

BMJ Open AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile

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To cite: Boender TS, Smit C, Sighem A, *et al.* AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. *BMJ Open* 2018;**8**:e022516. doi:10.1136/bmjopen-2018-022516

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-022516>).

Received 13 March 2018

Revised 20 June 2018

Accepted 6 August 2018



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ABSTRACT

Purpose In 1998, the AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort was established to demonstrate the lifesaving effectiveness of triple combination antiretroviral therapy, including HIV-protease inhibitors, that had recently been made available for clinical use. Subsequently, the HIV Monitoring Foundation was established by the Dutch Ministry of Health, Welfare and Sport to continue ATHENA as an open cohort in order to continue the registration and monitoring of all HIV-positive people as an integral part of HIV care in all 26 HIV treatment centres in the Netherlands.

Participants To date, a total of 25 036 participants have been enrolled in the cohort, with 263 600 person-years of follow-up. As of 1 January 2017, 19 035 HIV-1-positive participants were known to be in care: 18 824 adults (81% men and 19% women) and 211 children (47% boys and 53% girls). The remaining 6001 participants had either died (46%), were lost to care (29%) or had moved abroad (25%).

Findings to date Today, with over 20 years of follow-up, the ATHENA cohort has provided extensive knowledge on HIV treatment, comorbidities and coinfections and created insight into the transmission dynamics of the HIV epidemic.

Future plans ATHENA continues to enrol and monitor HIV positive people entering HIV care in the Netherlands. Future research will continue to provide tangible input into HIV care and prevention policies in the Netherlands and internationally.

INTRODUCTION

The AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort is a nationwide observational cohort that monitors HIV management of all HIV-positive people in HIV care in the Netherlands, since the introduction of highly active antiretroviral therapy (HAART nowadays known as combination antiretroviral therapy (cART)) when the first HIV-protease inhibitor (PI) became available. As a result of the decisive action taken by the late Dutch Minister of Health, Welfare and Sport, Professor Dr Els Borst, cART including this PI became available in the Netherlands in September 1996. However,

Strengths and limitations of this study

- The AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort was established in 1998, following the introduction of triple combination antiretroviral therapy (cART) in 1996.
- The ATHENA cohort collects clinical data from 98% of all adults and children in HIV care in the Netherlands (2% *opt-out*).
- ATHENA is an open cohort, as new participants continue to be enrolled on entry into HIV care, following a positive HIV diagnosis.
- The data are extracted from medical records: the availability of the data depends on the frequency of patient visits and the completeness and detail of the medical record.
- Findings are limited to those observed during follow-up in HIV care.

its swift introduction was conditional on the following: only specialised HIV treatment centres were allowed to prescribe cART, and the effectiveness of cART in clinical practice had to be demonstrated. Accordingly, in November 1997, the Dutch National Health Insurance Council provided a grant to the Academic Medical Center of the University of Amsterdam for the ATHENA cohort to assess the effectiveness of cART in clinical practice. The ATHENA cohort was highly successfully in its mission to ‘assess the implications for the course of HIV disease, public health and health care of the introduction of new anti-HIV treatment, the monitoring of that new treatment, as well as the economic costs and benefits of the new treatment’.

Subsequently, in 2000, the Ministry of Health, Welfare and Sport institutionalised the national registration and monitoring of HIV-positive people in care by establishing *Stichting HIV Monitoring (SHM; HIV Monitoring Foundation)*. Under the responsibility of SHM, the ATHENA cohort was continued and extended to all HIV-positive people in

HIV care in the designated HIV centres (irrespective of the use of cART). Today, the mission of SHM and the ATHENA cohort is to further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and coinfections (notably viral hepatitis), in HIV-positive people in outpatient HIV care in the Netherlands.

COHORT DESCRIPTION

Setting and location

The ATHENA cohort is an observational, open cohort of all HIV-positive adults and children who enter HIV care in the Netherlands. On 1 November 2000, prior to expansion, the cohort comprised 3449 HIV-positive people, of whom 554 participated in a focus group for substudies on antiretroviral drug resistance and therapeutic drug monitoring, adherence, quality of life and costs of treatment.¹ The original cohort enrolled people who had died or were otherwise no longer in care, but who had used any of the antiretroviral drugs newly licenced in 1996 or later. Subsequently, the cohort enrolled all HIV-positive people entering HIV care in one of the designated HIV treatment centres for adults and children in the Netherlands (figure 1), including those not yet on cART.

Since November 2005, on the initiative of the Curacao Red Cross Blood Bank, SHM has also assisted in the registration and monitoring of HIV-positive people in care at St. Elisabeth Hospital in Willemstad, Curacao.^{2,3} Because data collection on Curacao is not part of the ATHENA cohort, this will not be discussed further as it is beyond the scope of this profile.

Eligibility criteria and recruitment

Registration with SHM and enrolment in ATHENA is an ongoing process. First, *all* newly diagnosed HIV-positive adults and children entering HIV care are registered at SHM by their treating HIV physician. Subsequently, enrolment in the ATHENA cohort is based on an *opt-out* principle (see also: *Ethical approval and Patient consent*). By 1 January 2017, SHM had registered a cumulative number of 25 564 HIV-positive adults and children in the Netherlands, of whom 525 (2.1%) adults and 3 (1.2%) children opted-out of further data collection⁴ (table 1). Subsequently, a total of 25 036 (97.9%) adults and children were enrolled in the cohort with a total follow-up time of 263 600 person-years. The majority were HIV-1 positive (n=24 773; 98.9%); the remainder were HIV-2 positive (n=97; 0.4%) or had HIV-1 and HIV-2 dual infection (n=60; 0.2%) or no serological results (n=106; 0.4%).

