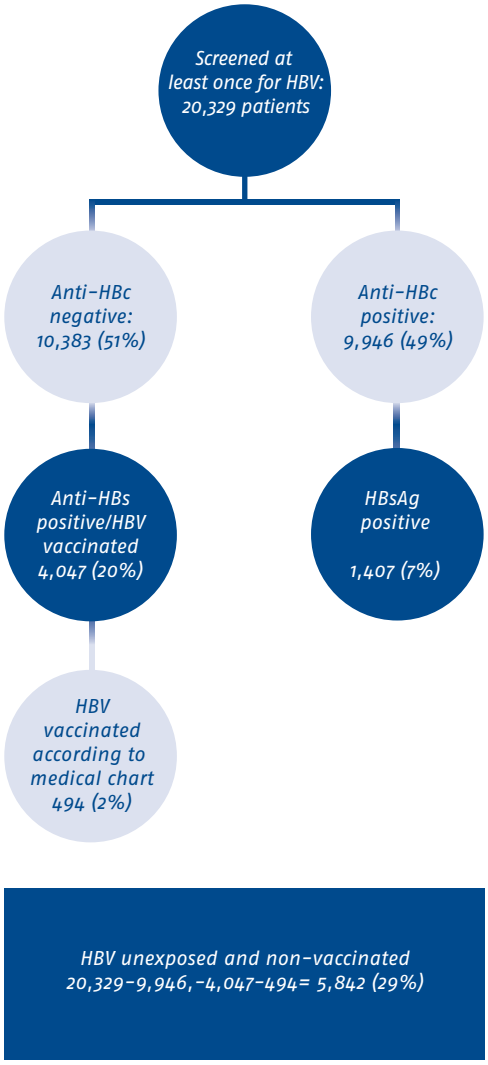
HBV

Forty-six percent of the 20,329[2] HIV-infected patients ever registered in the SHM database and ever screened for hepatitis B core antibody (anti-HBc) tested positive during screening and thus have been exposed to HBV.

In total, 10,383 (51%) HIV-infected patients tested negative for anti-HBc. Of those patients, 4047 (20%) were anti-HBc-negative and anti-HBs-positive, indicating that they had been successfully vaccinated against HBV *(Figure 5.8)*. This figure was 24% for MSM, 15% for heterosexuals, and far lower (5%) for IDU and former IDU. For 494 patients (2%) who had not been tested for anti-HBs and anti-HBc, the HIV-treating physician had noted HBV vaccination in their medical record; 353 of these patients were MSM.

[2]The total number of patients screened for HBV differs from the total number of patients screened for HCV, as not all patients screened for HBV are also screened for HCV.

Figure 5.8: Flowchart of HIV-infected patients tested at least once for hepatitis B virus.



Legend: HBV=hepatitis B virus; HBc=hepatitis B core antigen; HBs=hepatitis B surface antigen.

Therefore, overall, approximately 29% of the HIV-infected patients remained at risk of HBV infection because they had not been exposed to HBV, had not been vaccinated, or had been unsuccessfully vaccinated (100%-49% exposed-20% serological evidence of successful vaccination-2% former successful vaccination otherwise documented=29%). Furthermore, 24% of MSM remained at risk (100%-49% exposed-24% serological evidence of successful vaccination-3% former successful vaccination otherwise documented=24%). Patients in these categories could be offered HBV vaccination, although they may be protected from acquiring HBV infection by the use of tenofovir as part of their cART regimen, as suggested by findings reported by one of the Dutch HIV treatment centres and an international study by Quirck et al.[190,191]. Among the patients with no exposure to HBV infection, 72% are currently being treated with a cART regimen including tenofovir.

HBV co-infection was found in 1,407 of the 20,329 (7%) HIV-infected patients ever screened for HBV, which, similar to HCV co-infection, is considerably higher than the rate of HBV infection in the general Dutch population. Patients co-infected with HBV were predominantly male (1,204/1,407, 86%), also similar to those co-infected with HCV (*Table 5.2*). However, compared to patients co-infected with HCV, those co-infected with HBV were more likely to have been born in Sub-Saharan Africa and to have acquired HIV through heterosexual contact. HBV co-infection was less common than HCV co-infection amongst IDUs and former IDUs.

Table 5.2: *Demographic characteristics of HIV-infected patients with an active chronic hepatitis B virus (HBV) infection registered in the SHM database, 1998–2014.*

	Total	Hepatitis B surface antigen (HBsAg) positive
Total number of patients screened for HBV	20,329	1,407
Male gender n, (%)*	16,442 (81)	1,204 (86)
Region n, (%)		
Netherlands	11,622 (57)	702 (50)
Europe	1,338 (7)	89 (6)
Sub-Saharan Africa	3,019 (15)	315 (22)
Caribbean/Latin America	2,332 (11)	145 (10)
Southeast Asia	698 (3)	58 (4)
Other	1,320 (6)	98 (7)
HIV transmission group n, (%)		
Homosexual	12,039 (59)	824 (59)
Heterosexual	6,337 (31)	416 (30)
Injecting drug user	695 (3)	70 (5)
Other	1,258 (6)	97 (7)
cART n, (%)	18,207 (90)	1,307 (93)
Deaths n, (%)	2,001 (10)	210 (15)

**n represents the total and (%) represents the percentage of the total for each column.*

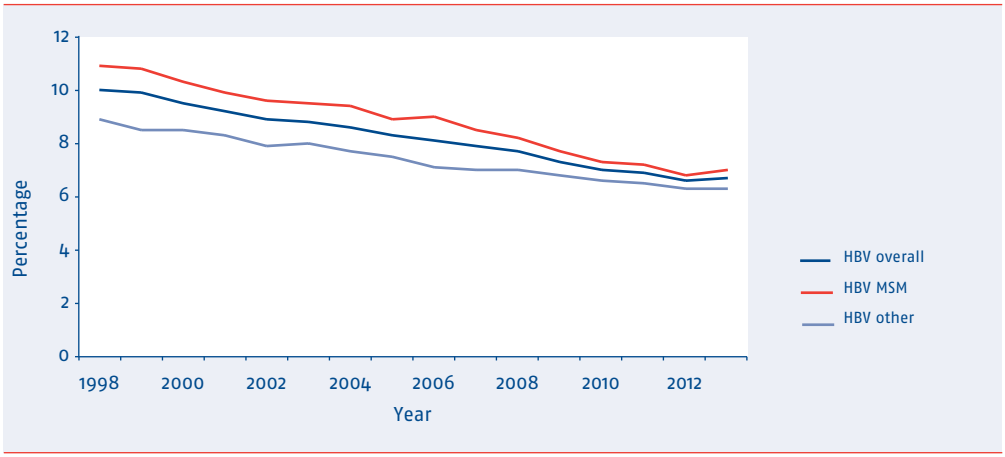
Testing for HBV infection over time

Screening for HBV infection amongst HIV-infected patients in care improved over calendar time. In 1998, 27% of the patients were not screened for the presence of HBV infection. A strong decrease was subsequently observed for the proportion of HIV-infected patients with an unknown HBV status. In 2013, 0.3% of all patients in care had an unknown HBV status *(Figure 5.2)*.

Prevalence

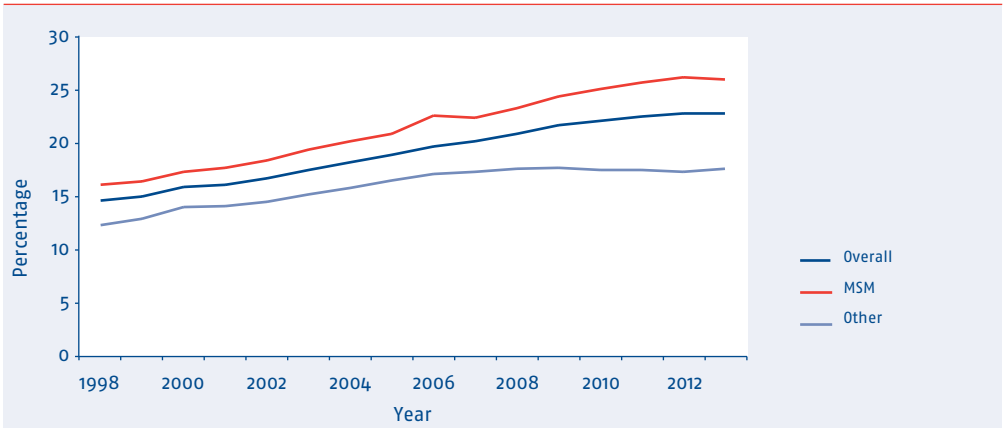
The overall prevalence of chronic active HBV infection among patients in care decreased from 10% in 1998 to 6.7% in 2013. The highest prevalence was found amongst MSM. In 1998, 11% of the MSM had chronic active HBV infection, decreasing to 8% in 2012 *(Figure 5.9)*. This decreasing prevalence of chronic HBV infection might be the result of increasing HBV vaccination rates among patients. *(Figure 5.10)*.

Figure 5.9: *Prevalence of chronic hepatitis B virus co-infection per calendar year.*



Legend: *HBV=hepatitis B virus; MSM=men who have sex with men.*

Figure 5.10: Prevalence of patients vaccinated for hepatitis B virus per calendar year.



Legend: HBV=hepatitis B virus; MSM=men who have sex with men.

Treatment for chronic HBV infection

Since chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg+), therapy is aimed at lowering the level of HBsAg to achieve HBsAg negativity in a subgroup of patients. Persistent HBsAg negativity, together with the development of antibodies against HBV surface antigen (anti-HBs), is known as HBs seroconversion. HBs seroconversion is the penultimate goal of HBV therapy. In those patients who are also e-antigen positive (HBeAg+), a similar seroconversion from HBeAg positivity to HBeAg negativity can occur, with subsequent development of anti-hepatitis B e-antigen (anti-HBe) antibodies. This so-called e-seroconversion is an important secondary treatment parameter, since studies have shown that it results in a clinically important lowering of HBV DNA. Lastly, HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues. Therefore, HBV DNA undetectability is the best surrogate marker for treatment response, and persistent lowering of HBV DNA levels to <20 IU per millilitre has been shown to delay progression of liver fibrosis to cirrhosis. Several antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly tenofovir, are also active against HBV.

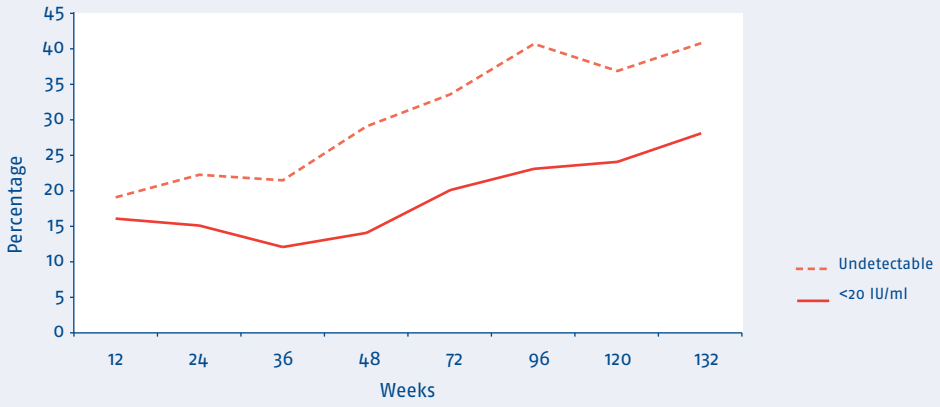
Of the 1,407 patients with HIV in the SHM database co-infected with chronic HBV, 1,307 (93%) have ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 100 patients not having received anti-HBV treatment included: death before being able to start treatment (n=17), recent entry into care (n=12), non-receipt of cART most likely because of high CD4 counts (n=10), lost to follow-up (n=38), unavailability of sufficient information (n=23).

Most patients (n=743/1,307, 57%) initially received lamivudine as monotherapy against HBV. Of these patients, 290 (39%) switched to a regimen containing tenofovir-lamivudine after a median of 1.6 years (IQR 0.3-4.0), and 209 (28%) switched to a tenofovir-emtricitabine-containing regimen after a median of one year (IQR 0,3-2,8) of prior exposure to lamivudine monotherapy for HBV. For 564 of 1,307 patients (43%), their initial cART regimen included tenofovir and one additional agent with activity against HBV; for 115 of these 564 patients (20%), the additional agent was lamivudine, and for 449 patients (80%) the additional agent was emtricitabine.

It has been shown that a persistently inactive HBV carrier state with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC in the majority of HBV mono-infected patients.

Figure 5.11 shows the percentage of patients with an undetectable HBV DNA level below 20 IU/ml. For HBV DNA measurements with a different detection limit, we used the detection limit of the specific assay (<100, <200, <400, <1000 or <2000 IU/ml). Twelve weeks after the start of HBV treatment, 19% of the patients had an undetectable HBV DNA level based on the detection limit of the assay used at that moment, and 16% had an HBV DNA level below 20 IU/ml. The percentage of patients with an undetectable HBV DNA level, based on the detection limit of the specific assays used at that moment, was 22% after the first year of treatment, with an increase to 41% two years after the start of treatment and 45% three years after the start. The percentage of patients with an HBV DNA level below 20 IU/ml one year after the start of treatment was 14%, after two years 23%, and after three years 31%.

Figure 5.11: *Percentage of patients with undetectable hepatitis B virus (HBV) DNA levels (<100, <200, or <2000 IU/ml) or HBV DNA levels <20 IU/ml since the start of HBV treatment.*



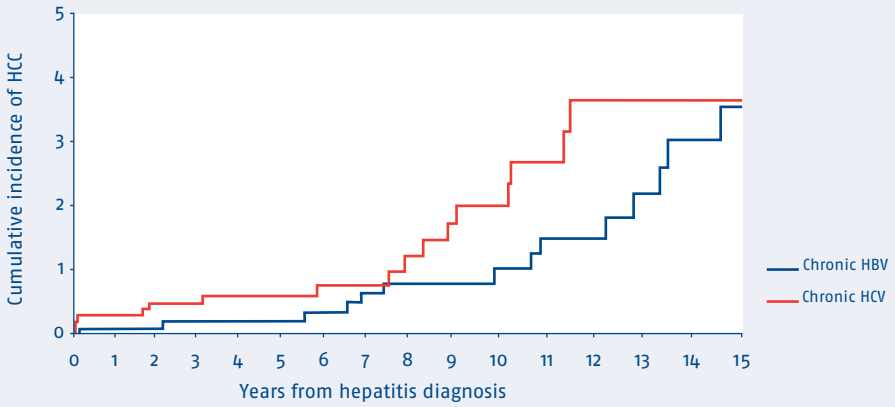
Among the 1,307 patients whose cART regimen ever included one or more agents with activity against HBV, 306 of the 627 patients (49%) had a documented positive test result for HBeAg. Of these 306 patients, 174 (57%) were retested, with 93 (53%) converting from HBeAg positivity to negativity and HBe antibodies developing in 48 (28%).
Of 1,307 patients for whom either repeat HBsAg or anti-HBs antibody test results were available following the start of treatment, HBsAg clearance during HBV treatment was measured in 1,002 patients, and HBs seroconversion was detected in 800 patients. The HBsAg clearance rate was 25% (255/1,002) and anti-HBs seroconversion rate was 8% (62/800), which is higher than reported in HBV mono-infected patients on long-term tenofovir therapy.

Morbidity and mortality in HCV and/or HBV co-infected patients

Liver-related morbidity

Additional data on pathology reports from liver biopsy, transient elastography (FibroScan), or both, were available for 1,162 of the 1,515 patients with chronic and acute HCV infection, and for 897 of the 1,407 patients with an HBV infection. Review of these additional data showed that severe chronic liver disease by our definition was considered present (presumptive and definitive categories combined) in 415 of the 1,162 patients (36%) with HCV infection and in 295 of the 897 HBV co-infected patients (33%). Definitive severe chronic liver disease was documented for 84 patients with an HCV infection and 138 with HBV infection.
HCC was diagnosed in 17 out of 1,221 patients (1.4%) with a chronic HCV infection, of whom 13 were born in the Netherlands. HCC was found in 19 patients (1.4%) with a chronic HBV infection, 11 of whom were born in the Netherlands, 4 in Sub-Saharan Africa, and 1 each in Latin America, Asia, the United States, and Australia. *Figure 5.12* shows the cumulative incidence of HCC. It should be noted, however, that the time between diagnosis of hepatitis co-infection and HCC is likely to have been shorter in patients with an HCV infection. Ten years after a known diagnosis of viral hepatitis, HCC had developed in 3.0% (95% CI 1-4%) of patients with HCV infection and in 1.0% (95% CI 0.5-2%) of those with active HBV infection.

Figure 5.12: Cumulative incidence of hepatocellular carcinoma (HCC) among co-infected patients with HIV and hepatitis C virus (HCV) or hepatitis B virus (HBV). Kaplan-Meier estimate was used to determine the time to HCC. Follow-up time was from the date of HIV diagnosis to the date of last contact, diagnosis of HCC, or 1 January 2014.



Legend: HCC=hepatocellular carcinoma; HBV=hepatitis B virus; HCV=hepatitis C virus.

Mortality

All-cause mortality

The overall rate of death from any cause was 15% for the 1,515 patients with an HCV infection *(Table 5.3)*. The cumulative incidence of death from any cause was higher among patients who were diagnosed with HCV or HBV before 2000 compared to those who were diagnosed in later calendar years *(Figure 5.13)*. When the risk of death from any cause was adjusted for differences in demographic and clinical characteristics (age at HIV diagnosis, gender, region of origin, HIV transmission risk group, calendar year of cART initiation, CD4 count and HIV RNA level at time of cART initiation, alcohol use and smoking, time since HIV diagnosis and calendar year of HIV diagnosis), there was no significant difference in the risk of death between HIV mono-infected patients and patients with HIV and HCV co-infection diagnosed before 2000. However, for patients with an HCV co-infection diagnosed after 2000, the overall risk of death remained higher compared to that in HIV mono-infected patients.

Table 5.3: Morbidity and mortality in hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infected patients registered at SHM.

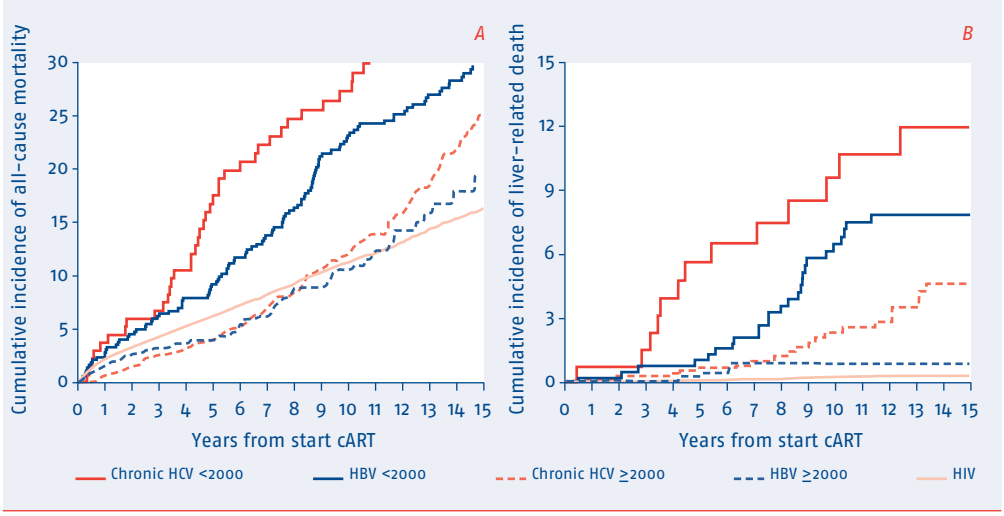
	HCV infection	HBV infection
Total	1,515	1,407
Severe chronic liver disease#, n (%)	415 (27)	295 (21)
HCC, n (%)	17 (1.4)	19 (1.4)
Deaths from any cause*, n (%)	227 (15)	210 (15)
Liver-related deaths, n(%)	44 (3)	25 (1.8)

**including liver-related death*

#including presumptive and definitive liver disease.

***Legend:** HCC=hepatocellular carcinoma.*

Figure 5.13: Cumulative incidence of all-cause mortality (A) and liver-related death (B), stratified by calendar time period. Kaplan-Meier estimate was used to determine the time to death. Follow-up time was from the date of HIV diagnosis to the date of last contact, death, or 1 January 2014.



***Legend:** cART=combination antiretroviral therapy; HBV=hepatitis B virus; HCV=hepatitis C virus.*

For patients with a chronic HBV co-infection diagnosed both before 2000 and after 2000, the overall risk of death was higher compared to that in HIV mono-infected patients *(Table 5.4)*.

Table 5.4: Adjusted hazard ratios of time from start of cART to all-cause mortality and liver-related death amongst HIV-infected patients with hepatitis co-infection compared to patients who are infected with HIV only. To evaluate the impact of HBV and HCV co-infection on risk of death, time on cART to death was estimated by a Cox proportional hazard model. Follow-up time was from the date of cART initiation until date of last contact, most recent follow-up visit, death or 1 January 2014.

	Risk of death from any cause Hazard ratio* (95% CI)	p value	Risk of liver-related death Hazard ratio* (95% CI)	p value
HIV	1	<0.001	1	<0.0001
HIV/chronic HCV, <2000	1.07 (0.77-1.48)		12.4 (5.31-29.1)	
HIV/chronic HCV, ≥2000	1.56 (1.27-1.92)		10.59 (5.04-22.3)	
HIV/chronic HBV, <2000	1.40 (1.15-1.71)		15.4 (8.22-28.8)	
HIV/chronic HBV, ≥2000	1.31 (1.02-1.68)		6.64 (2.43-18.18)	

Legend: cART=combination antiretroviral therapy; HBV=hepatitis B virus; HCV=hepatitis C virus; CI=confidence interval.

**adjusted for age, gender, region of origin, transmission risk group, calendar year of cART initiation, baseline CD4 and HIV RNA levels, alcohol use and smoking, duration of HIV infection and calendar year of HIV diagnosis.*

Liver-related death

In total, 69 patients co-infected with hepatitis died of a liver-related cause *(Table 5.3)*. Ten years after cART initiation, 10% (95%CI 5-15) of the chronically HCV co-infected patients who were diagnosed with HCV before 2000 died of a liver-related cause. This proportion was lower (6%, 95% CI 5-10) among patients with an HCV diagnosis after 2000. Among those with HBV co-infection, 8% of patients diagnosed before 2000 died of a liver-related cause (95%CI 5-11), which dropped to 1% (95%CI 0-1) in those diagnosed after 2000 *(Figure 5.13)*.

After adjustment for demographic and clinical characteristics, HBV co-infected patients and those co-infected with HCV diagnosed both before and after 2000 remained more likely to have a liver-related cause of death than HIV mono-infected patients *(Table 5.4)*. However, the risk of death from a liver-related cause strongly decreased in HBV co-infected patients from a hazard ratio (HR) of 15.4 (95%CI 8.22-28.8) in patients diagnosed with HBV before 2000 to an HR of 6.6 (95% CI 2.43-18.18) in patients diagnosed from 2000 onwards. This strong decrease in risk of death from a liver-related cause was less pronounced in HCV co-infected patients.

International collaborations

Eurosida: in an earlier study, Eurosida demonstrated that HIV/HCV co-infected patients were more likely to stop their cART regimen because of toxicity compared to HIV mono-infected patients[192]. In a recently published study, Eurosida investigated the role of HCV viraemia in the risk of antiretroviral therapy discontinuation among HIV-infected patients with an HCV co-infection. The influence of liver fibrosis on the risk of treatment discontinuation was analysed in patients who were tested for plasma hyaluronic acid, which is a biomarker for the presence of liver fibrosis. Eurosida included 9,535 patients with data available from different centres across Europe, Israel, and Argentina. This study showed that patients with viraemic HCV infection and higher levels of hyaluronic acid, which may be a marker for advanced liver fibrosis, were at increased risk of treatment discontinuation due to toxicity. This effect was seen mainly in patients using a PI-based regimen and the older nucleoside reverse transcriptase inhibitors[193].

Conclusion

Screening for HCV and HBV co-infection in the HIV-infected population continues to improve over time. While approximately 30% of the patients in care in 1998 were not screened for co-infection with HBV or HCV, this figure decreased to less than 1% in 2013.

Six percent of the HIV-infected patients registered in the SHM database were documented to be chronically infected with HCV, and acute HCV infection was documented in 1.5% of patients. Seven percent of the HIV-infected patients ever in care had chronic HBV infection. The prevalence of HBV decreased over time, which might be a result of the increased proportion of patients of non-Dutch origin being vaccinated for HBV or could be a consequence of the use of tenofovir in cART-treated patients. Nonetheless, an estimated 29% of HIV-infected patients, overall, and 24% of MSM either have not been exposed to HBV or have not been successfully vaccinated and may remain at risk of acquiring HBV. Seventy-two percent of the patients still at risk of acquiring HBV infection receive a cART regimen that includes tenofovir and may thereby be at less risk due to sustained chemoprophylaxis.

Patients co-infected with HCV or HBV are at increased risk of progression to chronic liver disease[180,181]. Thirty percent of the chronically HCV co-infected patients had evidence of severe chronic liver disease. In both HCV and HBV co-infected patients, we observed an increase in the proportion of patients with hepatocellular carcinoma in relation to the duration of hepatitis infection. Overall, patients with chronic HCV or HBV co-infection remain at increased risk of having a liver-related cause of death, although this likelihood was lower for patients with chronic HBV diagnosed after 2000, possibly as a result of increasingly effective treatment through the use of tenofovir-containing cART.

With the availability of highly effective antiviral therapies, ongoing and optimised screening for HCV and HBV co-infection and the management of these infections in individuals with HIV are needed to further limit the impact of co-infection on liver-related morbidity and mortality.

Although there has been a remarkable improvement in the uptake of HCV treatment, approximately half of the patients remain untreated. It should be noted that a considerable proportion of patients prematurely discontinued treatment with PEG-IFN alpha and RBV therapy because of insufficient response or side effects, or both. Among those treated with a combination of PEG-IFN alpha and RBV, only 41% could be considered cured, overall. Thus, more than two-thirds of HCV/HIV co-infected patients currently in HIV care in the Netherlands remain in need of efficacious HCV treatment to prevent progression of liver disease and long-term complications, including hepatocellular carcinoma. From the beginning of 2012 onwards, boceprevir and telaprevir, two DAAs that are active only against HCV genotype 1 infection, have become available in the Netherlands [194]. A small number of patients have received treatment with one of these direct-acting antiviral agents. The results in this small group of patients show improved SVR rates compared to therapy with PEG-IFN alpha and RBV among both acute and chronically HCV co-infected patients. Among the HIV/HCV co-infected patients registered with SHM, the overall SVR among patients treated with boceprevir or telaprevir was 83% and 52% in patients with an acute and chronic HCV infection, respectively. However, the use of these agents currently remains limited in the Netherlands, mainly due to clinically significant toxicities, potentially important drug-drug interactions with cART [195] (www.hep-druginteractions.org), and the continued need for an extended treatment period with PEG-IFN. However, a large number of additional oral DAAs against multiple genotypes, rather than just against genotype 1, are currently in advanced stages of clinical development [194], with reported SVR rates of >90% in HCV/HIV co-infected patients. Some of these drugs have already been registered and will likely become available for use in the Netherlands from the end of 2014 onwards. It is expected that these new agents may allow the use of interferon-free, all-oral combination regimens for the treatment of HCV infection in HIV-infected patients.

Recommendations

Continued efforts must be made to ensure that all patients with HIV are adequately assessed for the presence of HBV and HCV co-infection. In addition, HBV vaccination for the substantial proportion of HIV-infected patients who may be at particular increased risk of becoming infected with HBV could be an important goal. Further evaluation of the many novel DAAs against HCV in patients with concomitant HIV infection is important. This should lead to markedly improved treatment options, including for the populations that are more difficult to treat, such as those with no or only a partial response to currently available treatments or those with relapse after treatment; those with chronic liver disease including cirrhosis; those intolerant to PEG-IFN or ineligible to receive it; and IDUs. Over the long term, these improved treatments will contribute to reducing the burden of severe chronic liver disease, hepatocellular carcinoma, and liver-related mortality among persons living with HIV. Continued monitoring of the population co-infected with HIV and hepatitis in the Netherlands will thus be key not only for monitoring the epidemiology of these infections and the response to existing and novel treatments but also for assessing the impact of treatment on reducing the burden of morbidity and mortality from chronic liver disease.

Definitions:

Chronic hepatitis C virus (HCV) infection: Patients who remain HCV RNA positive for longer than 6 months after their first known HCV RNA positive test result.

Acute HCV infection:

1) Positive anti-HCV IgG and a documented negative anti-HCV IgG within the previous 12 months.
2) Detectable HCV-RNA in the presence of either a documented negative HCV-RNA or a documented anti-HCV IgG seroconversion within the previous 12 months [196].

Spontaneously cleared HCV infection:

1) Patients with a documented positive test result for HCV antibody with a subsequent negative HCV RNA test result.
2) Patients who fulfilled the criteria above for acute HCV who subsequently had a negative HCV RNA test without having received HCV treatment.
3) Patients who did not fulfil the definition of acute HCV infection but had a positive HCV RNA test result and became negative within 6 months without treatment.

Chronic hepatitis B virus (HBV) infection: Two or more consecutive positive test results for hepatitis B surface antigen (HBsAg) over a consecutive period of at least 6 months.

SVR: sustained virological response, defined as a negative HCV RNA test result 24 weeks after treatment discontinuation in patients treated for prior documented acute or chronic HCV infection.

Severe (chronic) liver disease was defined:
presumptively by clinically documented evidence of:

- Bleeding from gastric or oesophageal varices, hepatic encephalopathy or hepatorenal syndrome and/or
- Chronic liver disease based on radiographic or endoscopic documentation of the presence of portal hypertension by oesophageal varices, ascites, splenomegaly and reversal of portal blood flow and/or cirrhosis.

and definitively if:

- combined with a pathology or FibroScan report documenting severe liver fibrosis or cirrhosis (metavir score F3-F4 or FibroScan stiffness≥8kPa).

6. Distinct populations: HIV-1 infected children in the Netherlands

Colette Smit, Annemarie van Rossum and Peter Reiss

Background

Healthcare for HIV-1-infected children living in the Netherlands is provided mostly by four paediatric HIV-1 treatment centres, although some of the older children receive care in one of the HIV-1 treatment centres for adult care. As with adult patients, diagnosis, treatment and follow-up of these children are monitored by Stichting HIV Monitoring (SHM). Overall, demographic and clinical data have been collected by SHM for 512 children aged up to 18 years at the time of their HIV-1 diagnosis, representing an increase of 23 children compared to last year's report.

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-1-infected children worldwide[197-199]. In particular, early initiation of cART in HIV-1-infected children has been proven to benefit the survival of these children[200-204]. Results from birth cohort studies of children infected vertically suggest that 70% to 80% of untreated children survive to only 5 years of age. Until 2010, the World Health Organization (WHO) recommended starting cART in all children less than 2 years of age, regardless of their CD4 T-cell count or clinical status[205]. However, as of June 2013, this recommendation has been extended to include all children less than 5 years old[206]. Demonstrating a relation between age at initiation of cART and clinical outcome is difficult because clinical disease progression is rare in children receiving cART. For this reason, virological and immunological outcomes are used as alternative endpoints. Given that normal CD4 cell counts in younger children are highly age-dependent, it is more appropriate to analyse time-dependent CD4 count trajectories whilst expressing CD4 counts as z-scores, in which counts are standardised in relation to age.

Here we report the demographics, clinical characteristics, and long-term virological and immunological response to treatment in the 512 HIV-1-infected children ever cared for in one of the paediatric and/or adult HIV-1 treatment centres in the Netherlands.

Population

Ever in care

In this chapter we define 'children' as those diagnosed with HIV-1 before the age of 18 years. The majority of children received care in a paediatric HIV-1 treatment centre. However, children who are diagnosed with HIV-1 at an older age, and who are predominantly infected with HIV-1 through sexual transmission, are often under clinical observation in an adult HIV-1 treatment centre *(Table 6.1)*. All HIV-1 infected patients diagnosed with HIV-1 before the age of 18 years under clinical observation in a paediatric HIV-1 treatment centre or in an adult HIV-1 treatment centre are included in the analyses.

Table 6.1: Demographics and characteristics of 512 HIV-1-infected children in care in the Netherlands.

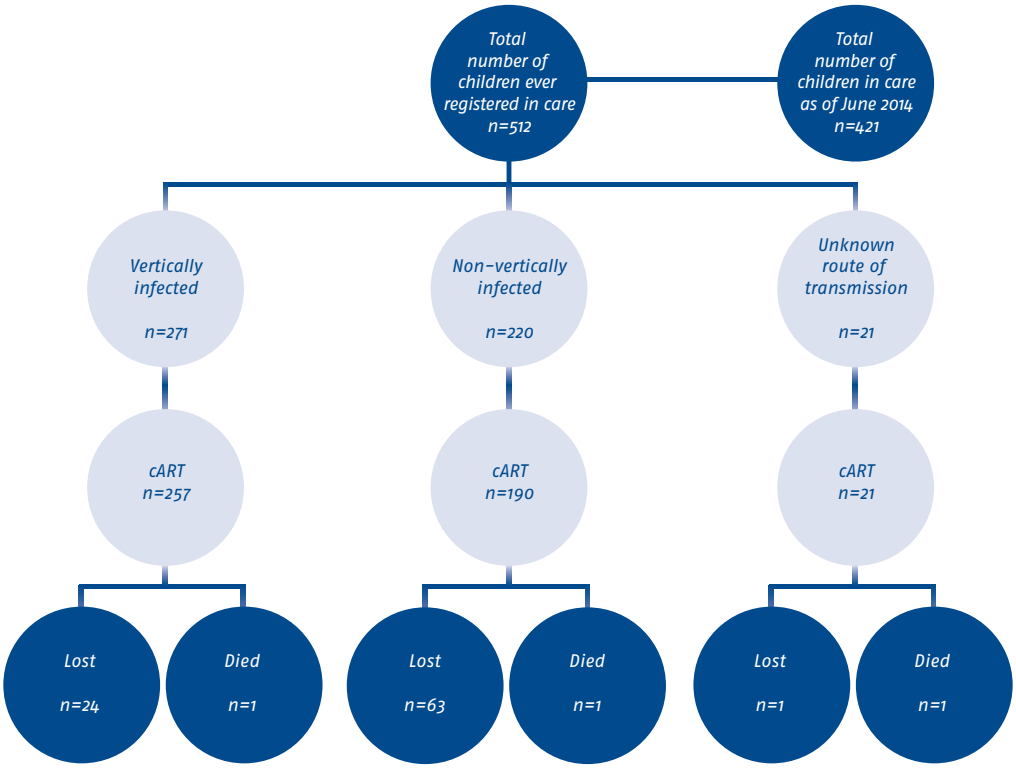
Characteristics	Vertically acquired HIV-1 infection n (%)	Non-vertically acquired HIV-1 infection n (%)	Route of transmission unknown n (%)
Total	271 (53)	220 (43)	21 (4)
HIV-1 treatment centre			
Child care	263 (97)	31 (14)	14 (67)
Adult care	8 (3)	189 (86)	7 (33)
Gender			
Male	135 (50)	90 (40)	14 (67)
Female	136 (50)	130 (58)	7 (33)
Country of origin child			
The Netherlands	106 (39)	57 (26)	2(10)
Sub-Saharan Africa	130 (48)	118 (55)	16 (76)
Other	35 (13)	45 (20)	3 (14)
Country of origin mother			
The Netherlands	21 (8)	5 (2)	2 (10)
Sub-Saharan Africa	166 (61)	35 (16)	8 (38)
Other/unknown	84 (31)	180 (82)	11 (52)
Age at HIV-1 diagnosis	2 (0.5-5)	17 (15-18)	11 (4-16)
CDC* event at HIV-1 diagnosis			
CDC-b	20 (8)	8 (4)	3 (14)
CDC-c	42 (16)	13 (6)	1 (5)
Current age in years	14 (8-19)	29 (25-32)	24 (18-28)
cART treated	257 (95)	190 (86)	21 (100)
Therapy-naive at cART initiation	218 (85)	149 (78)	21 (100)
CD4 at cART initiation	480 (222-1090)	280 (160-400)	343 (190-550)
VL (log cps/ml) at cART initiation	5.1 (4.5-5.8)	4.4 (3.7-5.1)	4.9 (4.8-5.4)
cART regimen			
NNRT+≥ 2 NRTIs	80 (31)	75 (40)	10 (48)
PI+≥ 2 NRTIs	172 (66)	102 (54)	8 (38)
NNRTI+PI+2NRTIs	4 (2)	11(6)	1 (5)
3 NRTIs	1 (0.5)	2 (1)	2 (10)

Data are number (%) of children or median (interquartile range)

***Legend:** *Categories as defined by the Centers for Disease Control and Prevention; cART=combination antiviral therapy; VL=viral load; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.*

As of June 2014, 512 HIV-1-infected children have been ever registered by SHM. Of those, 271 were vertically infected with HIV-1, and 220 were non-vertically infected *(Figure 6.1)*. For a small group of children, 21 in total, the route of HIV-1 transmission was unknown.

Figure 6.1: Overview of HIV-1 infected children registered by Stichting HIV Monitoring as of June 2014.



Legend: cART = combination antiretroviral therapy.

Vertically infected children

A total of 271 children were vertically infected with HIV-1. The median age at HIV-1 diagnosis for the children vertically infected was 2 years (Interquartile range [IQR] 0.5-5 years). Although 39% of the children were born in the Netherlands, only 3% of these children (9 out of 271) had parents who both originated from the Netherlands, whilst 78% (211 out of 271) had at least one parent who originated from Sub-Saharan Africa *(Table 6.1)*. Of the 271 vertically infected children, 97% received care in a paediatric HIV-1 treatment centre, and 257 of these 271 children had started cART.

Non-vertically infected children

Of the 512 HIV-1 infected children ever registered, 220 were non-vertically infected. The non-vertically infected children were far older at the time of HIV-1 diagnosis than the vertically infected children, with a median age at diagnosis of 17 years (IQR 15-18). The majority of the 220 non-vertically infected children received care in an adult HIV-1 treatment centre

(189/220, 86%). The main route of HIV-1-transmission was sexual contact. Of the non-vertically infected children, 133 out of 220 (60%) were infected through heterosexual contact, 30 (14%) were infected by homosexual contact and 41 (19%) by contaminated blood or blood product. The remaining 16 children were infected by injecting drug use or by accident through contaminated needles. Fifty-five percent of the non-vertically infected children were born in Sub-Saharan Africa. Of the 220 non-vertically infected children, 190 (86%) received cART *(Table 6.1)*.

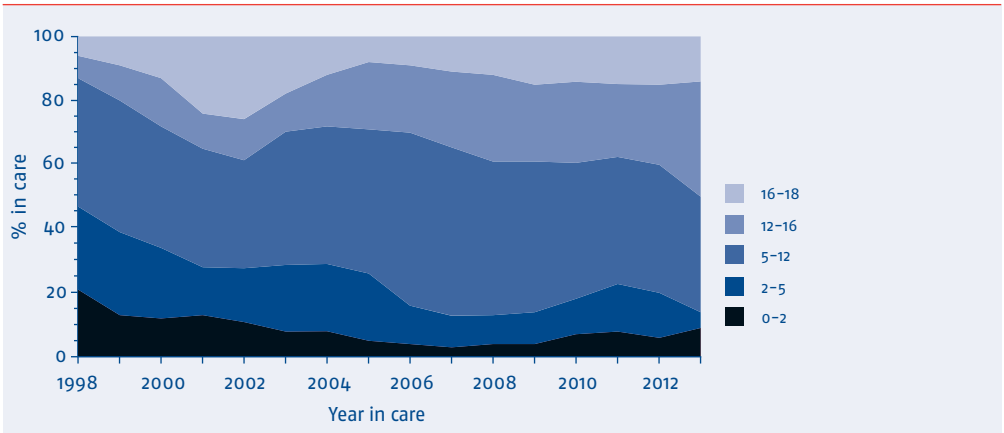
Unknown route of HV-1 transmission

For 21 of the 512 HIV-1-infected children, the route of transmission was unknown. Their median age at diagnosis was 11 years (IQR 4-16) years, and 14 of these children were in care at a paediatric HIV-1 treatment centre. All 21 children started cART *(Table 6.1)*.

Age distribution

The age distribution of the HIV-1-infected children ever in care over calendar time demonstrates a gradual increase in the proportion of children more than 12 years of age (*Figure 6.2)*.

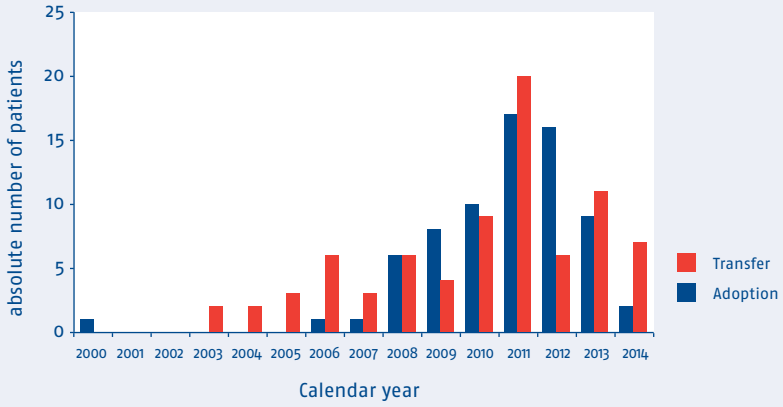
Figure 6.2: Time-dependent age distribution of HIV-1 infected children in care.



Adopted children

In total, 74 children in care for HIV-1 infection were adopted by Dutch parents. The majority of these children were born in Sub-Saharan Africa (88%) and diagnosed with HIV-1 before the age of 2.5 years (80%). The number of children adopted varied between 1 and 17 per calendar year *(Figure 6.3)*.

Figure 6.3: Number of HIV-1 infected children who entered paediatric care through adoption and HIV-infected children who transferred to adult care, by calendar year.



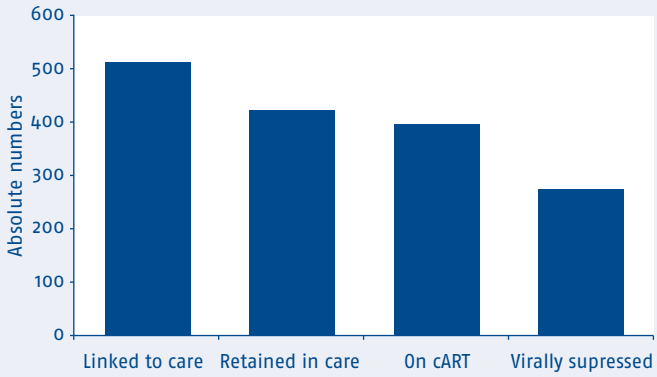
Children currently in clinical care

Of the 512 HIV-1-infected children ever registered by SHM, 421 (82%) are still under clinical observation (*Figure 6.1*). Of these 421 children, 246 (58%) were vertically infected, 156 (37%) non-vertically infected, and 19 had an unknown mode of transmission. Of the 91 children who were no longer in clinical care, 3 (3%) had died, and 88 (97%) were lost to care.

Cascade of care

On the basis of the total number of HIV-1-infected children ever registered by SHM, a 'cascade of care' was constructed. This is a way of depicting engagement in HIV-1 care across a few key indicators, the last one being the number of children with suppressed viral load (*Figure 6.4*). Of the 82% of children retained in care (421/512), 94% had started cART. Overall, 69% of those starting cART had a suppressed viral load.

Figure 6.4: Cascade of care of HIV-1 infected children registered by Stichting HIV Monitoring.

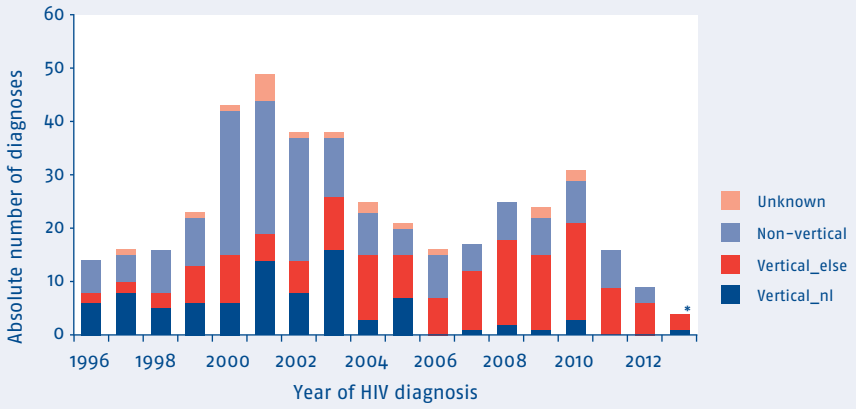


Legend: cART=combination antiretroviral therapy.

Registered HIV-1 diagnoses and vertical transmission of HIV-1 in the Netherlands

Figure 6.5 shows the number of newly registered HIV-1 diagnoses among children by year of diagnosis and according to mode of transmission. As can be seen from the figure, vertical transmission of HIV-1 in the Netherlands was relatively frequent prior to 2004 (16 cases in 2003), after which it markedly declined, with a single documented case of vertical transmission in the Netherlands in 2013. This newborn was diagnosed with HIV-1 infection at three months of age.

Figure 6.5: Number of registered HIV-1 diagnoses among children according to year of diagnosis, route of transmission, and region of origin.



**Delay in registration may explain the low numbers in 2013.*

This decline is most likely due to compulsory HIV-1 screening among pregnant women, which was introduced in 2004 [207,208]. Nine children born with HIV-1 in the Netherlands have been reported to SHM since the introduction of the screening. Two of these children were born in 2004 to women who became pregnant before January 1 2004. Five children were born to mothers who tested positive after giving birth; the mothers of three children tested negative during the screening and became infected during the pregnancy. One child was born to a mother who was known to be infected with HIV-1, but who was not receiving treatment during her pregnancy for an unknown reason. The remaining child was born to a mother without a known screening or known HIV-1 status during pregnancy.
Therefore, the majority of children with a newly registered diagnosis of HIV-1 infection through vertical transmission in recent years were infected outside the Netherlands, and the number fluctuates each year (e.g., 18 cases in 2010 and 5 cases in 2012).
The number of children who acquired HIV-1 infection by another mode of transmission ranged between 0 and 27 per calendar year.

Mortality

During follow-up, 3 out of 512 children (0.5%) died at less than 18 years of age. These were all boys born outside the Netherlands who died at the ages of 11, 12 and 17 years in 2009, 1998, and 2001, respectively. The boy who was 11 years old at time of death had been infected by blood or blood products and was diagnosed with HIV-1 when he was 10 years old. He never received cART and died of multi-organ failure 1.5 years after the diagnosis. The boy who was 12 years of age at time of death had been vertically infected with HIV-1 and diagnosed when he was 9 years old. He died 3 years after the diagnosis from an AIDS-related event, having been treated with cART for 14 months. The 17-year-old boy was diagnosed when he was 16, and his route of HIV-1 transmission was unknown. He died 10 months after HIV-1 diagnosis from toxoplasmosis, having been on cART for 2 months.

Treatment

In total, 468 of the 512 children started cART; 376 started with a cART regimen before 2010, 76 started between 2010 and 2013, and 16 started cART in 2013.
The majority of HIV-1-infected children ever registered in the Netherlands have received cART *(Table 6.1)*. Most children (55%) were treated with a first-line regimen including a protease inhibitor (PI) and 2 or more nucleoside reverse transcriptase inhibitors (NRTIs); 32% of the children received a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with 2 or more NRTIs. The median time on first-line regimens was 12 months (IQR 3-30). Not taking into account weight-related dose changes, 398 children (85%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART regimens included toxicity (14%), low drug plasma concentrations (13%), simplification (13%), and parental non-adherence (8%). Virological failure and poor patient adherence accounted for 6% and 3.5% of the reasons, respectively. Other reasons were decisions by parents and/or child, those on the basis of protocol, or unknown.

Median CD4 counts at time of cART initiation were higher in children who initiated cART from 2010 onwards compared to children who started before 2010 *(Table 6.2)*, reflecting the implementation of newer treatment guidelines.

Table 6.2: Median CD4 cell counts at treatment initiation stratified by calendar year and age categories according to World Health Organization (WHO) treatment guidelines for different calendar years.

cART initiation*	<2010	≥2010 and <2013	≥2013
0–1 year	1,155 (490–1,890)		
1–3 years	695 (310–1,520)		
3–5 years	630 (420–1,030)		
0–2 years		1,959 (1,567–2,220)	
2–5 years		810 (615–860)	
<5 years			–
≥5 years	268 (132–400)	340 (272–460)	510 (360–740)

**Median (IQR, interquartile range).*

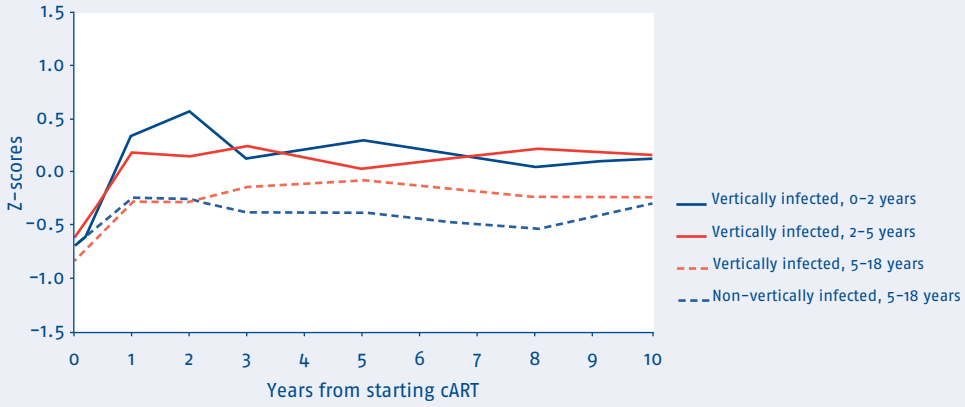
Immunological response

The clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[73]. To investigate long-term CD4 cell count changes, we stratified the children who were vertically infected according to their age at the time of cART initiation. These categories were as follows: (1) Vertically infected, 0-1 year; (2) Vertically infected, 2-5 years; and (3) Vertically infected, 5-18 years. The children who were non-vertically infected were classified as (4) non-vertically infected or unknown mode of HIV-1 transmission, 5-18 years[209]. The number of children with an unknown route of HIV-1 transmission is too small to include as a separate category in the analysis. These children had a same age distribution as those who were non-vertically infected. For these two reasons, the children with an unknown route of HIV-1 transmission were included in the category of non-vertically infected. *Web Table 6.2* shows the differences in CD4 counts between younger and older HIV-1-infected children.

CD4 z-scores, which represent the standard deviation from the reference values for HIV-1-negative children, were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into z-scores by subtracting the age-related reference value for the age at the time of the CD4 measurement[210] and dividing this by the age-related standard deviation. A z-score of zero represents the age-appropriate median. A CD4 z-score of minus 1 indicated that a child's CD4 cell count is 1 standard deviation below the age-specific median of the HIV-1-negative population.

The youngest children (less than two years of age at cART initiation) had the highest absolute CD4 cell counts at cART initiation, but the age-adjusted CD4 z-scores did not differ significantly between groups. In the first two years after cART initiation, CD4 z-scores increased significantly in all children *(Figure 6.6)*. This increase was lower in both vertically and non-vertically infected patients aged 5-18 years at cART initiation, compared to vertically infected children less than two years of age.

Figure 6.6: Changes in z-scores for CD4 T-cell counts among HIV-1 infected children stratified by age at initiation of combination antiretroviral therapy (cART).



Legend: cART=combination antiretroviral therapy.

Virological response to cART

At the time of cART initiation, children less than two years of age had significantly higher HIV-1 RNA levels compared to older children (*Table 6.1*). Virological response after the start of cART was analysed for the vertically and non-vertically infected children stratified by age at cART initiation (these are the same groups as those presented in the paragraph on immunological response to cART). Twelve months after starting cART, 82% of all children had a successful virological response. A successful virological response was defined as two consecutive HIV-1 RNA levels below 500 copies/ml, as the lower limit of detection of follow-up tests of HIV-1 viral load decreased from less than 1,000 copies/ml in 1996 to less than 40 copies/ml today, and a large number of tests have a lower detection limit of 500 copies/ml[211].

The poorest virological responses were observed among those less than two years of age (74% reached an undetectable HIV-1 RNA level 12 months after the start of cART) and those aged two to four years (80%). The best responses were among children aged five years or more who were either vertically infected (93%) or non-vertically infected (88%) (*Figure 6.7*). *Figure 6.8* shows the longitudinally modelled long-term virological response to cART over a period of 10 years. In all groups, HIV-1 RNA levels significantly decreased during the first six months on cART ($p<0.0001$), with a slower decrease among children aged zero to two years. However, two years after the start of cART, virological response to cART was no longer statistically significant, although median HIV-1 RNA levels were somewhat higher in non-vertically infected children aged 5 years or more.

Figure 6.7: Kaplan-Meier estimates of the percentages of HIV-1 infected children with initial suppression (<500 copies/ml) during the first year after starting combination antiretroviral therapy (cART), by age at cART initiation and HIV transmission mode.

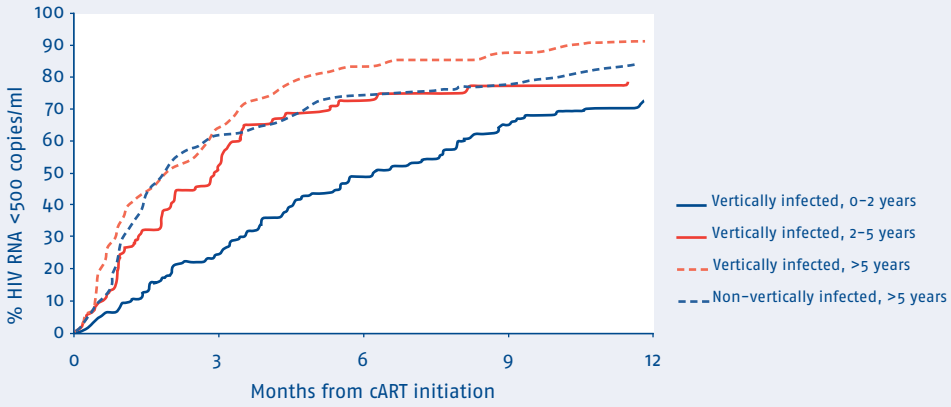
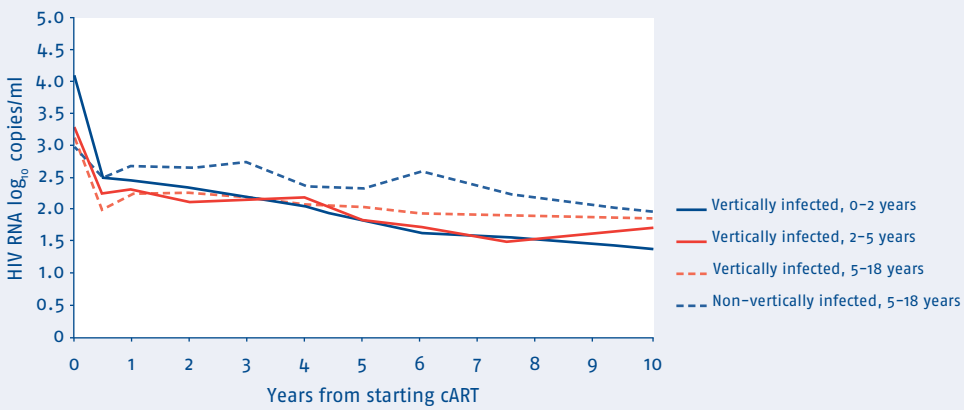


Figure 6.8: Changes in HIV RNA levels among HIV-1 infected children stratified by age at initiation of combination antiretroviral therapy (cART), virological responses were assessed in a random effects model; time is in years since start of cART.



Legend: *cART=combination antiretroviral therapy.*

Seventy-four of the 512 children were adopted by Dutch parents. Of these 74 adopted children, 72 received cART during follow-up in clinical care in the Netherlands, six of whom were treated with monotherapy or dual therapy before the start of a cART regimen. All 74 children are currently alive and in care. All children who started cART currently remain on treatment, and 64 (87%) had an undetectable viral load at the last known time point.

Transfer to adult care

As of June 2014, 79 children who started care in a paediatric HIV-1 treatment centre had transferred from paediatric care to adult care because they had reached the age of 18 years. The number of children who transferred to an adult centre varied from two children in 2003 to 20 in 2011 (*Figure 6.3*). The median age at transfer was 19 years (IQR 18-20). The median time in care after transfer was 2.3 years (IQR 0.3-4.1). Of the children who transferred to adult care, six were lost to follow-up, three moved abroad, and one objected to further data collection. The remaining 69 are currently alive and in care. Sixty-four (93%) of the 69 patients are currently on a cART regimen, 20 of whom (31%) had a detectable viral load at the last known time point; their current median CD4 count is 580 cells/mm^3 (IQR 390-770). Transferred children with a currently undetectable HIV-1 RNA level were likely to be living with a father and mother at the time of transferring to an adult centre (39% vs 27% of all children transferring to adult care).

Summary and conclusions

The majority of HIV-1-infected children ever in care in the Netherlands have received cART. During the first six months of treatment, a significant decline in HIV-1 RNA levels was seen in children of all ages. At cART initiation, vertically infected children aged less than two years had higher HIV-1 RNA levels than the other age groups. Although we observed a somewhat poorer initial virological response during the first year of treatment in these children, the long-term virological response was comparable to that in older children. The slower initial virological response that has previously been described by others[212] might be explained by difficulties in performing regular dosing adjustments in young children[213]. The protease inhibitors nelfinavir and (boosted) indinavir were used in the early years of cART[214] and have since been replaced by improved regimens, which include ritonavir-boosted lopinavir or efavirenz as the most frequently used NNRTI, in line with current guidelines[210, 211, 215, 216].

The younger children less than five years of age have significantly higher CD4 counts at cART initiation than the older children, which reflects the natural age-related difference in children's CD4 cell counts regardless of HIV-1 status. Age-adjusted CD4 z-scores at cART initiation did not differ between groups. CD4 z-scores significantly increased in the first 6 months after cART initiation in children of all age groups. However, after 3 to10 years of treatment, children who were less than two years of age when starting cART had higher CD4 z-scores than children who started cART when they were five years of age or more.

We observed low mortality rates in HIV-1-infected children in care in the Netherlands. A large proportion (15%) of the children have survived into adulthood and are now in care in

one of the adult HIV-1 treatment centres. The majority of these children are on cART, but the high rate of detectable HIV-1 viral load in these children is of concern. Children who currently have detectable viral loads were less likely to have been living with family before transferring to adult care, which may indicate barriers to successful transition to adult care. Currently, a study is being conducted within the paediatric HIV-1 treatment centres to gain more insight into the determinants of successful transfer to adult care.

The substantial decline in vertically HIV-1-infected infants born within the Netherlands from 2004 onwards can be explained by the successful introduction of an HIV-1 screening programme in the first trimester of pregnancy [207]. However, this measure cannot completely exclude mother-to-child transmission. Furthermore, screening for HIV-1 only during the first trimester does not completely rule out maternal infection, as incident primary HIV-1 infection may occur during the second or third trimester. In addition, if testing is performed shortly after primary infection of the mother, test results may still be negative. However, because the prevalence of HIV-1 infection among pregnant women in the Netherlands is between only 0.04 and 0.08% [208], a nationwide second screening during pregnancy is not likely to be cost-effective.

Recommendations

The provision of care for HIV-1-infected children living in the Netherlands has resulted in generally favourable outcomes and should be continued. A large proportion of the children have survived into adulthood and have transitioned to adult care. Although all are alive and most are receiving cART, it is striking that one-third of them currently have detectable HIV-1 viral loads. Improved insight into the determinants of successful transfer to adult care is needed and is currently the subject of ongoing research. HIV-1-infected children face lifelong treatment with cART. For these children, maintaining lifelong adherence to cART and achieving lifelong virological suppression will be particularly challenging.

7. Distinct populations: Pregnancies in HIV-1 infected women in the Netherlands

Colette Smit and Liesbeth van Leeuwen

Introduction

Transmission of HIV from an infected mother to her child is the most common route of transmission among children aged 0 to 15 years worldwide [2]. Mother-to-child transmission (MTCT) can take place *in utero*, during labour and delivery, and postnatally during breastfeeding. Without intervention, the risk of MTCT varies between 15% and 20% [217]. However, since the introduction of combination antiretroviral therapy (cART) in pregnant women, the risk of MTCT has been dramatically reduced to less than 1% [218,219].

Knowledge of a woman's HIV status during pregnancy is necessary for timely initiation of cART and, thus, to reduce the risk of MTCT. In January 2004, voluntary HIV antibody testing of pregnant women with the possibility of opting out was introduced in the Netherlands [220]. Since then, 281 women who were unaware of their HIV infection have been diagnosed during their pregnancy and reported to SHM. By June 2014, a total of 2,056 pregnancies in 1,249 women were registered among the total 4,897 HIV-infected women monitored by SHM. Overall, 55% of the pregnant women were diagnosed with HIV before the onset of pregnancy.

Demographics

Maternal characteristics

Characteristics of HIV-infected women with a registered pregnancy are presented in *Table 7.1*. Of the 1,249 women with a documented pregnancy, 1,040 (83%) were of non-Dutch origin and 209 women (17%) originated from the Netherlands. The majority of women of non-Dutch origin were born in Sub-Saharan Africa (n=709, 57%) or in the Caribbean/Latin American region (n=178, 14%). Women of Dutch origin were more often aware of their HIV infection before they became pregnant (72% versus 51% respectively, p<0.0001). Women of Dutch origin were significantly older at the time of their first registered pregnancy, with a median age of 31 years (Interquartile range [IQR] 27-35), compared with a median age of 29 years for non-Dutch women (IQR 25-33). Heterosexual contact was the most common route of HIV transmission in both groups of women (94%). However, women of Dutch origin were more likely to be infected with HIV by another route than women of non-Dutch origin (p<0.0001). Injecting drug use was reported as the route of transmission in 11 women of Dutch origin (5%); only one transmission occurred in 2010, all other transmissions occurred before 2001. Twenty-three mothers were documented as having died during follow-up, with a median time between the onset of pregnancy and death of 5.5 years (IQR 1.9-9.9).

Two mothers died within 1 month of parturition: the cause of death was unknown in one woman and acidosis and rhabdomyolysis in the second woman.
In total, 215 women were lost to follow up, and this was more common in women of non-Dutch origin (19%) than those of Dutch origin (7%).

Table 7.1: Characteristics of HIV-infected pregnant women registered and monitored by Stichting HIV Monitoring up to 1 June 2014.

	Total	Dutch	Non-Dutch
Maternal characteristics	**n (%)**	**n (%)**	**n (%)**
Total no. of women	1,249	209	1,040
HIV diagnosis before pregnancy (%)	683 (55)	152 (73)	531 (51)
Age at start of first pregnancy occurring in HIV infection (years*)	29 (25-34)	31 (27-35)	29 (25-33)
HIV transmission route			
Heterosexual (%)	1,175 (94)	184 (88)	991 (95)
Other (%)	74 (6)	25 (12)	49 (5)
Ever CDC-c** event	217 (17)	35 (17)	182 (18)
Deaths	23 (2)	6 (3)	17 (2)
Lost to follow-up	215 (17)	14 (7)	201 (19)
Total no. of pregnancies	2,056	342	1714
Maximum number of pregnancies after HIV diagnosis			
1	738 (59)	125 (60)	613 (59)
2	313 (25)	54 (26)	259 (25)
3	134 (11)	18 (9)	116 (11)
≥4	64 (5)	12 (6)	52 (5)
Mode of delivery			
Vaginal	895 (44)	178 (52)	717 (42)
Caesarean	579 (28)	71 (21)	508 (30)
Unknown	582 (28)	93 (27)	489 (29)
Pregnancy outcome			
Partus	1,524 (74)	256 (75)	1,268 (74)
Miscarriage	90 (4)	13 (4)	77 (4)
Abortion	233 (11)	37 (11)	196 (11)
Abortion, no additional data	187 (9)	35 (10)	152 (9)
Unknown	22 (1)	1 (0.3)	21 (1)

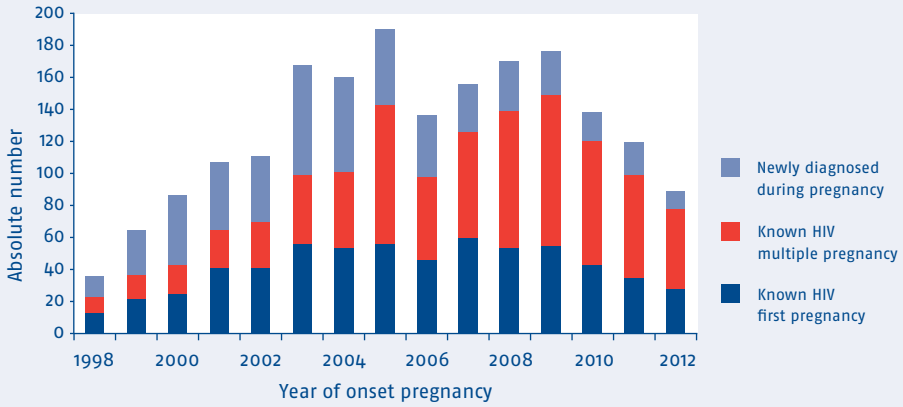
	Total	Dutch	Non-Dutch
Pregnancy duration			
≥37 weeks	1,219 (59)	212 (62)	1,007 (60)
32-37 weeks	183 (9)	26 (8)	157 (9)
<32 weeks	75 (4)	13 (4)	62 (4)
Missing	579 (28)	91 (27)	488 (29)
Birth weight (grams)*	3,080 (2,670-3,400)	3,165 (2,730-3,480)	3,070 (2,650-3,385)
Gender			
Boy	789 (51)	132 (51)	657 (52)
Girl	720 (47)	122 (48)	598 (47)
Unknown	15 (10)	2 (1)	13 (1)
Perinatal deaths	56 (4)	8 (3)	48 (4)
First CD4 cell counts (cells/µl) in first pregnancy*	400 (255-550)	520 (334-723)	380 (240-530)
Start combination antiretroviral therapy (cART)			
Before pregnancy	1,197 (58)	203 (59)	994 (58)
During pregnancy	735 (36)	108 (31)	627 (37)
No cART during pregnancy	124 (6)	31 (9)	93 (5)
HIV RNA plasma levels before delivery in first pregnancy			
HIV RNA available	1,124 (90)	194 (93)	932 (90)
Undetectable	793 (71)	57 (29)	274 (29)
Detectable	331 (29)	137 (71)	656 (70)
Unknown	125 (10)	15 (7)	108 (10)

**Median, Interquartile Range (IQR); **CDC-c=US Centers for Disease Control and Prevention, category C.*

Trends in number of pregnancies amongst HIV-infected women

The absolute annual number of pregnancies varied between 65 pregnancies in 1999 and 190 in 2005 (*Figure 7.1*), with a decrease from 2009 onwards. The number of women who were diagnosed with HIV during pregnancy increased from 13 in 1998 to 59 in 2004, when the national pregnancy screening was started, and varied between 11 and 47 from 2004 onwards. The majority of women were aware of their HIV infection at the time of their pregnancy. In 55% of the women, HIV was diagnosed before the onset of pregnancy. The number of subsequent pregnancies after HIV diagnosis increased from 10 in 1998 to 94 in 2009 (*Figure 7.1*).

Figure 7.1: Absolute number of pregnancies per year, stratified by known HIV infection at onset of pregnancy.



Pregnancy-related characteristics

Overall, 1,249 women accounted for 2,056 registered pregnancies. Fifty-nine percent of the women had one registered pregnancy, 25% had two registered pregnancies, and 16% of the women had three or more registered pregnancies (*Table 7.1*).

The 2,056 pregnancies gave rise to 1,524 (74%) newborns. Ninety pregnancies (4%) ended in miscarriage, and 233 (11%) in abortion, whilst 187 (9%) pregnancies were recorded as having been terminated, but could not be defined as either a miscarriage or abortion owing to a lack of information. The mode of delivery was unknown for the remaining 22 pregnancies. In total, 789 (52%) boys and 720 (47%) girls were born, and for 15 deliveries, the gender could not be documented. Fifty-eight percent of the newborns were delivered vaginally; 69% of the women of Dutch origin delivered vaginally compared to 56% of the women of non-Dutch origin ($p<0.0001$). A total of 579 newborns were delivered by Caesarean section. Elective Caesarean delivery is known to reduce the risk of MTCT if the maternal viral load is detectable, but such a delivery is less beneficial if viral load suppression is achieved following successful treatment with cART[221,222]. The proportion of elective Caesarean deliveries in first pregnancies decreased over time from 36% in 2000 to 16% in 2012 (*Figure 7.2*). In accordance with the decrease in elective Caesarean sections, the proportion of women with a viral load above 500 copies/ml at the time of delivery decreased over time (from 39% in 1998 to 13% in 2012, $p<0.0001$) (*Figure 7.3*). Although we observed a difference in the proportion of Caesarean deliveries between women of Dutch origin and those of non-Dutch origin, the proportion of women with a detectable HIV RNA load at the time of delivery did not differ significantly between these two groups (*Table 7.1*).

Figure 7.2: Absolute number of pregnancies per year, stratified by mode of delivery.

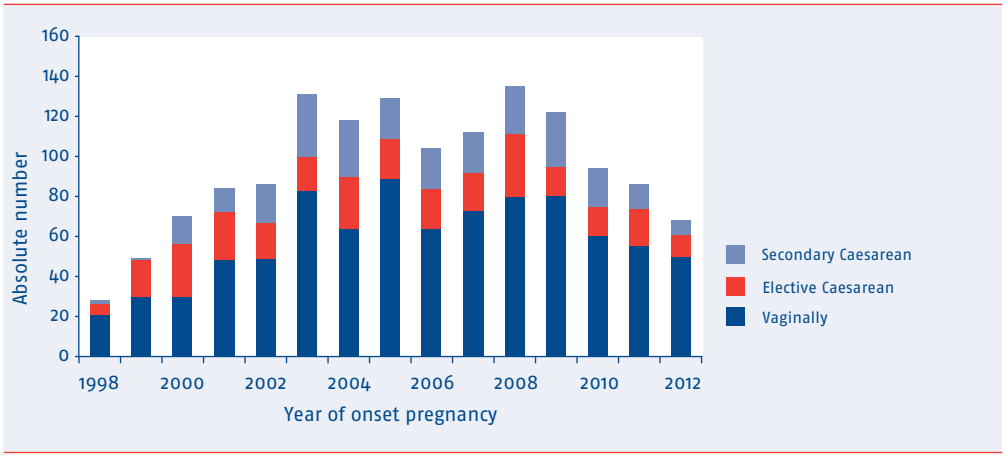
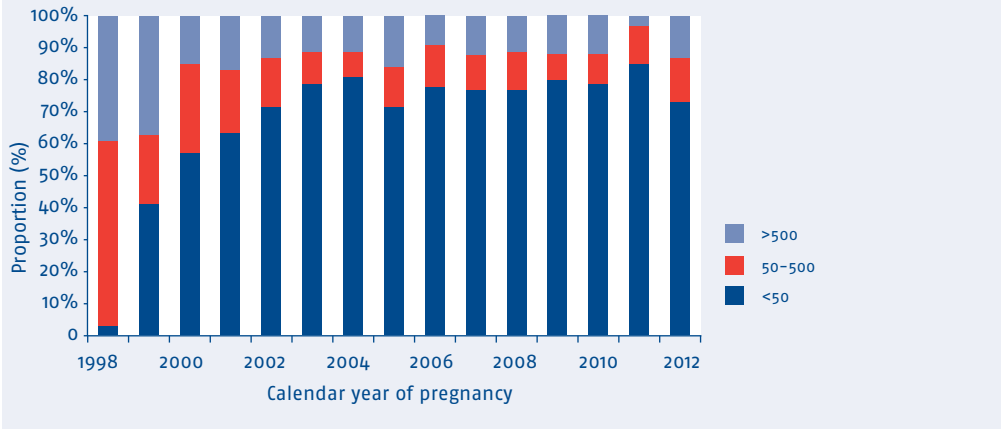


Figure 7.3: Distribution of women with HIV RNA level < 50 copies/ml, 50-500 copies/ml, and > 500 copies/ml at the time of delivery.



Overall, 80% of the pregnancies lasted at least 37 weeks. The median weight of newborns was 3,080 g (IQR 2,670-3,400). Among newborns with a known birth weight and duration of pregnancy, a total of 321 (17%) were preterm births. The proportion of premature births varied from 26% in 1999 to 21% in 2012. In 1999, 8% were early-premature births (pregnancy duration less than 32 weeks), whilst in 2012 this figure was 1.5%. Perinatal death occurred in 2.7% (n=56) of the births; 75% of these deaths occurred after a pregnancy duration of less than 32 weeks. No significant differences in pregnancy duration, birth

weight, and perinatal death were found between women of Dutch and non-Dutch origin. The earliest median CD4 count measured during pregnancy was significantly higher in women of Dutch origin ($p<0.0001$). This may be due to a higher proportion of these women having already been diagnosed and treated for HIV prior to the onset of pregnancy. This explanation is consistent with the median first CD4 count being significantly lower in women who were first diagnosed with HIV during pregnancy (320 cells/mm^3, IQR 200-520) than in women who became pregnant whilst already known to be HIV-infected (434 cells/mm^3, IQR 310-590, $p<0.0001$).
The majority of women used cART during their pregnancy; 58% started cART before the onset of the pregnancy, and 36% started whilst pregnant.

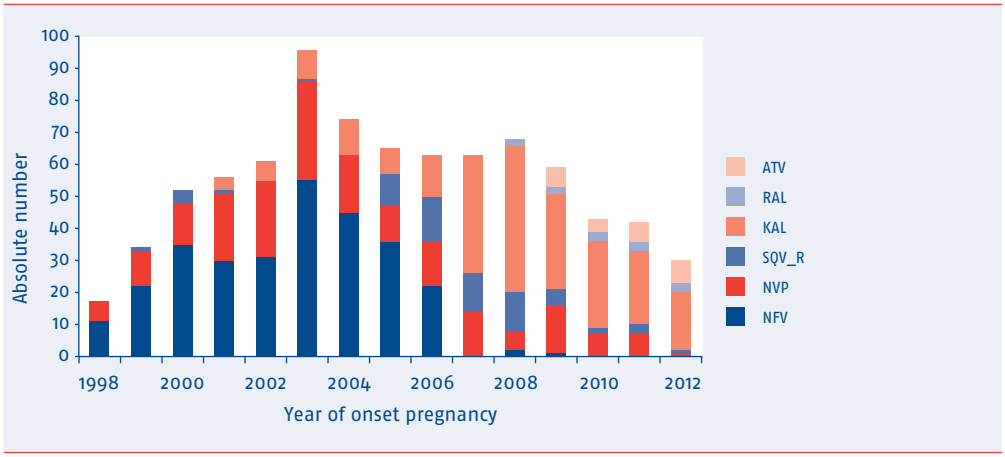
Mother-to-child transmission

Of the 1,524 children born from registered pregnancies from 1996 onwards, 9 newborns were vertically infected with HIV. The mothers of seven of these newborns did not receive cART during pregnancy, and five mothers were diagnosed with HIV during pregnancy. The reasons for not starting cART are unknown. One mother tested positive for HIV infection on the day of delivery, and one mother tested positive the day after delivery. Two mothers of vertically-infected newborns started cART during pregnancy. One mother had a detectable HIV RNA level during delivery, and the newborn was delivered spontaneously. The other woman had an undetectable HIV RNA load (<50 copies/ml) at time of delivery and underwent a Caesarean section; her child was thought to have become infected with HIV *in utero*.

Response to cART in pregnant women

Between 1 January 1998 and 1 June 2014, cART was used in 1,933 pregnancies out of a total of 2,056 (94%); cART was initiated before the start of the pregnancy in 1,197 cases and during the pregnancy in 735 cases.
Figure 7.4 shows the most commonly used treatment regimens during the first registered pregnancy in women between 1998 and 2012. A nelfinavir-containing regimen was most commonly used between 1998 and 2006. Nevirapine was also often prescribed between 2001 and 2006. From 2007 onwards, a lopinavir/ritonavir-containing regimen became the most commonly used regimen among pregnant women at the time of delivery. From 2008 onward, raltegravir-containing and atazanavir-containing regimens were also prescribed for women during their pregnancy.

Figure 7.4: Most common combination antiretroviral therapy (cART) regimens during first pregnancy.

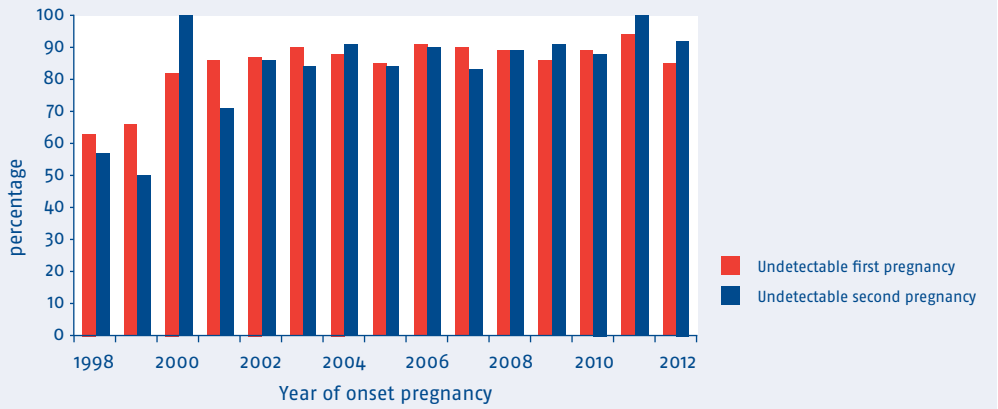


Legend: *ATV=atazanavir; RAL=raltegravir; KAL= kaletra; SQV-r= boosted saquinavir; NVP=nevirapine; NFV=nelfinavir.*

As expected, CD4 counts at treatment initiation were significantly lower in women who started cART before pregnancy compared to those who started during their pregnancy (p<0.0001), because a proportion of women were treated only to prevent MTCT rather than for their own health. Furthermore, median HIV RNA levels were significantly lower in women who started cART during their pregnancy compared to women who started before they became pregnant (p<0.0001). *(Table 7.2)*

Figure 7.3 shows the percentage of women over time with an undetectable load at time of delivery; HIV RNA levels were categorised as <50 copies/ml, 50-500 copies/ml, and >500 copies/ml. Overall, 73% of the women had an HIV RNA level <50 copies/ml at the time of delivery, and 14% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with HIV RNA <500 copies/ml at the time of delivery increased from 61% in 1998 to 87% in 2012. One newborn became vertically infected with HIV after being delivered with detectable maternal HIV RNA. *Figure 7.5* shows the differences in having an undetectable HIV RNA level at time of delivery in the first and second registered pregnancies. In more recent years, there has been a statistically non-significant trend towards women being more likely to have an HIV RNA level below 50 copies/ml at the time of delivery in a second pregnancy, compared to their first pregnancy.

Figure 7.5: Proportion of first and second deliveries with an undetectable load and preterm deliveries.

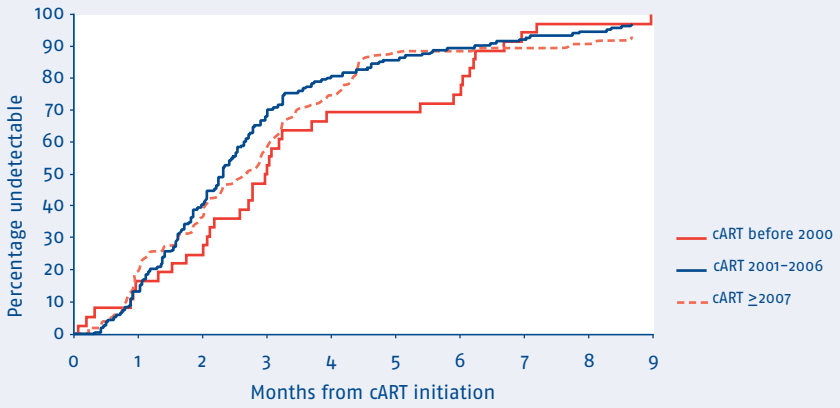


Time to initial virological success

Time from cART initiation to the first of two consecutive plasma HIV RNA concentrations of <50 copies/ml (or 500 copies/ml, depending on the detection limit of the HIV RNA assay used) in pregnant women who started cART during pregnancy was compared between women who started cART before the year 2000, from 2001 through to 2006, and from 2007 onwards.

By six months after the start of cART, 88% of the women had experienced a virological response (two consecutive HIV RNA levels <50 or 500 copies/ml). Although not statistically significant (p value log-rank test=0.35, *Figure 7.6)*, the most marked responses were observed in women who started cART during their pregnancy between 2001 and 2006 (90%, 95% confidence interval [CI] 85-94) and in women who started cART after 2007 (90%, 95% CI 83-95). Poorer response was seen in women who started cART during their pregnancy before 2000 (78%, 95% CI 64-90).

Figure 7.6: Time to initial viral suppression of HIV RNA to 50 (or 500) copies/ml after the start of combination antiretroviral therapy (cART) among pregnant women who started cART during their pregnancy. Women were divided by calendar year of cART initiation. The Kaplan-Meier method was used to estimate the time between the start of cART and virological suppression.



Legend: cART=combination antiretroviral therapy.

Virological failure after delivery

Among the 1,130 women who received cART either before the onset of the pregnancy or who started cART during their first registered pregnancy, 271 (24%) discontinued treatment within one year of delivery. The proportion of women who discontinued cART in the first year after delivery was significantly higher among women who started cART during their pregnancy compared to women who were already using cART before becoming pregnant (32% versus 12%, p<0.0001). Of note, a considerable number of women discontinued cART after pregnancy at relatively high CD4 counts, as they received cART only to prevent MTCT *(Table 7.2)*.

Table 7.2: Characteristics of 1,130 HIV-infected pregnant women who initiated combination antiretroviral therapy (cART) between 1 January 1998 and 1 June 2014.

		cART initiation
	Before pregnancy	During pregnancy
Total women (n=1,127)	453 (40)	677 (60)
Age at start cART*	29 (25-32)	28 (24-32)
Region of origin		
Netherlands	87 (20)	97 (14)
Other	366 (81)	577 (86)
Calendar year of cART initiation		
<2000	123 (27)	52 (7)
2001-2006	232 (51)	407 (60)
≥2007	98 (22)	215 (32)
At start of cART		
CD4-cell counts (cells/mm^3)*	210 (110-310)	340 (210-505)
HIV RNA levels (log_{10} copies/ml)*	4.7 (4.0-5.3)	4.0 (3.3-4.5)
At parturition		
CD4-cell counts (cells/mm^3)*	430 (310-590)	450 (290-620)
HIV RNA levels (log_{10} copies/ml)*	1.7 (1.6-1.7)	1.7 (1.7-2.0)
Detectable HIV RNA levels	45 (10)	75 (11)

**Median, Interquartile Range (IQR)*

***Legend:** cART=combination antiretroviral therapy.*

The remaining 859 of 1,130 pregnant women continued cART following delivery. Of these women, 158 (18%) with known prior HIV RNA suppression experienced virological failure (HIV RNA level >500 copies/ml) in the first year following delivery. The rate of virological failure was markedly different between the women already receiving cART at the time they became pregnant and those first starting treatment during pregnancy (5% vs. 30%, p<0.0001). The proportion of virological failure in the women who remained on cART after delivery is comparable to that in non-pregnant women who had been using cART for at least 24 weeks (*Chapter 3, Figure 3.2c*).

Summary and conclusions

The absolute number of pregnancies in HIV-infected women in the Netherlands has declined over time. This is probably the result of women in follow-up having become increasingly older, but it may also reflect the general decline in the number of newborns in the Netherlands during the recent economic crisis (www.cbs.nl). Viral load, the most important factor in preventing MTCT, was generally low near the time of delivery in women treated with cART. However, approximately 10% of the cART-treated women had a detectable HIV RNA level at the time of delivery, resulting in at least one vertical transmission of HIV. The proportion of women with non-suppressed HIV RNA levels at the time of delivery in our

population was lower than in other reports[223]. In our population, time to virological suppression improved over calendar time. From 2000 onwards, time between the start of cART and viral suppression has become shorter. Factors associated with a detectable load at delivery are lower CD4 counts and higher HIV RNA levels at the start of pregnancy[224,225]. Improvement in virological response may also be a result of more effective and safer cART regimens that have become available over time. A higher proportion of women had an undetectable HIV RNA level at the time of delivery in their second pregnancy than in their first pregnancy. It has been shown that women who were treated with short-course protease-inhibitor-based cART during their first pregnancy were not at increased risk of detectable HIV RNA levels at time of delivery in a subsequent pregnancy[226]. The percentage of women who delivered by Caesarean section was comparable to the national rate of Caesarean sections, suggesting that the main reason for this type of delivery was not HIV, but rather obstetric indications. In a large European cohort of HIV-infected pregnant women, the percentage of Caesarean deliveries was higher than that seen among the Dutch population of HIV-infected women[227]. This may be because, unlike in other European countries, vaginal delivery has become widely accepted in HIV-infected women in the Netherlands[227].

A substantial number of women discontinued cART after pregnancy, possibly because CD4 counts in women initiating cART during pregnancy were above the recommended CD4 cut-off values of the time for initiating treatment for the mother's own health. However, a recent study among women diagnosed with HIV showed that a large proportion of women not on cART at the beginning of their second pregnancy had an indication for immunological treatment[228]. With the new guidelines recommending cART initiation regardless of CD4 count[9], it is expected that women with high CD4 cell counts will continue cART after delivery. In women who continued to use cART during the first year after giving birth, we observed a marked difference in virological failure between those who started cART prior to pregnancy (5%) and those who started cART during pregnancy (30%). Several studies have demonstrated that adherence to cART may deteriorate in the postpartum period[229-233]. A possible explanation for this phenomenon is that women may be more motivated during pregnancy to take medication to prevent vertical transmission than for their own health. Clinicians caring for postpartum women who are receiving cART should specifically address adherence, including an evaluation of specific facilitators and barriers to adherence.

Recommendations

Although the proportion of HIV-infected pregnant women with appropriately suppressed viraemia at the time of delivery has markedly increased over time, there remains room for improvement. As a result of changes in recent guidelines on HIV and pregnancy, cART will be given earlier in pregnancy. This may lead to a greater level of viral suppression at the time of delivery. Robust evidence is lacking to support the idea that starting cART at 12 weeks leads to a greater proportion of women with suppressed viraemia at time of delivery than starting cART at 20 weeks of pregnancy. Exposure to cART in the first trimester is associated with more prematurity, and it is unknown whether longer exposure to cART is

harmful to the foetus. Clinical trials and monitoring of pregnant women using cART during the first trimester of their pregnancy is needed to gain more insight into the impact of cART exposure on the foetus. Furthermore, women may suffer from severe nausea, particularly during the first 12 weeks of pregnancy, which may lead to less adherence and treatment failure. These factors must be considered when cART is initiated. Finally, women infected with HIV who become pregnant require a high level of clinical support not only during pregnancy but also after delivery. Continued monitoring of HIV-infected women after pregnancy, is necessary to prevent decreased motivation to adhere to cART and for early detection of virological failure.

Special reports

8. Mathematical modelling and molecular genetic epidemiology

Ard van Sighem, Daniela Bezemer, Christophe Fraser, Rob van den Hengel, Mirjam Kretzschmar, Oliver Ratmann and Mikaela Smit

Introduction

Mathematical modelling is a powerful tool to gain more insight into the HIV epidemic and its underlying dynamics. It also yields information on quantities that cannot be observed directly and allows the investigation of hypothetical or future scenarios. Additional understanding of how HIV is spreading may be gained by studying transmission networks with information on HIV genotypic sequences. This special report describes a selection of ongoing projects that employ mathematical modelling, molecular epidemiology, or both, and that are carried out by Stichting HIV Monitoring (SHM) in collaboration with national and international partners.

Size and characteristics of the undiagnosed HIV population

Ard van Sighem

Undiagnosed HIV infections

A large proportion of HIV-infected individuals in the Netherlands are not aware of their infection because they have either never or not recently been tested for HIV. Accurate estimates of the number of people living with HIV, including those not yet diagnosed, are of paramount importance for understanding the burden of HIV and for projecting the need for combination antiretroviral treatment (cART). In 2010, the European Centre for Disease Prevention and Control (ECDC) commissioned a multi-year collaborative project to improve the tools used to estimate HIV incidence and prevalence, thus providing more accurate estimates of the number of undiagnosed HIV infections in Europe. SHM has a leading role in this project and collaborates with other international partners, including the Department of Infectious Disease Epidemiology at Imperial College in London, University College London, the Medical Research Council Biostatistics Unit in Cambridge, and the Institute of Social and Preventive Medicine at the University of Bern.

Back-calculation

One of the methods explored in the project is an extended back-calculation method[234,235]. Using data on newly diagnosed HIV infections, this method is able to back-calculate the annual number of HIV infections in previous years. This method uses CD4 counts at the time of HIV diagnosis, which give information on the approximate duration between

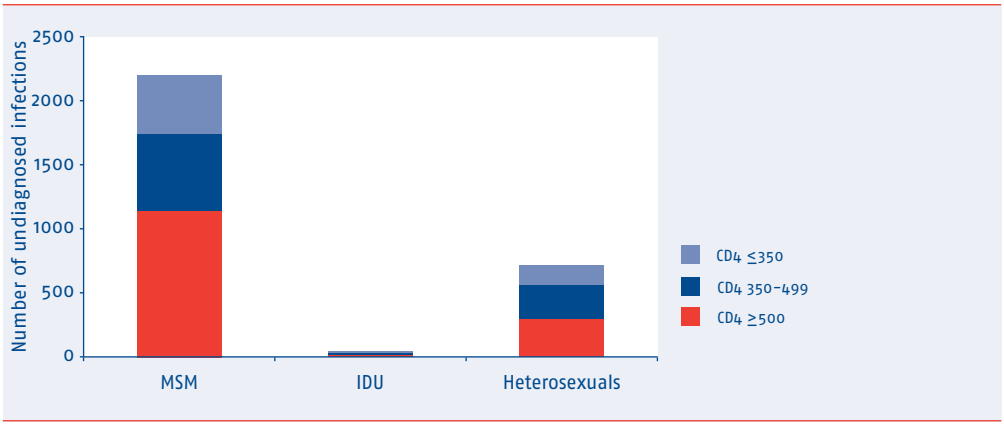
infection and diagnosis[8]. At the same time, the method estimates the probability of an individual being diagnosed with HIV, depending on CD4 count and calendar time. Once the number of HIV infections and the probabilities of diagnosis are known, it is relatively straightforward to determine the number of undiagnosed infections.

Undiagnosed HIV by CD4 count category

We used this back-calculation method to estimate the number of undiagnosed infections in the Netherlands among men who have sex with men (MSM), injecting drug users (IDU), and heterosexual men and women originating from the Netherlands[236]. By the end of 2011, approximately 2,938 of the total 19,750 infections estimated to have occurred since the start of the HIV epidemic were still undiagnosed, including 2,207 in MSM, 16 in drug users, and 715 in heterosexual men and women.

Among the undiagnosed individuals, 1,142 (52%) MSM, 4 (28%) IDU, and 293 (41%) heterosexual men and women were estimated to have a CD4 cell count ≥500 cells/mm^3 (*Figure 8.1*). Although MSM represented the largest group of HIV-infected individuals unaware of their infection, the estimated CD4 distribution suggested that approximately half of them were in an early stage of infection having been infected only recently. The number of undiagnosed individuals with CD4 counts less than 350 cells/mm^3 and, thus, in immediate need of treatment was 600 (27%) for MSM, 8 (51%) for IDU, 268 (37%) for heterosexual men and women.

Figure 8.1: *Total estimated number of HIV infections that were still undiagnosed by the end of 2011 stratified by CD4 count (cells/mm^3) for men who have sex with men (MSM), injecting drug users (IDU), and heterosexual men and women of Dutch origin.*



Legend: *MSM=men who have sex with men; IDU=injecting drug users.*

Molecular genetic epidemiology based on partial HIV *pol* sequences

Daniela Bezemer, Oliver Ratmann

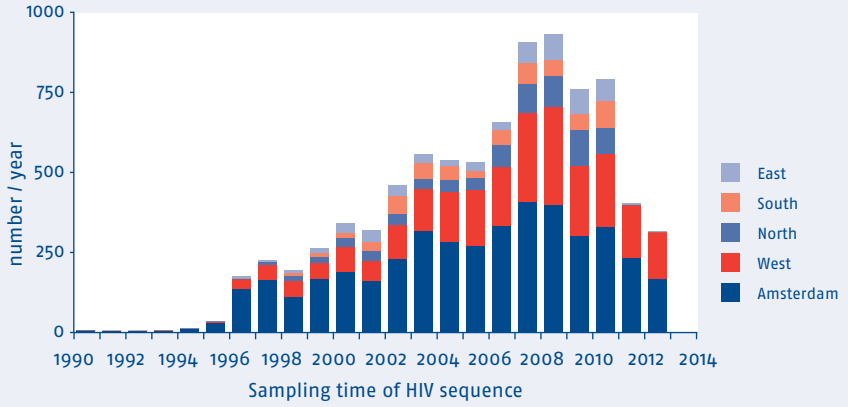
HIV transmission among MSM

The HIV-1 epidemic among MSM remains disproportionately severe, despite increasing frequency of HIV testing and increasing coverage with antiretroviral therapy[15]. To gain further insights into onward HIV transmission among MSM, we used partial HIV *pol* sequences that were collected from a subset of patients from samples obtained either before treatment initiation or after treatment initiation for drug resistance testing[16]. These viral sequences are usually highly divergent because of the high nucleotide mutation rate of the virus. Thus, similar viral sequences may provide clues about HIV transmission networks in the Netherlands, the presence of core networks, and demographic or clinical variables associated with onward transmission. Two related studies are currently underway to characterise HIV onward transmission among MSM on the basis of sequence data. Results are regularly presented at specialist and major international conferences, with plans for future publications, and they continue to inform and influence changes in national HIV prevention policies.

Partial HIV pol sequences data

As of March 2013, 8,377 subtype B sequences with a known sampling date were available from 6,260 patients; 4,749 (76.6%) of these patients were MSM. The majority of sequences were obtained from HIV treatment centres in Amsterdam and the western region of the Netherlands (*Figure 8.2*). Although viral sequences are generally not sampled for every patient and data entry is incomplete after January 2011, the sampling fraction is very high in an international context and allows for detailed phylogenetic analyses. A large fraction of sequences is obtained for the purpose of drug resistance testing after antiretroviral therapy (ART) initiation (3734/8377=44.6%), so that particular patient groups are potentially biased in the sequence data set.

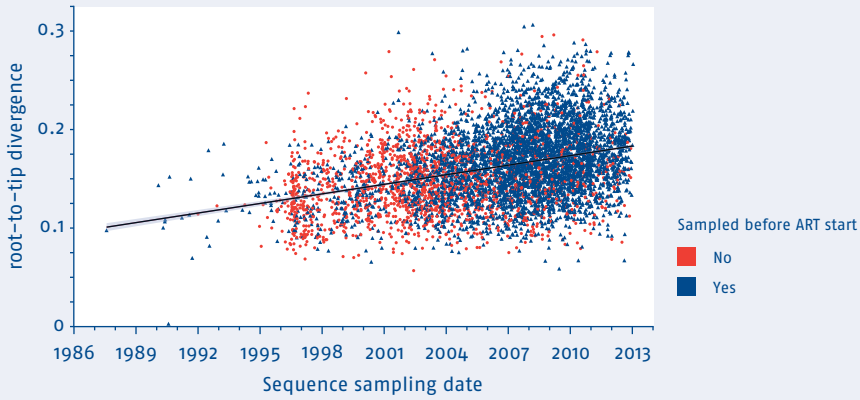
Figure 8.2: Number of partial HIV-1 B pol sequences as of March 2013 by sampling date and region of care of the HIV treatment centre providing the sample.



HIV molecular epidemiology

Sophisticated molecular genetic tools were used to reconstruct a phylogenetic tree of all available subtype B sequences. This tree forms the backbone of all further analyses, because it estimates the evolutionary distance between viral sequences, and, by extension, between patients whose sequences were sampled. Large-scale computing resources at the Imperial College High Performance Computing service were used to generate and analyse this tree, totalling more than 1.8 years in computation time on a single desktop computer. Overall, results show that the evolution of the subtype B virus during the HIV epidemic in the Netherlands has been remarkably complex. The evolutionary distance from the root sequence to the Dutch subtype B sequences was calculated from the phylogenetic tree and is plotted in *Figure 8.3* against the sequence sampling date. Calendar time explains only 10.6% of the variation in the estimated evolutionary root-to-tip divergence. This highlights the high diversity in viral evolution during the HIV epidemic in the Netherlands.

Figure 8.3: Variation in HIV-1B evolution during the HIV epidemic in the Netherlands. The evolutionary distance from the root to each observed partial HIV-1 pol sequence, the root-to-tip divergence, was calculated from the reconstructed phylogenetic tree of all subtype B sequences, and is plotted against sequence sampling time. In a linear regression (black line), calendar time explains R^2=10.6% of the variation in root-to-tip divergence, reflecting the complex evolution of the HIV virus. Grey and red dots indicate patients who were sampled before or after the start of antiretroviral therapy, respectively.



HIV transmission networks

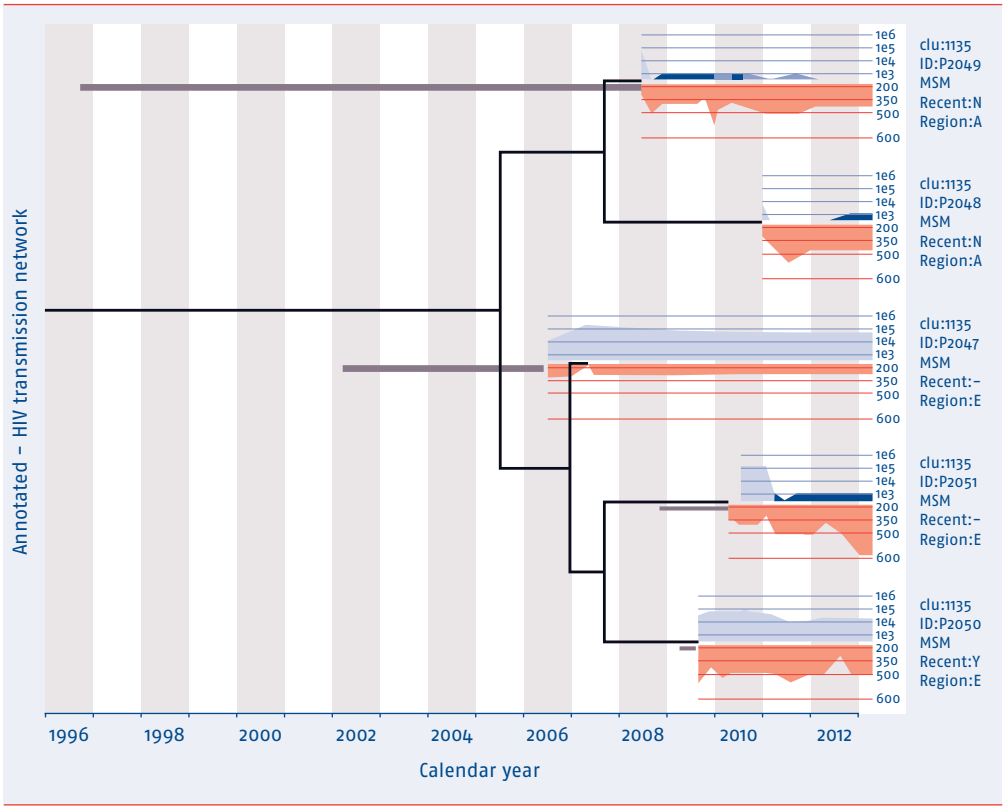
The aim of the first ongoing study, led by Daniela Bezemer (SHM), is to identify transmission networks of patients who were infected with a similar virus through consecutive infections[237]. The study is based on data as of November 2011 and has not been updated to the most recent data set due to the considerable time involved in curating the data and generating phylogenetic trees. As of November 2011, the database contained subtype B sequences from 5,852 patients. Besides MSM, most drug users were also infected with a subtype B virus, and although most heterosexuals were infected with other subtypes, a considerable number were also involved in the subtype B epidemic. We identified 106 subtype B transmission networks, including 3,061 (52%) sequences. Half of the HIV cases among MSM registered in the Netherlands (2,128 of 4,288) were included in 91 MSM-majority networks. Strikingly, at least 54 (59%) of these 91 MSM transmission networks were already circulating before 1996, when cART was introduced, and have persisted to the present day. Of the total 3,460 diagnoses among MSM after 1996, 1,226 (35%) were found in these 54 long-standing networks. When stratified by network, the mean age of MSM at diagnosis increased by 0.45 years/year, and most networks included MSM from younger generations (i.e., born after 1970).

Only 15 of the 106 networks were not dominated by MSM. Six of these 15 networks were dominated by sequences from patients living or born in the former Dutch Antilles, whilst one was a mixed Latin Caribbean network. Four networks included 69 heterosexuals (and 6 MSM) originating from Surinam. The largest identified network included 66% of the 207 injecting drug users in our study. Another small cluster included sequences of injecting drug users of Central European origin. The other two networks were mixed MSM-heterosexual networks. More detailed information will be presented in a research paper (under submission at time of writing).

HIV transmission risk groups

The aim of the second ongoing study is to estimate the proportion of transmissions originating from transmitters in particular demographic and clinical risk groups. The study is led by Oliver Ratmann (Imperial College London) and uses data as of March 2013. Phylogenetic transmission networks identify individuals infected with a similar virus but do not provide information on the direction of HIV transmission. In total, 715 MSM in HIV transmission networks were diagnosed with recent HIV infection and were considered as recipient MSM. We identified individuals within the same transmission network who may have directly transmitted the virus to each recipient MSM. As partial HIV *pol* sequences are relatively short, these assignments are inherently unreliable and cannot be used to identify with certainty who infected whom. Nonetheless, across all identified recipient MSM, some groups of potential transmitters are more likely to transmit HIV than others. To define transmission risk groups, we annotated HIV transmission networks with demographic and clinical variables as shown in *Figure 8.4*. These combined epidemiological and phylogenetic data are used to estimate the proportion of transmissions that originate from transmitters in particular demographic and clinical risk groups.

Figure 8.4: Annotated HIV transmission network #1135. The viral phylogeny (black) identifies five patients with a similar virus. This transmission network was annotated with the seroconversion interval (dark grey) if the last negative serological HIV test was known, CD4 progression (red) after first CD4 measurement, viral load progression (red) after first viral load measurement, and treatment episodes (viral load, dark or light blue). MSM P2050 was diagnosed with recent HIV in the eastern Netherlands. According to the seroconversion interval, infection occurred in early to mid-2009. Patient P2051 is most closely related to P2050, but the time of the most recent common ancestor of the viruses from P2050 and P2051 predates the time of infection of P2051. It is unlikely that the viral lineage leading to P2050 evolved in P2051, and, therefore, unlikely that P2051 infected P2050. P2047 may have transmitted to P2050, as the time of the most recent common ancestor of the two corresponding lineages is consistent with transmission from P2047 to P2050. At the time of infection, P2050 was diagnosed with CD4 count less than 350 cells/mm³ and had not started therapy. This potential transmitter, therefore, contributes to the risk group of diagnosed potential transmitters before the start of antiretroviral therapy. If P2049 was infected four years before diagnosis, he would also be a potential transmitter to P2047. In addition, the actual transmitter may be unobserved because sequences are not available for all infected individuals. Therefore, the identification of particular potential transmitters is unreliable, but across many recipient MSM, particular groups of potential transmitters may be more likely to transmit than others.



Legend: *MSM=men who have sex with men; N=no; Y=yes; A=Amsterdam; E=Eastern Netherlands.*

Comprehensive monitoring of the diagnosed HIV-infected individuals and routine sequencing of patients are vital for molecular epidemiological studies and, in particular, for the analysis of recent changes in HIV transmission dynamics.

The BEEHIVE Study

Christophe Fraser

This is a brief summary of the BEEHIVE project. The project, entitled 'Bridging the Evolution and Epidemiology of HIV in Europe' (BEEHIVE), is funded by a European Research Council Advanced Grant. It started on 1 April 2014 and is scheduled to last five years.

To provide new insights into the HIV epidemic in Europe, the BEEHIVE project brings some of Europe's best-characterised cohorts of HIV seroconverters (individuals whose date of infection is known to within one year) together with a leading team of virologists, clinicians, analysts, and mathematical modellers. The first step in the project will be the generation of full genomes of the virus that will be sampled from early and untreated infection in at least 3,000 seroconverters with clinical follow-up of good quality. The genomes will be generated with next-generation sequencing, so that the whole genome of the virus is obtained and the diversity of the viral quasi-species within each sample is also characterised.

The scientific aims of the project are: 1) to determine the viral genetic determinants of disease severity in untreated infection; 2) to shed new light on the pan-European epidemiology of HIV-1, currently resurgent in high-risk MSM populations; and 3) to determine the clinical relevance of quasi-species aspects in treated individuals.

The core investigating teams for the BEEHIVE project are based at Imperial College London (led by Christophe Fraser and Frank de Wolf – analysis and overall project leadership), Stichting HIV Monitoring (SHM) (led by Peter Reiss – analysis and data management), the Academic Medical Center of the University of Amsterdam (led by Marion Cornelissen and Ben Berkhout – virology and analysis), and the Wellcome Trust Sanger Institute (led by Paul Kellam – sequencing and analysis). Key collaborations are currently underway with the following patient cohorts: the ATHENA/SHM cohort (also using samples collected in the Amsterdam Cohort Studies), Seroconverter Cohort, UK Register of Seroconverters, the ANRS Primo-Co cohort, the Swiss HIV Cohort Study, and the Swedish InfCare Cohort. The team is also creating a new retrospective seroconverter cohort in the Netherlands based on SHM's prior work. To set up this cohort, approximately 1,500 seroconverters registered with SHM are currently being invited to participate in the BEEHIVE study, thus forming this new retrospective seroconverter cohort. Collaboration with several other cohorts is under discussion.

The team has completed a large range of pilot studies and expects to generate at least 500 full genomes by the end of 2014. These data will be discussed and analysed at a two-day BEEHIVE kick-off workshop in October 2014, where the team, key collaborators, and other stakeholders will attend, present, and discuss ideas and preliminary results.

An ageing HIV population: the future challenge to clinical care of the HIV epidemic

Mikaela Smit

More than 30 years after HIV started spreading and almost 20 years after combination antiretroviral therapy (cART) became available, the profile of the HIV epidemic in Europe is changing, characterised by an ageing HIV-infected population suffering increasingly from age-related non-communicable diseases (NCDs)[238,239]. More NCDs have been shown to develop in HIV-infected individuals than in the age-matched uninfected population, and development of NCDs may occur at an earlier age in HIV-infected individuals[124,240,241]. Treatment of NCDs can cause problems, including increased pill burden and drug-interactions with HIV medication. Thus, in view of this ageing HIV-infected population, which could potentially reverse the improvements achieved in HIV care to date[55], it is important to quantify the scale of the problem facing HIV care in Netherlands in the future.

Mathematical models provide a powerful tool to carry out projections of the HIV epidemic. Such models make use of valuable datasets, such as SHM data. By analysis of various trends in clinical variables over time and their incorporation into a mathematical model, these trends can be projected into the future. The projections can provide an insight into the future of HIV clinical care, including the future age structure of the HIV-infected population, an estimate of the number of people who will suffer from NCDs, and the potential complications they will consequently experience.

Earlier this year, a clinical care model of the Dutch HIV-population was constructed with SHM data. This is an individual-based model that follows all patients on HIV treatment in the Netherlands until 2030 as they age, have a number of NCDs that include cardiovascular disease, diabetes, chronic kidney diseases, osteoporosis, and non-AIDS malignancies, and start co-medication for these NCDs.

Using this model, we can estimate the future age structure of HIV-infected patients in the Netherlands, as well as the future burden of NCDs. The model allows investigation of the potential complications that HIV-infected patients will experience in terms of drug interactions. We expect to publish these projections soon. The next step will be to use the model to explore the potential impact of different types of interventions aimed at preventing the rising burden of NCDs amongst HIV patients. Classical interventions, such as the introduction of a smoking cessation programme and increasing physical activity, can be tested with this model, as well as interventions specifically tailored to HIV-infected populations, for example, extensive

monitoring and treatment of cardiovascular disease within HIV care and the impact of modifications to HIV treatment guidelines (i.e., earlier treatment and optimal HIV treatment to reduce risk factors for HIV-related NCDs). By working with health economists and policy makers, this work will be able to guide future HIV guidelines to ensure continued high-quality care.

Consequences of increased testing and earlier start of therapy on the HIV epidemic among MSM in the Netherlands

Rob van den Hengel

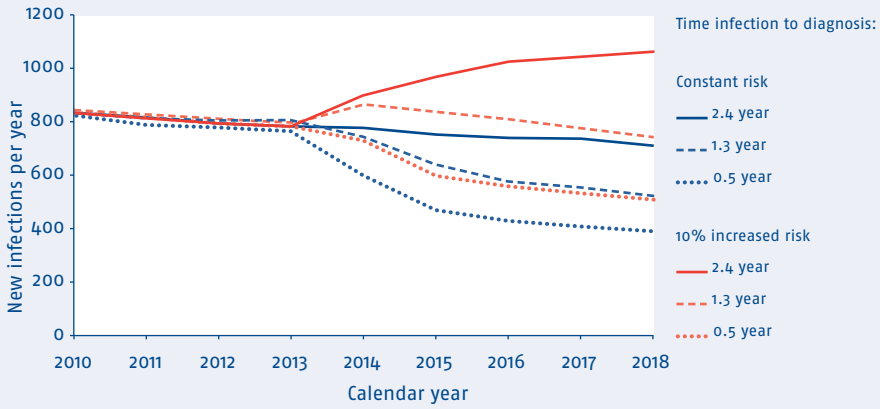
As part of a project funded by Aids Fonds, we have developed an individual-based model to simulate the spread of HIV among MSM in the Netherlands. This model can be used to quantify the impact of different control strategies on the HIV epidemic among MSM in the near future. In the model, we focussed on two interventions (namely, more testing and earlier start of combination antiretroviral therapy [cART]) that reduce the average time between infection and viral suppression. Currently, the estimated average time between infection and diagnosis is 2.4 years, and the average time between diagnosis and viral suppression is 1.4 years. For both interventions, we performed a range of simulations in which the average times between infection and diagnosis and between diagnosis and viral suppression varied between 0.5 and 2.4 years and between 0.5 and 1.4 years, respectively.

For each scenario, the main outcome of interest is the annual number of new infections over a period of five years. The model outcomes are very sensitive to changes in sexual risk behaviour[15,16]. Therefore, we also considered scenarios in which risk behaviour would increase by up to 10%. This 10% increase is realistic because results from the Amsterdam Cohort Studies have shown that changes of this magnitude in the proportion of MSM who have unprotected anal intercourse can occur within a few years[242,243].

The model was fitted to data available at SHM. We estimated that 780 new HIV infections among MSM occurred in 2013. If nothing were to change over the next five years, we estimated that the number of new infections would decrease to 710 in 2018. If, on the other hand, risk behaviour were to increase by 10% over the next five years, the number of new infections was expected to increase to 1,060 in 2018.

Reducing the average time between infection and diagnosis to 0.5 years, while keeping risk behaviour the same, would reduce the estimated annual number of new infections to 390 by 2018 (*Figure 8.5*). On the other hand, when the average time between diagnosis and viral suppression decreased to 0.5 years, the simulations showed no significant change in the estimated annual number of new infections by 2018. A possible explanation as to why an earlier start of therapy alone is not enough to reduce the annual number of new infections is that, according to the model, only 10% of the new infections are caused by MSM who have been diagnosed with HIV, while the majority are caused by men who are as yet unaware of being infected.

Figure 8.5: Estimated number of new infections per year among men who have sex with men for scenarios in which risk behaviour remains constant (blue) or increases by 10% (red). Dotted lines depict scenarios with a different average time between infection and diagnosis.



In conclusion, these preliminary results show that an earlier start of therapy in isolation does not seem to have a major influence on the HIV epidemic among MSM in the Netherlands, even though timely start of treatment greatly benefits individual patients. Reducing the average time between infection and diagnosis has a marked impact, but this strongly depends on the development of risk behaviour in the population. It is, therefore, important to focus preventive efforts not only on earlier treatment, but also on earlier diagnosis.

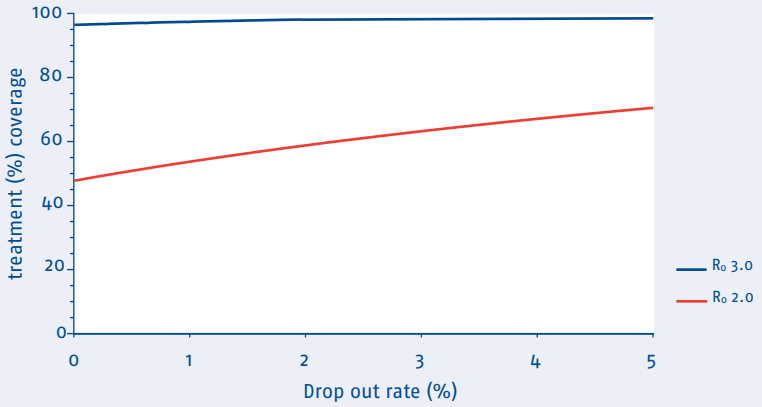
Prospects of eliminating HIV among MSM in the Netherlands

Mirjam Kretzschmar

Following insights into the possible impact of HIV treatment on its incidence and the prospects of eliminating HIV through scaling-up treatment in high prevalence populations, SHM is participating in another project funded by Aids Fonds. This project is led by Mirjam Kretzschmar, the Julius Center for Health Sciences and Primary Care at the University Medical Center Utrecht, and the National Institute of Public Health and the Environment and analyses the impact of treatment on future HIV incidence in MSM. The aim of this project that has recently started is to use mathematical models in combination with a variety of data sources to study the feasibility of HIV elimination, the key factors on which elimination depends, and the possible risks of transmission of resistant strains. The project will draw on information from the early spread of HIV in the MSM population in the Netherlands to estimate key epidemiological quantities, such as the basic reproduction number R_0. Furthermore, behavioural data collected in the Amsterdam Cohort Studies will

be used to estimate the influence of behaviour changes on transmission potential and effective reproduction number. Even if elimination turns out to be an overly ambitious goal, the project will provide information on the intervention effort needed to achieve substantial reductions in HIV prevalence in MSM in the coming years (*Figure 8.6*).

***Figure 8.6:** Illustration of how the elimination threshold of HIV among men who have sex with men depends on annual treatment uptake and dropout rate for two values of the basis reproduction number R_0. For parameter combinations above the lines, elimination is possible; for combinations below the lines, elimination is not possible (Figure from[244]).*



***Legend:** R_0=basic reproduction number.*

9. The Amsterdam Cohort Studies on HIV infection: annual report 2013

Ineke Stolte and Maria Prins for the ACS

Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were started shortly after the first cases of AIDS were diagnosed in the Netherlands. Since October 1984, men who have sex with men (MSM) have been enrolled in a prospective cohort study. A second cohort involving drug users (DU) was initiated in 1985. In 2013, the cohorts reached 29 years of follow-up. The initial aim of the ACS was to investigate the prevalence and incidence of HIV-1 infection and AIDS and their risk factors, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 29 years, these aims have remained primarily the same, although the emphasis of the studies has changed. Early on, the primary focus was to elucidate the epidemiology of HIV-1 infection, whereas later more in-depth studies were performed to investigate the pathogenesis of HIV-1 infection. In recent years, the focus has shifted to also include the epidemiology and natural history of other blood-borne and sexually transmitted infections (STI) among the participants in the ACS.

From the beginning, research in the ACS has taken a multidisciplinary approach (epidemiology, social science, virology, immunology and clinical medicine). This unique collaboration has been very productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection. This expertise has contributed directly to advances in prevention, diagnosis, and management of HIV infection.

As of 31 December 2013, 2,553 MSM and 1,661 injecting and non-injecting drug users were included in the ACS. Every three to six months, participants complete a standardised questionnaire designed to obtain information regarding medical history, sexual and drug use behaviour, underlying psychosocial determinants, healthcare use, depression, psychological disorders, and demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, also HIV-negative drug users), and blood is collected for diagnostic tests and storage. The ACS has been conducted in accordance with the ethical principles set out in the declaration of Helsinki, and participation in the ACS is voluntary; written informed consent (the most recent version was approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the DU cohort) is obtained from each participant.

Of the 2,553 MSM, 604 were HIV-positive at entry into the study, and 240 seroconverted during follow-up. Of the 1,661 DU, 322 were HIV-positive at entry, and 99 seroconverted

during follow-up. By 31 December 2013, 354 MSM and 538 DU had died, and several other participants were asked to leave the study or left at their own request. In total, the Public Health Service of Amsterdam (PHSA) was visited 53,466 times by MSM and 27,409 times by DU.

Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together the data and biological sample collections and to conduct research. These include the PHSA (Infectious Diseases Cluster, Department of Research), the Academic Medical Center (AMC) of the University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, Internal Medicine, Division of Infectious Diseases; HIV treatment centre, Emma Kinderziekenhuis), University Medical Center Utrecht (UMCU, Department of Immunology), Stichting HIV Monitoring (SHM), the Jan van Goyen Medical Centre (Department of Internal Medicine) and the HIV Focus Centre (DC Klinieken) Amsterdam. From the start, Sanquin Blood Supply Foundation has been involved in the ACS and, until 2007, research in the ACS was conducted by the Department of Clinical Viro-Immunology at Sanquin Research. Sanquin financially supports the maintenance of the biobank of viable peripheral blood mononuclear cells at the Department of Experimental Immunology at the AMC. In addition, there are numerous collaborations between the ACS and other research groups both within and outside of the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control of the Netherlands National Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu,* RIVM).

The ACS in 2013

Scientific evaluation

An international Scientific Evaluation Committee (SEC), led by Chairman Prof. A. Hofman of Erasmus University Medical Center (Erasmus MC) in Rotterdam, visited Amsterdam on 23 January 2013 to review the ACS. This review was requested by the main funder of the Amsterdam Cohort Studies, the RIVM. Both the scientific achievements of the past five years and the scientific plans for the future were examined.

In February, the SEC sent its evaluation, which was a strong endorsement of the ACS. The major conclusions were: 1. The scientific output is both quantitatively and qualitatively high; 2. The ACS is a unique and internationally very important prospective cohort study, particularly because of its emphasis on HIV-negative participants and long-term follow-up; 3. The research issues of the ACS are well positioned to answer major questions and make important contributions. The SEC recommended the continued funding of the ACS. Following this positive evaluation, the RIVM decided to continue funding the ACS. Based on research plans and the state of the epidemic in the Netherlands, the ACS project leaders proposed that the group of HIV-negative MSM should be expanded during the next few years and that follow-up of the group of DU should be reduced. The SEC agreed to these suggestions, and implementation of these changes was initiated in January 2014.

The cohort of men having sex with men

In 2013, 664 MSM were in active follow-up within the ACS. Of the MSM in active follow-up by the end of 2013, 543 were HIV-negative, and 121 were HIV-positive. The median age of the MSM was 40.9 years (interquartile range (IQR) 35.7-46.2), 7.4% were non-Dutch, and 80.0% had attained a high level of education. The majority of the participants (85%) were residents of Amsterdam. Fifty-three participants were newly recruited, and two died in 2013.

Until 1995, men of all age groups were eligible to participate if they lived in or around Amsterdam and had had at least two male sexual partners in the previous six months. During the period 1995–2004, only men aged ≤30 years with at least one male sexual partner in the previous six months could enter the study. Since 2005, recruitment has been open to MSM of all ages with at least one sexual partner in the preceding six months.

In 1999, follow-up of HIV-positive participants was transferred from the PHSA to the Jan van Goyen Medical Centre in Amsterdam, and six-monthly behavioural follow-up ceased. However, since 2000, HIV-infected MSM in follow-up at the Jan van Goyen Medical Centre have again been asked to complete behavioural ACS questionnaires once a year.

In 2013, 176 of the HIV-positive MSM were in active follow-up at the Jan van Goyen Medical Centre or, as of October 2013, at the HIV Focus Centre. Of these 176 participants, 43 were HIV seroconverters, and 33 were defined as slow or non-progressors, or matched fast progressors in 1996, or had been HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/mm^3 after 10 years of HIV-positive follow-up without antiretroviral therapy. In total, 39 MSM in active follow-up at the Jan van Goyen Medical Centre completed the behavioural questionnaire.

Behavioural and clinical follow-up of individuals with a recent HIV infection at study entry at the PHSA and of HIV seroconverters during the period after 1999 was initiated in October 2003 in accordance with the 'HIV Onderzoek onder Positieven' (HOP) protocol (*HIV Research in Positive Individuals*). These participants return for follow-up at the PHSA or at an HIV treatment centre. All ACS behavioural data are collected on a six-monthly basis, and clinical data are provided by SHM. Of the 83 HIV-positive MSM in active follow-up in 2013 in accordance with the HOP protocol, 13 were newly included, and 55 were HIV seroconverters. A behavioural questionnaire was completed by 80 HIV-positive MSM as part of the HOP protocol.

In 2006, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants were also invited to participate in the ACS. Thirteen HIV discordant and 3 HIV-positive concordant couples were included in this partner study, of which 3 couples were still in active follow-up in 2013.

Since November 2008, all MSM followed at the PHSA have been routinely screened for STI.

The cohort of drug users

In 2013, 252 DU were followed at the PHSA. The median age of the DU was 51.7 years (IQR 44.9-56.5), 15.9% were non-Dutch, and 8.7% had attained a high level of education. Two hundred and thirty-eight (94.4%) were residents of Amsterdam. Of the 252 DU followed in 2013, 16 were HIV-positive at entry, 12 seroconverted for HIV during follow-up in the ACS.

Since July 2009, individuals between 18 and 30 years who regularly use hard drugs in Amsterdam and individuals older than 30 years who started injecting hard drugs in the preceding two years in Amsterdam have been eligible for inclusion in the ACS. No new participants were recruited in 2013, which might be because injecting drug use has become less common in Amsterdam.

The Drug Users Treatment for Chronic Hepatitis-C (Dutch-C) study was started in 2005 within the DU cohort to evaluate the possibility of HCV testing and treatment combined with methadone programmes. This project aimed to offer HCV screening and treatment to all DU participating in the ACS and to develop guidelines for HCV treatment of active DU outside a clinical setting. Drug users were offered HCV testing and, if chronically infected, medical and psychiatric screening and HCV treatment. Various specialists collaborated to provide optimal HCV care at the PHSA. The first active DU chronically infected with HCV genotype 1 started treatment with telaprevir combined with pegylated interferon and ribavirin at the PHSA in 2012. In collaboration with the AMC, treatment of HCV-infected DU at the PHSA continued in 2013.

Subgroup studies and affiliated studies

AGE$_h$iV Cohort Study

The AGE$_h$iV Cohort Study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health, and Amsterdam Institute of Global Health and Development, the PHSA, and SHM, was started in October 2010. The aim of the study is to assess the prevalence and incidence of a broad range of co-morbidities and known risk factors for these co-morbidities in HIV-infected patients aged ≥45 years and to determine the extent to which co-morbidities, their risk factors and their relation to quality of life differ between HIV-infected and uninfected groups. Participants undergo a comprehensive assessment for co-morbidities and fill in a questionnaire at intake and 2 years afterwards.
In total, 598 HIV-1-infected participants and 550 HIV-uninfected individuals completed a baseline visit between October 2010 and September 2012. HIV-1-infected participants were included through the AMC HIV outpatient clinic and HIV-uninfected participants from the same HIV exposure groups were included through the STI clinic of the PHSA (n=486) or the ACS (n=64). All participants were aged ≥45 years and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. By the end of 2013, the second data wave was still ongoing, and 402 HIV-1-infected participants and 319 HIV-uninfected individuals had returned for their second visit.

ACS biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies, have resulted in a large collection of stored samples.
The ACS biobank includes plasma and peripheral blood mononuclear cell samples collected within the context of the Primo-SHM study (a national randomised study on the effects of

early temporary antiviral therapy as compared to no therapy among patients who presented with primary HIV-1 infection at the AMC outpatient clinic and ACS seroconverters). These samples are stored at the AMC. At present, the biological samples are still being collected prospectively for Primo-SHM participants visiting the AMC clinic until one year after they have recommenced therapy.
The ACS biobank also includes plasma and peripheral mononuclear cell samples that were collected from both HIV-infected and HIV-exposed children at the Emma Kinderziekenhuis in the AMC until 2008. These are also stored at the AMC. Currently, no new samples are being collected within the ACS setting.
All stored samples are available for ACS research.

The HIV epidemic

HIV incidence

Two MSM and no DU participating in the ACS seroconverted for HIV in 2013. The observed HIV incidence among MSM declined to 0.39 per 100 person years in 2013.
The HIV incidence in drug users has been stable since 2008, with less than one case per 100 person years. *Figures 9.1* and *9.2* show the yearly observed HIV incidence rates for MSM and DU from the start of the ACS through 2013.

Figure 9.1: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2013.*

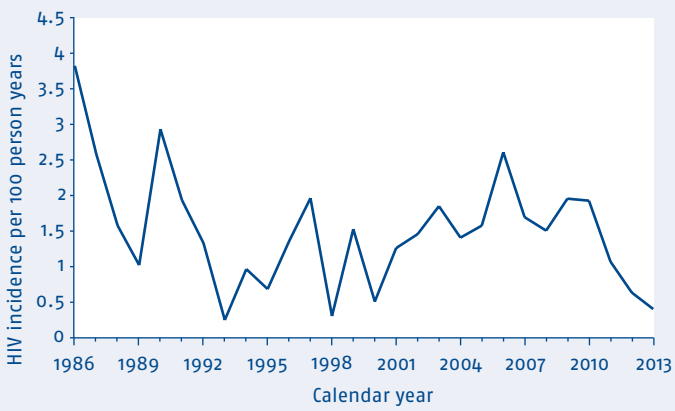
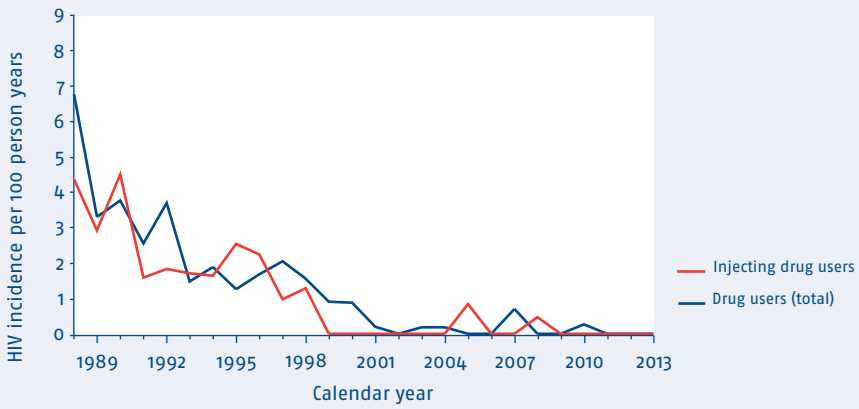


Figure 9.2: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among drug users, 1986–2013.



Transmission of therapy-resistant HIV strains

In 2013, surveillance of transmission of drug-resistant HIV-1 strains was performed for four MSM seroconverters who had their first visit after being found to be HIV-positive in 2013 (two of them had an estimated seroconversion moment in 2012) and for five MSM who were seropositive at study entry. One of these five MSM experienced an acute HIV-1 infection at study entry. One of the seroconverters was infected with a virus harbouring a so-called 215-revertant (215S) mutation in the reverse transcriptase gene. In all individuals, naturally occurring sequence variation was found in the protease gene. Phylogenetic analysis showed a variety of HIV-1 subtypes: six individuals harboured subtype B HIV-1 strains; one had subtype A1; one had subtype F1; and one had subtype G.
In the cohort of drug users, there were no seroconversions or seropositive entries.

Highly active antiretroviral therapy (HAART) uptake

Of all 210 HIV-positive MSM from the ACS visiting the Jan van Goyen Medical Centre or one of the other HIV treatment centres in the Netherlands in 2013 and for whom treatment data were available, 206 (98%) received some form of antiretroviral therapy. Of 206 MSM for whom viral load results were available in 2013, 194 (94%) had a viral load of <50 copies/ml (assays M2000rt). Of the 27 HIV-positive DU who visited the PHSA in 2013 and for whom treatment data were available, 26 (96%) received some combination of antiretroviral therapy. Of the 27 DU, 25 (93%) had an undetectable viral load (≤150 copies/ml [assay: M2000rt]) at their latest visit.

HPV in MSM

The H2M (HIV and HPV in MSM) study is a successful collaboration between the Centre for Infectious Disease Control (CIb), PHSA, the Jan van Goyen Medical Centre, VU University Medical Center (VUmc), and the AMC. The study aims to compare the prevalence, incidence, and clearance of high-risk (hr) human papillomavirus (HPV) infections between HIV-negative and HIV-infected MSM.

The participants were recruited from three sites: the ACS (n=520; mostly HIV-negative), the PHSA STI clinic (n=120; all HIV-infected), and the Jan van Goyen Medical Centre (n=160; all HIV-infected). Recruitment was carried out in 2010 and 2011, and participants were followed for 24 months. Participants provided self-collected swabs from the anus and penile shaft, as well as oral rinse-and-gargle specimens. These were tested for the presence of HPV DNA and, if positive, HPV types were determined. Serum was tested for L1 HPV antibodies.

The study found that hrHPV infections are more common in HIV-infected than in HIV-uninfected men. This was true for oral, penile, and anal infections. For example, HPV-16 was found in the anus of 22% of HIV-infected men and in 13% of HIV-uninfected men. HIV-infected men were also significantly more often seropositive for hrHPV types. In this cohort, anal infections were much more strongly associated with seropositivity than penile infections.

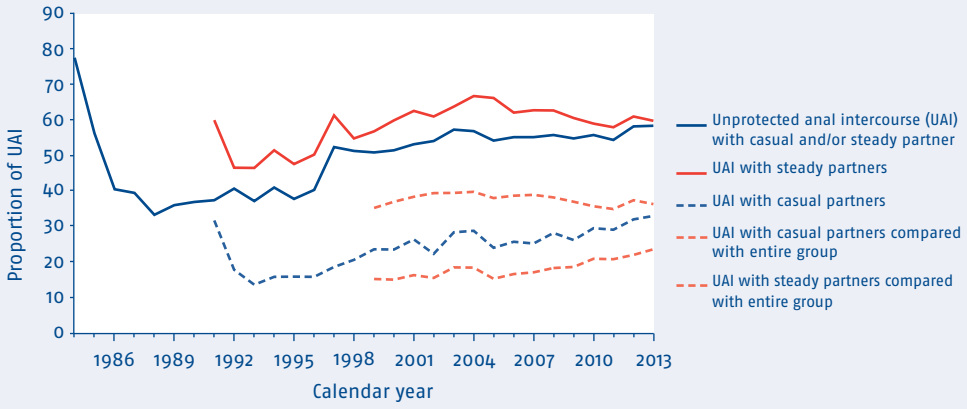
It is known that HPV vaccines induce high antibody concentrations and that vaccination prevents infection and re-infection (presumably through high antibody titres). The H2M study showed that concentrations observed after natural infection were much lower than those induced by vaccines. Importantly, in this cohort the presence of these natural antibodies was not protective against subsequent infections.

Analyses of the incidence of hrHPV infections over the two-year follow-up period are underway.

Risk behaviour of MSM

Information from the questionnaires completed by 545 HIV-negative MSM during cohort visits in 2013 resulted in 295 (54%) reports of unprotected anal intercourse (UAI) in the preceding six months. Higher proportions of UAI were reported for steady partners (60%) compared to casual partners (33%). Trends in UAI among HIV-negative MSM who are participants in the ACS, especially those with casual partners, continue to show a slow increase from 1996 onwards. (*Figure 9.3*).

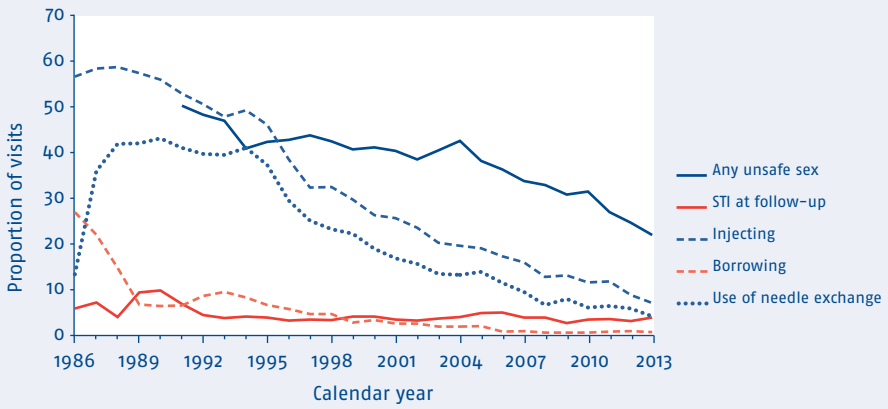
Figure 9.3: Trends shown by the Amsterdam Cohort Studies (ACS) in unprotected anal intercourse (UAI) in the past six months among HIV-negative men having sex with men (MSM) with a casual and/or steady partner, 1984-2013.



Risk behaviour of DU

In HIV-negative DU, reports of both injection and borrowing needles significantly declined over the period 1985-2013. Reports of high-risk sexual behaviour at follow-up visits decreased before 1996, then remained relatively stable until 2005, and further decreased to approximately 22% in 2013. Reports of STI have remained relatively stable at approximately 3% in recent years (see *Figure 9.4*).

Figure 9.4: Proportion of visits per calendar year at which injecting and high-risk sexual behaviour was reported amongst 1,339 drug users (DU) who were HIV-negative on entry to the Amsterdam Cohort Studies (ACS), 1986-2013.



Legend: STI = sexually-transmitted infection.

STI screening among MSM in ACS

Since October 2008, all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Cases of syphilis are detected by *Treponema pallidum* haemagglutination assay (TPHA). In 2013, a total of 604 MSM from the ACS were screened for STI. The overall prevalence of any STI was 5.9% (66/1,110).

ACS 2013 research highlights

The emergence of HIV variants (X4-HIV) that use chemokine receptor 4 (CXCR4) is associated with accelerated disease progression in the absence of antiretroviral therapy. However, the effect of X4-HIV variants on the treatment response remains unclear. In a recent study, we observed that patients harbouring X4-HIV variants prior to the start of treatment show a delay in time to viral suppression below the viral load detection limit. This delay in viral suppression was independently associated with high viral load and the presence of X4-HIV variants. Furthermore, absolute CD4+ T cell counts were significantly lower in patients harbouring X4-HIV variants at all time points during follow-up. However, no differences were observed in the increase in absolute CD4+ T-cell numbers after treatment initiation, indicating that the reconstitution of CD4+ T cells is independent of the presence of X4-HIV variants. The emergence of X4-HIV has been associated with an accelerated CD4+ T cell decline during the natural course of infection and, therefore, patients in whom X4-HIV variants develop may benefit from earlier treatment initiation to achieve faster reconstitution of the CD4+ T cell population to normal levels [245].

Current HIV-1 envelope glycoprotein (Env) vaccines are unable to induce cross-reactive neutralising antibodies. Such antibodies are elicited in 10% to 30% of HIV-1 infected individuals, but it is unknown why these antibodies are induced in some individuals and not in others. We hypothesised that the Envs of early HIV-1 variants in individuals who have cross-reactive neutralising activity (CrNA) might also have unique characteristics that support the induction of CrNA. We retrospectively generated and analysed Env sequences of early HIV-1 clonal variants from 31 individuals with diverse levels of CrNA two to four years after seroconversion. These sequences revealed a number of Env signatures that coincided with CrNA development, including a statistically shorter variable region 1 and a lower probability of glycosylation, as implied by a high ratio of NXS versus NXT glycosylation motifs. Furthermore, the lower probability of glycosylation at position 332, which is involved in the epitopes of many broadly reactive neutralising antibodies, was associated with the induction of CrNA. Finally, Sequence Harmony identified a number of amino acid changes associated with the development of CrNA. These residues mapped to various Env subdomains, but, in particular, to the first and fourth variable region as well as the underlying α2 helix of the third constant region. These findings imply that the development of CrNA might depend on specific characteristics of early Env. Env signatures that correlate with the induction of CrNA might be relevant for the design of effective HIV-1 vaccines [246].

The largest population of people at risk for HCV infection is injecting drug users (IDU). We hypothesise that recurrent exposure to HCV by continuing risk behaviour influences the development of an HCV-specific T-cell response. Therefore, we studied the association between repeated exposure to HCV and the height and focus of the HCV-specific T-cell response in HCV antibody-positive injecting DU (n=18) with ongoing risk behaviour ('high risk'), nine with and nine without detectable HCV RNA), and nine never-injecting DU ('low risk', HCV RNA+). Both total HCV-specific T-cell response and the T-cell response against HCV non-structural proteins were significantly higher in IDU compared to never-injecting DU. Interestingly, the high-risk HCV RNA-negative group had no measurable CD4(+) T-cell response to HCV Core protein, compared to detectable responses to Core in the HCV RNA+ group. Thus, both ongoing risk behaviour and presence of HCV RNA affect the HCV-specific T-cell response in both magnitude and specificity, which may have implications for vaccine development [247].

Individuals with HIV infection are frequently also infected with hepatitis C virus (HCV) (co-infection), but little is known about its effects on progression of HIV-associated disease. In this study we determined the effects of HCV co-infection on mortality not only from HIV and/or AIDS but also from hepatitis- or liver-related, natural, and non-natural mortality. Data were used from the CASCADE cohort, which is a database of patients with well-established dates of HIV infection from Europe, Australia, and Canada. The ACS contribute data from HIV seroconverters among MSM and DU. Of 9,164 individuals with HIV infection, 2,015 (22.0%) were also infected with HCV. Among individuals infected with only HIV or with co-infection, the mortality from HIV infection and/or AIDS-related causes and hepatitis or liver disease decreased significantly after 1997, when combination antiretroviral therapy

(cART) became widely available. However, after 1997, HIV and/or AIDS-related mortality was higher among co-infected individuals than those with only HIV infection. Compared to individuals infected with only HIV, co-infected individuals had a higher risk of death from hepatitis or liver disease. This underscores the importance of early diagnosis of HCV infection in HIV-infected individuals and the need for routine screening of HCV among high-risk groups. The authors conclude that it is necessary to evaluate the effects of HCV therapy on HIV progression[248].

Hepatitis B virus (HBV) is divided into eight definite (A-H) and two putative (I, J) genotypes that show a geographical distribution. HBV genotype G, however, is an aberrant genotype of unknown origin that demonstrates severe replication deficiencies and very little genetic variation. HBV-G infections are mainly noticeable after infection with a "helper" HBV strain, and especially during HIV-1 co-infection that decreases HBV immune control and increases HBV replication. There are indications that mixed HBV infections that include an HBV-G strain are associated with increased liver fibrosis, suggesting that patients infected with HBV-G should be monitored more closely. At the Academic Medical Center, the prevalence of HBV-G was determined in 96 HBV-infected patients with a newly developed real-time PCR assay that detects HBV-A and HBV-G. Ten HBV-G infections were detected exclusively in HIV-1 infected men as co-infection with HBV-A. These findings suggest a strong association of HBV-G in the Netherlands with the HIV-1 infected male risk group, as has been reported from other countries[249].

Steering committee: 'The politburo'

In 2013, the politburo met four times. Twenty proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: three from the AMC Experimental Immunology department, six from the AMC Medical Microbiology department, six from the UMCU, four from the PHSA, and one from the AMC internal medicine division. Seventeen requests were approved, some after revision, and three requests were denied. Three of the approved proposals were collaborations with groups abroad (outside the ACS).

Publications in 2013 that include ACS data

1. de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar ME. **Decline in incidence of HIV and Hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction?** *Addiction 2013 Jun;108(6):1070-81.*

2. Euler Z, van Gils MJ, Boeser-Nunnink BD, Schuitemaker H, van Manen D. **Genome-wide association study on the development of cross-reactive neutralizing antibodies in HIV-1 infected individuals.** *PLoS One 2013;8(1):e54684.*

3. Gijsbers EF, van Sighem A, Harskamp AM, Welkers MR, de Wolf F, Brinkman K, Prins JM, Schuitemaker H, van 't Wout AB, Kootstra NA. **The presence of CXCR4-using HIV-1 prior to start of antiretroviral therapy is an independent predictor of delayed viral suppression.** *PLoS One 2013 Oct 1;8(10):e76255.*

4. Gijsbers EF, Feenstra KA, van Nuenen AC, Navis M, Heringa J, Schuitemaker H, Kootstra NA. **HIV-1 replication fitness of HLA-B*57/58:01 CTL escape variants is restored by the accumulation of compensatory mutations in gag.** *PLoS One 2013 Dec 5;8(12):e81235.*

5. Grady BP, Schinkel J, Thomas XV, Dalgard O. **Hepatitis C virus reinfection following treatment among people who use drugs.** *CID 2013 Aug 15;57(suppl.2):S105-S110.*

6. Grebely J, Page K, Sacks-Davis R, Schim van der Loeff M, Rice TM, Bruneau J, Morris MD, Hajarizadeh B, Amin J, Cox AL, Kim AY, McGovern BH, Schinkel J, George J, Shoukry NH, Lauer GM, Maher L, Lloyd AR, Hellard M, Dore GJ, Prins M; the InC3 Study Group. **The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C Virus infection.** *Hepatology 2013 Aug 2 [Epub ahead of print].*

7. Grebely J, Morris MD, Rice TM, Bruneau J, Cox AL, Kim AY, McGovern BH, Shoukry NH, Lauer G, Maher L, Lloyd AR, Hellard M, Prins M, Dore GJ, Page K; InC Study Group. **Cohort Profile: The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC3) Study.** *Int J Epidemiol 2013 Dec;42(6):1649-59.*

8. Grijsen ML, Vrouenraets SM, Wit FW, Stolte IG, Prins M, Lips P, Reiss P, Prins JM. **Low Bone Mineral Density, Regardless of HIV Status, in Men Who Have Sex With Men.** *J Infect Dis 2013 Feb;207(3):386-91.*

9. Jazaeri Farsani SM, Jebbink MF, Deijs M, Canuti M, van Dort KA, Bakker M, Grady BP, Prins M, van Hemert FJ, Kootstra NA, van der Hoek L. **Identification of a new genotype of Torque Teno Mini virus.** *Virol J 2013 Oct 30;10:323.*

10. Lambers FAE, Prins M, Davidovich U, Stolte IG. **High awareness of hepatitis C virus (HCV) but limited knowledge of HCV complications among HIV-positive and HIV-negative men who have sex with men.** *AIDS Care 2014 Apr 26(4):416-24.*

11. Lodi S, del Amo J, d'Arminio Monforte A, Abgrall S, Sabin C, Morrison C, Furrer H, Muga R, Porter K, Girardi E; CASCADE collaboration in EuroCoord. **Risk of tuberculosis following HIV seroconversion in high-income countries.** *Thorax 2013 Mar;68(3):207-13.*

12. McLaren PJ, Coulonges C, Ripke S, van den Berg L, Buchbinder S, Carrington M, Cossarizza A, Dalmau J, Deeks SG, Delaneau O, De Luca A, Goedert JJ, Haas D, Herbeck JT, Kathiresan S, Kirk GD, Lambotte O, Luo M, Mallal S, van Manen D, Martinez-Picado J, Meyer L, Miro JM, Mullins JI, Obel N, O'Brien SJ, Pereyra F, Plummer FA, Poli G, Qi Y, Rucart P, Sandhu MS, Shea PR, Schuitemaker H, Theodorou I, Vannberg F, Veldink J, Walker BD, Weintrob A, Winkler CA, Wolinsky S, Telenti A, Goldstein DB, de Bakker PI, Zagury JF, Fellay J. **Association study of common genetic variants and HIV-1 acquisition in 6,300 infected cases and 7,200 controls.** *PLoS Pathog 2013;9(7) [Epub 2013 Jul 25].*

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Michel de Vries - January 29, 2013: **Virus discovery and human parechoviruses.** Supervisor: Prof. B. Berkhout; Co-supervisor: Dr. C.M. van der Hoek

Anouk Urbanus - March 21, 2013: **Hepatitis C virus infection; spread and impact in the Netherlands.** Supervisors: Prof. R.A. Coutinho and Prof. M. Prins.

Esther Gijsbers - July 4, 2013: **HIV-1 evolution and adaptation to the host during the course of infection.** Supervisor: Prof. H. Schuitemaker; co-supervisor: Dr. N.A. Kootstra

10. Curaçao

Ard van Sighem, Ashley Duits, Gonneke Hermanides

Introduction

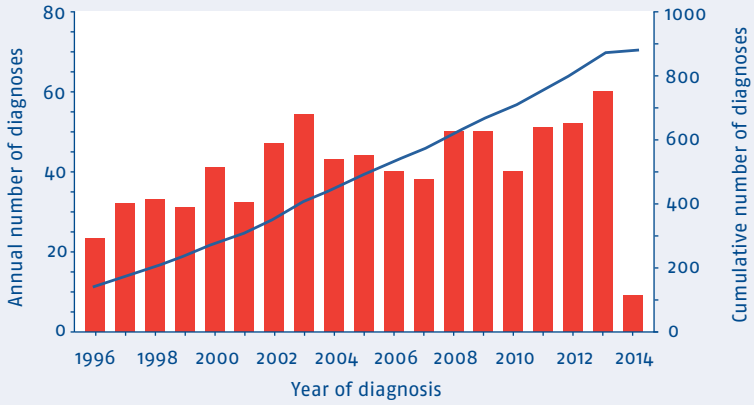
For almost a decade, Stichting HIV Monitoring (SHM) has assisted in collecting demographic and clinical data about HIV-infected individuals in clinical care at the St. Elisabeth Hospital in Willemstad in Curaçao. As a result of this registration and monitoring, an extensive database has been established, giving a clear picture of the HIV-infected population, the effectiveness of HIV care, and the challenges that are still present in this relatively small Caribbean setting. This special report endeavours to present a concise overview of the current state of HIV infection in Curaçao.

HIV-infected population

Of the total of 924 HIV-infected patients registered in Curaçao as of June 2014, 162 (18%) have died since the initial registration. The total follow-up for the entire group of 924 patients was 6,432 person years since HIV diagnosis. Of the 762 patients who were still alive as of June 2014, 526 (69%) were still in clinical care and had had at least one contact with the treating physician in Curaçao since January 2013.

In total, 271 (29%) of the registered patients were diagnosed with HIV in or before 2000; 83 (31%) of these patients died before June 2014 (*Figure 10.1; Web Appendix Table 10.1*).
Between 2001 and June 2014, 610 additional patients were diagnosed and entered care. For the remaining 43 patients, no information regarding the date of their first positive HIV test was available. Almost three-quarters of the registered population originated from the former Netherlands Antilles. The large majority of patients were infected with HIV-1, whilst two patients were infected with HIV-2, and 10 patients had antibodies against both HIV-1 and HIV-2. Two-thirds of the registered patients reported being infected via heterosexual contact (*Table 10.1*).

Figure 10.1: Annual and cumulative number of HIV diagnoses among 924 HIV-infected patients in Curaçao registered by Stichting HIV Monitoring as of June 2014. In total, 111 patients were diagnosed prior to 1996, whilst the year of diagnosis was unknown or not yet recorded for 43 patients.



Legend: bars=annual number of diagnoses; line=cumulative number of diagnoses since the start of the HIV epidemic.

Table 10.1: Characteristics of the HIV-infected population in Curaçao registered by Stichting HIV Monitoring as of June 2014.

	Alive, n=762		Deceased, n=162		Total, n=924	
	n / median	% / IQR	n / median	% / IQR	n / median	% / IQR
Sex						
Male	467	61	113	70	580	63
Female	295	39	49	30	344	37
Transmission						
MSM	157	21	17	10	174	19
Heterosexual	502	66	101	62	603	65
Other/unknown	103	14	44	27	147	16
Country of birth						
Antilles	535	70	144	89	679	73
Haiti	92	12	7	4	99	11
Dominican Republic	65	9	6	4	71	8
Other	70	9	5	3	75	8
Treated with cART						
No	127	17	57	35	184	20
Yes	635	83	105	65	740	80
Diagnosis						
CD4 (cells/mm^3)	349	162–495	99	41–352	330	104–476
RNA (log_{10} IU/ml)	4.4	3.9–5.0	4.9	3.9–5.4	4.5	3.9–5.0
Age (years)	38	30–47	41	32–56	39	30–48
AIDS	44	6	31	19	75	8
Time to cART	1.1	0.2–4.6	0.2	0.2–4.4	1.1	0.2–4.5
Follow-up (years)	6.1	2.2–11.8	2.7	0.3–7.2	5.5	1.7–10.9
Start of cART						
CD4 (cells/mm^3)	211	76–336	77	13–185	191	64–324
RNA (log_{10} IU/ml)	4.7	4.2–5.3	4.9	4.4–5.5	4.8	4.2–5.3
Age (years)	42	34–50	46	38–57	42	34–51
AIDS	82	11	52	32	134	15
Follow-up (years)	4.5	1.3–9.1	1.8	0.2–4.7	4.1	1.3–8.1
Present (June 2014)[a]						
CD4 (cells/mm^3)	508	327–708	-	-	508	327–708
RNA <80 IU/ml	365	73[b]	-	-	365	73[b]
RNA <40 IU/ml	341	69[b]			341	69[b]
Age (years)	49	39–55	-	-	49	39–55

Legend: IQR=interquartile range; MSM=men who have sex with men; cART=combination antiretroviral therapy [a]for 526 patients still in clinical care; [b]percentage of 497 patients with a viral load measurement.

Children and adolescents

Amongst HIV-infected patients ever registered in Curaçao, 15 patients were younger than 13 years of age ('children') at the time of diagnosis, and 17 were aged 13 to 18 years ('adolescents'). Most of the children, 12 in total, were infected by mother-to-child transmission. Adolescents were infected mainly via either heterosexual contact (n=12) or homosexual contact (n=4). In total, nine children and one adolescent have died. Ten adolescents, but none of the children, had a recorded contact with the treating HIV physician in 2013 or 2014.

The number of children in Curaçao infected *in utero*, during labour and delivery, or postnatally during breastfeeding via mother-to-child transmission as registered by SHM is lower than that reported by the Public Health Service in Curaçao. According to the Public Health Service, seven children were found to be HIV antibody-positive between 2001 and 2009. However, only two HIV-infected children were registered by SHM during this period, most likely because the other children were found to be HIV-negative after a second HIV test.

Country of infection

For 614 patients (66%) of the registered population, the most likely country of infection was known. For 546 (89%) of these patients, the country of infection was the former Netherlands Antilles. This percentage was even higher (95%) among the 476 patients who were also born in the former Netherlands Antilles. Of the 614 patients, 24 reported that they had been infected in the Netherlands, 17 in Haiti, and 11 in the Dominican Republic. All, but 4, of the 236 patients with a known HIV-1 subtype were infected with a subtype B virus, which is the most prevalent subtype in the Caribbean and among patients of non-African origin in the Netherlands.

Hepatitis B and C

In total, 48 patients of the 700 tested (7%) were co-infected with hepatitis B. The prevalence of hepatitis B did not differ by transmission risk group, but it appeared to be somewhat higher among men (9%) than women (4%). Co-infection with hepatitis C was found in only 12 patients, or 2%, of the 624 who were ever tested for hepatitis C.

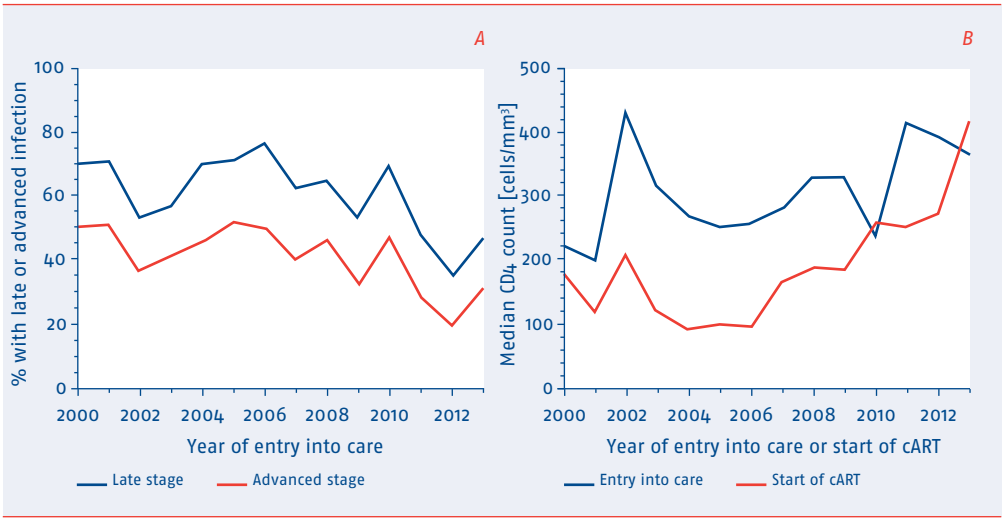
Late presentation and start of treatment

At the time of entry into care, 435 (60%) of the 728 patients who could be classified presented with late-stage HIV infection, that is, with a concurrent AIDS diagnosis or with CD4 counts below 350 cells/mm^3 (*Figure 10.2A*)[7]. Of these 435 patients, 299 (69%) were already in an advanced stage of their infection with less than 200 cells/mm^3. Late presentation probably reflects a combination of late testing and a delay between HIV diagnosis and entry into care.

As a result of late entry into care, median CD4 counts at the start of combination antiretroviral treatment (cART) were low, 191 cells/mm^3, which is markedly below any guideline's recommended threshold to start treatment. Nevertheless, only 15% of the patients had been diagnosed with an AIDS-defining event by the time treatment was started[250]. In recent

years, there has been an increase in CD4 cell counts at the start of cART (*Figure 10.2B*). Between 2010 and 2014, 32% of the patients for whom a CD4 count was available at the start of cART had less than 200 CD4 cells/mm³, whilst 32% had CD4 counts between 200 and 350 cells/mm³. During the same period, 91% of the patients entering care with less than 350 cells/mm³ were receiving treatment within six months.

Figure 10.2: *(Panel A) From 2000 onwards, 60% of patients entered clinical care with late-stage HIV infection, whilst 40% had advanced HIV infection. Late-stage infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 counts. Advanced-stage infection: CD4 counts below 200 cells/mm³ or having AIDS. (Panel B) From 2000 onwards, the median CD4 count at the time of entry was 311 cells/mm³ (interquartile range [IQR], 102-467), whilst the median CD4 count at the start of combination antiretroviral therapy (cART) was 201 cells/mm³ (IQR, 69-327). In recent years, CD4 counts at start of cART have clearly increased (416 cells/mm³ in 2013), indicating more timely diagnosis and start of treatment.*



Legend: *cART=combination antiretroviral therapy.*

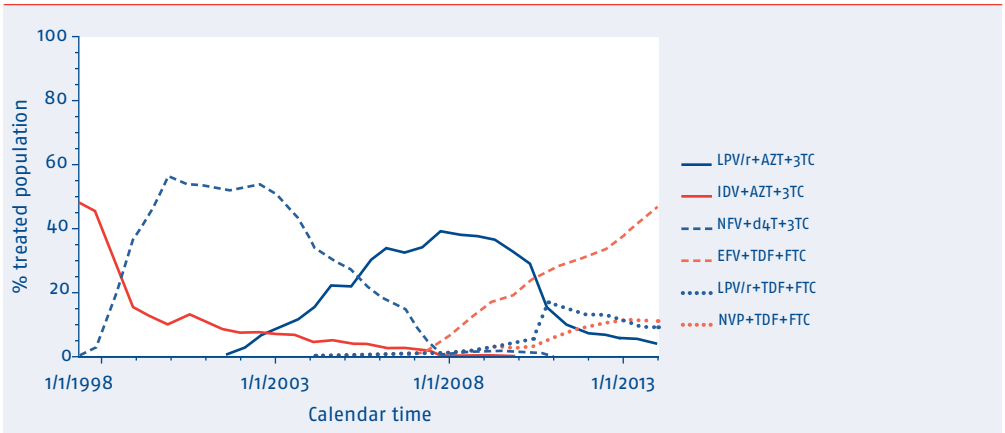
Patient monitoring

Current guidelines recommend monitoring HIV-infected patients two to three times a year, depending on CD4 count and treatment status [9]. In most recent years, these guidelines have been generally well followed in Curaçao. Between 2008 and 2013, on average, 2.0 immunology measurements were performed annually per patient. During the same period, the viral load was monitored 2.0 times per year, whilst follow-up visits for each patient averaged 2.5 per year.

Combination treatment

In total, 740 (80%) patients started cART. Of the 354 who did so between 2008 and 2014, 46% started with a combination of tenofovir/emtricitabine and efavirenz and 24% started on a combination of zidovudine/lamivudine and ritonavir-boosted lopinavir. Over time, there have been clear shifts in the treatment regimens prescribed in Curacao (*Figure 10.3*). Since 2008, a combination of tenofovir/emtricitabine with either efavirenz, nevirapine, or lopinavir has become more widely used. Of the 492 patients who started cART and were still in clinical care as of June 2014, 51% were receiving efavirenz, 16% lopinavir, and 17% nevirapine, whilst 69% were receiving tenofovir/emtricitabine and 7% zidovudine/lamivudine.

Figure 10.3: *Percentage of patients treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. The proportion of patients taking IDV+AZT+3TC decreased from 48% in 1998 to almost 0% after 2008. This decrease was counterbalanced by an increase in the proportion of patients treated with NFV+d4T+3TC. From 2002 to 2010, a combination of LPV/r+AZT+3TC was increasingly common. The use of EFV+TDF+FTC and LPV/r+TDF+FTC increased from 2008 onwards, and at the beginning of 2014, 46% of the patients were receiving EFV+TDF+FTC, 11% NVP+TDF+FTC, 9% LPV/r+TDF+FTC, and 4% LPV/r+AZT+3TC.*



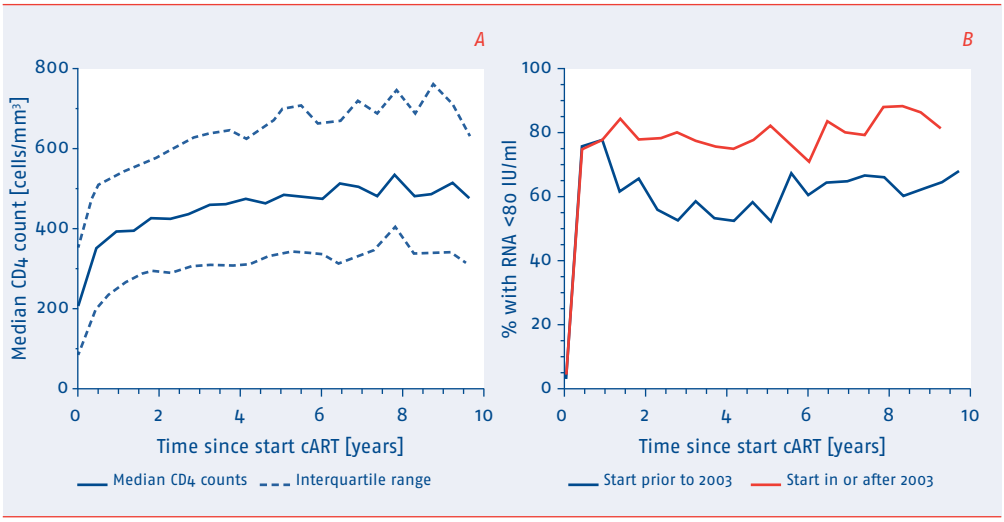
Legend: *LPV/r=ritonavir-boosted lopinavir; AZT=zidovudine; 3TC=lamivudine; NFV=nelfinavir; d4T=stavudine; EFV=efavirenz; TDF=tenofovir; FTC=emtricitabine; NVP=nevirapine; IDV=indinavir.*

Treatment outcome

For 45% of the 696 antiretroviral therapy-naive patients who started cART in 1995 or later, CD4 counts increased by at least 150 cells/mm^3 during the first six months of treatment; after two years, this proportion increased to 77%. At the same time, 75% of the patients reached a viral load level below 80 IU/ml within six months of starting treatment.

In patients who were still in clinical care as of June 2014, CD4 counts reached a plateau between 450 and 500 cells/mm³ after five years of cART (*Figure 10.4A*). During the same period, the proportion of patients with a viral load less than 80 IU/ml decreased from 77% after 48 weeks to 72% after five years of treatment. However, amongst those who started cART in 2003 or later, i.e., when more efficacious treatment combinations came into use in Curaçao, the proportion of patients who were able to maintain viral suppression remained approximately 75% (*Figure 10.4B*). For 73% of the patients still in clinical care, the most recent viral load result was less than 80 IU/ml, whilst 69% had a viral load less than 40 IU/ml. These proportions were the same irrespective of the period in which cART was started.

Figure 10.4: *CD4 cell counts and viral load in 488 treated patients who were still in care as of June 2014. (Panel A) Median CD4 counts (solid line; dotted line: interquartile range [IQR]) increased from 220 (IQR 86–349) cells/mm³ at the start of combination antiretroviral therapy (cART) to 352 (IQR 204–512) cells/mm³ after 24 weeks and reached a plateau between 450 and 500 cells/mm³ after five years. (Panel B) The proportion of patients with HIV RNA <80 IU/ml was 77% after 48 weeks, and it remained high among those who started cART in 2003 or later, but it gradually declined to between 50% and 65% after five years for those who started prior to 2003.*



Legend: *cART=combination antiretroviral therapy.*

Virological failure

As viral suppression rates appear to have increased, one may presume that, conversely, rates of virological failure have decreased. Indeed, when virological failure is defined as an HIV RNA level above 200 IU/ml despite at least four months of continuous treatment, the proportion of patients with virological failure steadily declined from approximately 36% between 2000 and 2004 to 10% in 2013.

Mortality and survival

Of the group of 844 patients who were still alive as of 1 January 2005 or who were diagnosed with HIV after that date, 82 had died by June 2014. Overall, the survival probability after seven years of follow-up was 87%. All together, 453 patients started cART in or after 2005, and of this group, 41 died, 17 of which died within six months of starting cART. After seven years, the survival probability was 86%.

Conclusion

In recent years, HIV-infected patients in Curaçao appear to be diagnosed increasingly earlier in their infection, as the proportion of patients entering care in a late or advanced stage of their infection is decreasing. As a consequence, cART can be started earlier and, thus, in a more timely manner. The quality of monitoring and treatment offered to HIV-infected patients in Curaçao has improved considerably. However, adherence to treatment is still not optimal, and levels of retention in care are worryingly low.

Recommendations

Curacao is in a unique position in the Caribbean in that data from HIV patients in care is collected and monitored; however, it is important that the quality of these data is maintained. In particular, special attention should be paid to the collection of data of HIV-infected children. Further, adherence to treatment and retention in care need to be improved to reduce the number of patients failing on treatment[251]. Finally, HIV infections need to be detected at an even earlier stage, so that patients can start antiretroviral treatment in accordance with current recommendations.

List of tables & figures

Web Appendix list of tables and figures

An appendix containing tables and figures supplementary to this report can be found on the Stichting HIV Monitoring website, *www.hiv-monitoring.nl*.

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HIV nurse consultants: A.S. Bosma, C.J. Brouwer, G.F. Geerders, K. Hoeksema, M.J. Kleene, I.B. van der Meché, A.J.M. Toonen, S. Wijnands
HIV clinical virologists/chemists: M.L. van Ogtrop

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HIV treating physicians: P.P. Koopmans, M. Keuter, A.J.A.M. van der Ven, H.J.M. ter Hofstede, A.S.M. Dofferhoff, R. van Crevel
HIV nurse consultants: M. Albers, M.E.W. Bosch, K.J.T. Grintjes-Huisman, B.J. Zomer
HIV clinical virologists/chemists: F.F. Stelma
HIV clinical pharmacology consultant: D. Burger

Rijnstate, Arnhem
HIV treating physicians: C. Richter*, J.P. van der Berg, E.H. Gisolf
HIV nurse consultants: G. ter Beest, P.H.M. van Bentum, N. Langebeek
HIV clinical virologists/chemists: R. Tiemessen, C.M.A. Swanink

Sint Elisabeth Hospitaal, Willemstad, Curaçao
HIV treating physicians: C. Winkel, A. Durand, F. Muskiet, R. Voigt
HIV nurse consultants: I. van der Meer

Sint Lucas Andreas Ziekenhuis, Amsterdam
HIV treating physicians: J. Veenstra*, K.D. Lettinga
HIV nurse consultants: M. Spelbrink, H. Sulman
Data collection: M. Spelbrink, E. Witte
HIV clinical virologists/chemists: M. Damen, P.G.H. Peerbooms

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HIV treating physicians: J.W. Mulder, S.M.E. Vrouenraets, F.N. Lauw
HIV nurse consultants: M.C. van Broekhuizen, H. Paap, D.J. Vlasblom
Data collection: E. Oudmaijer Sanders
HIV clinical virologists/chemists: P.H.M. Smits, A.W. Rosingh

Stichting Medisch Centrum Jan van Goyen, Amsterdam
HIV treating physicians: D.W.M. Verhagen
HIV nurse consultants: J. Geilings

St Elisabeth Ziekenhuis, Tilburg
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HIV clinical virologists/chemists: H.G.M. Niesters, A. Riezebos-Brilman

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Data collection: H.E. Nieuwenhuis, R. Frauenfelder.
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Drs. S. Zaheri

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Publications & presentations

The publications and presentations listed below are those available since the publication of the Monitoring Report 2013.

Publications

Missed opportunities among HIV-positive women to control viral replication during pregnancy and to have a vaginal delivery
Aebi-Popp K, Mulcahy F, Glass TR, Rudin C, Martinez de Tejada B, Bertisch B, Fehr J, Grawe C, Scheibner K, Rickenbach M, Hoesli I, Thorne C; for the European Collaborative Study in EuroCoord and the Swiss Mother & Child HIV Cohort Study.
J Acquir Immune Defic Syndr 2013 Sep 1;64(1):58-65

The effect of statin therapy on pneumonia in an HIV-infected population in the Netherlands
Janssen NE, van Lelyveld SF, Hoepelman AI, Gras L, Groenwold RH, Oosterheert JJ.
J Infect 2013 Sep;67(3):238-41

Advanced chronic kidney disease, end-stage renal disease and renal death among HIV-positive individuals in Europe
Ryom L, Kirk O, Lundgren J, Reiss P, Pedersen C, De Wit S, Buzunova S, Gasiorowski J, Gatell J, Mocroft A; EuroSIDA in EuroCoord.
HIV Med 2013 Sep;14(8):503-8

Risk factors and outcomes for late presentation for HIV-positive persons in Europe: Results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE)
Mocroft A, Lundgren JD, Sabin ML, Monforte AD, Brockmeyer N, Casabona J, Castagna A, Costagliola D, Dabis F, De Wit S, Fätkenheuer G, Furrer H, Johnson AM, Lazanas MK, Leport C, Moreno S, Obel N, Post FA, Reekie J, Reiss P, Sabin C, Skaletz-Rorowski A, Suarez-Lozano I, Torti C, Warszawski J, Zangerle R, Fabre-Colin C, Kjaer J, Chene G, Grarup J, Kirk O; Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study in EuroCoord.
PLoS Med 2013;10(9):e1001510

Age biases in a large HIV and sexual behaviour-related internet survey among MSM
Marcus U, Hickson F, Weatherburn P, Schmidt AJ.
BMC Public Health 2013 Sep 10;13:826

How effectively can HIV phylogenies be used to measure heritability?
G. Shirreff, S. Alizon, A. Cori, H.F. Günthard, O. Laeyendecker, A. van Sighem, D. Bezemer and C. Fraser.
Evol Med Public Health 2013 Sep;2013(1):209-24

Natural history of HIV control since seroconversion
Madec Y, Boufassa F, Porter K, Prins M, Sabin C, Monforte AD, Amornkul P, Bartmeyer B, Sannes M, Venet A, Lambotte O, Meyer L; on behalf of the CASCADE Collaboration in Eurocoord.
AIDS 2013 Sep 24;27(15):2451-60

Changes in first-line cART regimens and short-term clinical outcome between 1996 and 2010 in the Netherlands
Smit M, Smit C, Geerlings S, Gras L, Brinkman K, Hallett TB, de Wolf F; Athena Observational Cohort.
PLoS One 2013 Sep 30;8(9):e76071

The presence of CXCR4-using HIV-1 prior to start of antiretroviral therapy is an independent predictor of delayed viral suppression
Gijsbers EF, van Sighem A, Harskamp AM, Welkers MR, de Wolf F, Brinkman K, Prins JM, Schuitemaker H, van 't Wout AB, Kootstra NA.
PLoS One 2013 Oct 1;8(10):e76255

The incidence of AIDS-defining illnesses at a current CD4 count ≥200 cells/μL in the post-combination antiretroviral therapy era.
Mocroft A, Furrer HJ, Miro JM, Reiss P, Mussini C, Kirk O, Abgrall S, Ayayi S, Bartmeyer B, Braun D, Castagna A, d'Arminio Monforte A, Gazzard B, Gutierrez F, Hurtado I, Jansen K, Meyer L, Muñoz P, Obel N, Soler-Palacin P, Papadopoulos A, Raffi F, Ramos JT, Rockstroh JK, Salmon D, Torti C, Warszawski J, de Wit S, Zangerle R, Fabre-Colin C, Kjaer J, Chene G, Grarup J, Lundgren JD; for the Opportunistic Infections Working Group on behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study in EuroCOORD.
Clin Infect Dis 2013 Oct;57(7):1038-47

Non-AIDS defining cancers in the D:A:D Study – time trends and predictors of survival: a cohort study
Worm SW, Bower M, Reiss P, Bonnet F, Law M, Fätkenheuer G, D Arminio Monforte A, Abrams DI, Grulich A, Fontas E, Kirk O, Furrer H, De Wit S, Phillips A, Lundgren JD, Sabin CA.
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Hermanides H, Holman R, Gras L, Winkel C, Gerstenbluth I, de Wolf F, Duits A.
AIDS Res Hum Retroviruses 2013 Oct;29(10):1300-5

Gradually decreasing anal cancer incidence in the HIV+ population in the Netherlands after a decade of cART
Richel O, Van der Zee RP, Smit C, De Vries HJ, Prins JM.
Sex Health 2013 Nov;10(6):586

Associations between immune depression and cardiovascular events in HIV infection
Sabin CA, Ryom L, De Wit S, Mocroft A, Phillips AN, Worm SW, Weber R, D'Arminio Monforte A, Reiss P, Kamara D, El-Sadr W, Pradier C, Dabis F, Law M,Lundgren J; D:A:D Study Group.
AIDS 2013 Nov 13;27(17):2735-48

Symptomatic illness and low CD4 cell count at HIV seroconversion as markers of severe primary HIV infection
Lodi S, Fisher M, Phillips A, De Luca A, Ghosn J, Malyuta R, Zangerle R, Moreno S, Vanhems P, Boufassa F, Guiguet M, Porter K, for CASCADE Collaboration in EuroCoord.
PLoS One 2013 Nov 14;8(11):e78642

Long-term response to combination antiretroviral therapy in HIV-infected children in the Netherlands registered from 1996-2012
Cohen S, Smit C, van Rossum AM, Fraaij PL, Wolfs TF, Geelen SP, Schölvinck EH, Warris A, Scherpbier HJ, Pajkrt D; on behalf of the Dutch paediatric HIV study group.
AIDS 2013 Oct 23;27(16):2567-75

Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries
IeDEA and ART Cohort Collaborations.
J Acquir Immune Defic Syndr 2014 Jan 1;65(1):e8-16

Long-term effectiveness of combination antiretroviral therapy and prevalence of HIV drug resistance in HIV-1-infected children and adolescents in Rwanda
Mutwa PR, Boer KR, Rusine J, Muganga N, Tuyishimire D, Schuurman R, Reiss P, Lange JM, Geelen SP.
Pediatr Infect Dis J 2014 Jan;33(1):63-9

Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons
Ryom L, Mocroft A, Kirk O, Ross M, Reiss P, Fux CA, Morlat P, Moranne O, Smith C, El-Sadr W, Law M, Lundgren JD.
AIDS 2014 Jan 14;28(2):187-99

Blunted response to combination antiretroviral therapy in HIV elite controllers: An international HIV controller collaboration
Boufassa F, Lechenadec J, Meyer L, Costagliola D, Hunt PW, Pereyra F, Deeks S, Pancino G, Taulera O, Lichterfeld M, Delobel P, Saez-Cirion A, Lambotte O; ANRS CO HIV Controllers Cohort, the Cascade Collaboration in Eurocoord, the SCOPE Cohort and the International HIV Controllers Study.
PLoS One 2014 Jan 17;9(1):e85516

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Olson AD, Meyer L, Prins M, Thiebaut R, Gurdasani D, Guiguet M, Chaix ML, Amornkul P, Babiker A, Sandhu MS, Porter K; for C.A.S.C.A.D.E. Collaboration in EuroCoord.
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Immuno-virological discordance and the risk of non-AIDS and AIDS events in a large observational cohort of HIV-patients in Europe
Zoufaly A, Cozzi-Lepri A, Reekie J, Kirk O, Lundgren J, Reiss P, Jevtovic D, Machala L, Zangerle R, Mocroft A, Van Lunzen J; EuroSIDA in EuroCoord.
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Bezemer D, Faria NR, Hassan AS, Hamers RL, Mutua G, Anzala O, Mandaliya KN, Cane PA, Berkley JA, Rinke de Wit TF, Wallis CL, Graham SM, Price MA, Coutinho R, Sanders EJ.
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A comparison of estimated glomerular filtration rates using Cockcroft-Gault and the Chronic Kidney Disease Epidemiology Collaboration estimating equations in HIV infection
Mocroft A, Ryom L, Reiss P, Furrer H, D'Arminio Monforte A, Gatell J, de Wit S, Beniowski M, Lundgren J, Kirk O; for EuroSIDA in EuroCOORD.
HIV Med 2014 Mar;15(3):144-52

Development of a definition for Rapid Progression (RP) of renal function in HIV-positive persons: the D:A:D study
Kamara DA, Ryom L, Ross M, Kirk O, Reiss P, Morlat P, Moranne O, Fux CA, Mocroft A, Sabin C, Lundgren JD, Smith CJ; D:A:D study Group.
BMC Nephrol 2014 Mar 25;15:51

Sex differences in overall and cause-specific mortality among HIV-infected adults on antiretroviral therapy in Europe, Canada and the US
The Antiretroviral Therapy Cohort Collaboration (ART-CC).
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An update to the HIV-TRePS system: the development of new computational models that do not require a genotype to predict HIV treatment outcomes
Revell AD, Wang D, Wood R, Morrow C, Tempelman H, Hamers R, Alvarez-Uria G, Streinu-Cercel A, Ene L, Wensing A, Reiss P, van Sighem AI, Nelson M, Emery S, Montaner JS, Lane HC, Larder BA; on behalf of the RDI Study Group.
J Antimicrob Chemother 2014 Apr;69(4):1104-10

Long-term mortality in HIV positive individuals virally suppressed for more than three years with incomplete CD4 recovery
Engsig FN, Zangerle R, Katsarou O, Dabis F, Reiss P, Gill J, Porter K, Sabin C, Riordan A, Fätkenheuer G, Gutiérrez F, Raffi F, Kirk O, Mary-Krause M, Stephan C, de Olalla PG, Guest J, Samji H, Castagna A, Monforte AD, Skaletz-Rorowski A, Ramos J, Lapadula G, Mussini C, Force L, Meyer L, Lampe F, Boufassa F, Bucher HC, De Wit S, Burkholder GA, Teira R, Justice AC, Sterling TR, Crane H, Gerstoft J, Grarup J, May M, Chêne G, Ingle SM, Sterne J, Obel N; The Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Research Europe (COHERE) in EuroCoord.
Clin Infect Dis 2014 May;58(9):1312-21

A simplified combination antiretroviral therapy regimen enhances adherence, treatment satisfaction and quality of life: results of a randomized clinical trial
Langebeek N, Sprenger H, Gisolf E, Reiss P, Sprangers M, Legrand J, Richter C, Nieuwkerk P.
HIV Med 2014 May;15(5):286-90

High rate of hepatitis C virus (HCV) recurrence in HIV-infected individuals with spontaneous HCV RNA clearance
Peters L, Mocroft A, Soriano V, Rockstroh J, Kirkby N, Reiss P, Katlama C, Zakharova N, Flisiak R, Lundgren J; for EuroSIDA in EuroCoord.
HIV Med 2014 May 11

Increased risk of cardiovascular disease (CVD) with age in HIV-positive men: a comparison of the D:A:D CVD risk equation and general population CVD risk equations
Petoumenos K, Reiss P, Ryom L, Rickenbach M, Sabin C, El-Sadr W, d'Arminio Monforte A, Phillips A, De Wit S, Kirk O, Dabis F, Pradier C, Lundgren J, Law M; D:A:D study group.
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Cohort profile: Antiretroviral Therapy Cohort Collaboration (ART-CC)
May MT, Ingle SM, Costagliola D, Justice AC, de Wolf F, Cavassini M, D'Arminio Monforte A, Casabona J, Hogg RS, Mocroft A, Lampe FC, Dabis F, Fätkenheuer G, Sterling TR, del Amo J, Gill MJ, Crane HM, Saag MS, Guest J, Brodt HR, Sterne JA; Antiretroviral Cohort Collaboration.
Int J Epidemiol 2014 Jun;43(3):691-702

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Natural History Project Working Group for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.
AIDS 2014 Jun 1;28(9):1351-6

Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions
Caniglia EC, Cain LE, Justice A, Tate J, Logan R, Sabin C, Winston A, van Sighem A, Miro JM, Podzamczer D, Olson A, Arribas JR, Moreno S, Meyer L, Del Romero J, Dabis F, Bucher HC, Wandeler G, Vourli G, Skoutelis A, Lanoy E, Gasnault J, Costagliola D, Hernán MA; HIV-CAUSAL Collaboration.
Neurology 2014 Jul 8;83(2):134-41

Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients
Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, Fätkenheuer G, Reiss P7, Saag MS, Manzardo C, Grabar S, Bruyand M, Moore D, Mocroft A, Sterling TR, D'Arminio Monforte A, Hernando V, Teira R, Guest J, Cavassini M, Crane HM, Sterne JA; Antiretroviral Therapy Cohort Collaboration.
Clin Infect Dis 2014 Jul 15;59(2):287-97

Prognostic value of vitamin D level for all-cause mortality, and association with inflammatory markers, in HIV-infected persons
Shepherd L, Souberbielle JC, Bastard JP, Fellahi S, Capeau J, Reekie J, Reiss P, Blaxhult A, Bickel M, Leen C, Kirk O, Lundgren JD, Mocroft A, Viard JP; On behalf of EuroSIDA in EuroCOORD.
J Infect Dis 2014 Jul 15;210(2):234-43

Trends in underlying causes of death in people with HIV from 1999-2011 (D:A:D): a multicohort collaboration
Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, Kowalska JD, de Wit S, Law M, el Sadr W, Kirk O, Friis-Moller N, Monforte A, Phillips AN, Sabin CA, Lundgren JD, D:A:D Study Group.
Lancet 2014 Jul 19;384(9939):241-8

Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel
Günthard HF, Aberg JA, Eron JJ, Hoy JF, Telenti A, Benson CA, Burger DM, Cahn P, Gallant JE, Glesby MJ, Reiss P, Saag MS, Thomas DL, Jacobsen DM, Volberding PA.
JAMA 2014 Jul 23-30;312(4):410-25

A survey of ATRIPLA use in clinical practice as first-line therapy in HIV-positive persons in Europe
Mocroft A, Reiss P, Rakhmanova A, Banhegyi D, Phillips AN, De Wit S, Ristola M, Lundgren JD, Grarup J, Kirk O; for EuroSIDA in EuroCOORD.
Infection 2014 Aug;42(4):757-62

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Terminology

Acute infection
Any infection that begins suddenly, with intense or severe symptoms, is called acute (or primary). If the illness lasts more than a couple of weeks, it is called chronic.

Adherence
Adherence measures how faithfully a person takes all antiretroviral medications at the right time. Poor adherence is one of the main reasons antiretroviral combinations fail.

AIDS
Acquired Immunodeficiency Syndrome. A disease caused by a retrovirus, HIV (human immunodeficiency virus), and characterized by failure of the immune system to protect against infections and certain cancers.

Antibody
An immune system protein formed in response to invading disease agents such as viruses, fungi, bacteria, and parasites. Usually antibodies defend the body against invading disease agents, however, the HIV antibody does not give such protection.

Antigen
An invading substance that may be the target of antibodies.

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

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

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

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

cART
Combination antiretroviral treatment.

CD4 (T_4) cell
CD4+ T-lymphocyte, or T4-cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by the HIV virus. In the course of the HIV infection the number of CD4 cells may drop from normal levels (+ 500 per mm^3) to dangerously low levels (fewer than 200 CD4 cells per mm^3 of blood).

CDC
US Centers for Disease Control and Prevention.

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

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

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

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

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

DNA
Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert itself into the DNA molecules inside human cells and establish dormant infection.

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

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

GGD
Dutch municipal health service (www.ggd.nl).

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

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

Hepatic
Pertaining to the liver.

Hepatitis B virus (HBV)
A viral infection that affects the liver and is transmitted only through blood-to-blood and sexual contact.

Hepatitis C virus (HCV)
A viral infection that is transmitted primarily by blood and blood products, as in blood transfusions or intravenous drug use, and sometimes through sexual contact.

HIV
Human Immunodeficiency Virus; the virus that causes the Acquired Immunodeficiency Syndrome (AIDS). HIV attacks and destroys the immune system by entering and destroying the cells that control and support the immune response system.

HIV Type 1 (HIV-1)
The HIV type responsible for the majority of HIV infections worldwide.

HIV Type 2 (HIV-2)
A virus very similar to HIV-1 that has been found to cause immune suppression. HIV-2 infections are found primarily in Africa.

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

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

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

Mono-infection
When a person has only one infection.

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

MSM
Men who have sex with men.

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

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

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

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

Nucleotide Reverse Transcriptase Inhibitor (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. A single person year is 1 year lived by 1 person.

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

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

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

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

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

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

RIVM
Dutch National Institute for Public Health and the Environment (www.rivm.nl).

Seroconversion
The change from an absence of HIV antibodies in the blood to the presence of those antibodies.

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

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

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

Viraemia
The presence of a virus in the blood.

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

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

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

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

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