At initiation, the cohort was approved by the institutional review board of all participating centres. HIV-positive people in care can opt-out after being informed by their treating physician of the purpose of collection of data. Data are pseudonymised before being provided to investigators and may be used for scientific purposes. A designated quality management coordinator safeguards



Figure 1 HIV treatment centres in the Netherlands. Legend: adult HIV treatment centres: (1) Noordwest Ziekenhuisgroep, Alkmaar; (2) Flevoziekenhuis, Almere; (3) Academic Medical Center of the University of Amsterdam (AMC-UvA), Amsterdam; (4) DC Klinieken Lairese – HIV Focus Centrum, Amsterdam; (5) OLVG, Amsterdam; (6) MC Slotervaart, Amsterdam; (7) Medisch Centrum Jan van Goyen (MC Jan van Goyen), Amsterdam; (8) VUmc, Amsterdam; (9) Rijnstate, Arnhem; (10) HagaZiekenhuis (Leyweg site), Den Haag; (11) HMC (Haaglanden Medisch Centrum), Den Haag; (12) Catharina Ziekenhuis, Eindhoven; (13) Medisch Spectrum Twente (MST), Enschede; (14) Admiraal De Ruyter Ziekenhuis, Goes; (15) Universitair Medisch Centrum Groningen (UMCG), Groningen; (16) Spaarne Gasthuis, Haarlem; (17) Medisch Centrum Leeuwarden (MCL), Leeuwarden; (18) Leids Universitair Medisch Centrum (LUMC), Leiden; (19) MC Zuiderzee, Lelystad; (20) Maastricht UMC+ (MUMC+), Maastricht; (21) Radboudumc, Nijmegen; (22) Erasmus MC, Rotterdam; (23) Maastricht Ziekenhuis, Rotterdam; (24) ETZ (Elisabeth-TweeSteden Ziekenhuis), Tilburg; (25) UMC Utrecht (Universitair Medisch Centrum Utrecht), Utrecht; and (26) Isala Zwolle. Paediatric HIV treatment centres: (A) Emma Kinderziekenhuis (EKZ), AMC-UvA, Amsterdam; (B) Beatrix Kinderziekenhuis (BKZ) UMCG, Groningen; (C) Erasmus MC-Sophia Kinderziekenhuis, Rotterdam; and (D) Wilhelmina Kinderziekenhuis (WKZ), UMC Utrecht, Utrecht.

compliance with the European General Data Protection Regulation.⁵

Methods of data collection and follow-up

Detailed clinical and laboratory data from all enrolled HIV-positive adults and children are extracted from medical records by trained data collectors in cooperation with the responsible HIV-treating physician using an extensive, standardised protocol. In addition, 13 laboratories electronically forward test results directly to SHM.

Table 1 Registration at SHM and enrolment in the ATHENA cohort: cumulative number of HIV-positive adults and children by 1 January 2017

HIV-treatment centre	Location	Total		Alive		Deceased		Opt-out*		
		N	%	N	%	N	%	N	%	
Adults										
Noordwest Ziekenhuisgroep	Alkmaar	360	1.4	328	91.1	32	8.9	5	1.4	
Flevoziekenhuis	Almere	200	0.8	191	95.5	9	4.5	3	1.5	
AMC-UvA	Amsterdam	3 025	12.0	2 608	86.2	417	13.8	13	0.4	
Hiv Focus Centrum	Amsterdam	597	2.4	593	99.3	4	0.7	0	0.0	
MC Jan van Goyen	Amsterdam	312	1.2	270	86.5	42	13.5	4	1.3	
OLVG	Amsterdam	3 458	13.7	3 042	88.0	416	12.0	158	4.6	
Slotervaart-ziekenhuis	Amsterdam	860	3.4	701	81.5	159	18.5	12	1.4	
St Lucas Andreas	Amsterdam	468	1.8	417	89.1	51	10.9	0	0.0	
VUmc	Amsterdam	659	2.6	569	86.3	90	13.7	12	1.8	
Rijnstate	Arnhem	850	3.4	767	90.2	83	9.8	3	0.4	
HMC	Den Haag	1 108	4.4	1 018	91.9	90	8.1	45	4.1	
HagaZiekenhuis – Leyweg	Den Haag	756	3.0	649	85.8	107	14.2	32	4.2	
Catharina Ziekenhuis	Eindhoven	695	2.7	649	93.4	46	6.6	5	0.7	
MST	Enschede	619	2.4	505	81.6	114	18.4	4	0.6	
Admiraal De Ruyter Ziekenhuis	Goes	211	0.8	195	92.4	16	7.6	2	0.9	
UMCG	Groningen	946	3.7	846	89.4	100	10.6	31	3.3	
Kennemer Gasthuis	Haarlem	515	2.0	459	89.1	56	10.9	4	0.8	
MCL	Leeuwarden	310	1.2	278	89.7	32	10.3	1	0.3	
LUMC	Leiden	729	2.9	661	90.7	68	9.3	41	5.6	
MC Zuiderzee	Lelystad	81	0.3	80	98.8	1	1.2	1	1.2	
MUMC+	Maastricht	934	3.7	788	84.4	146	15.6	5	0.5	
Radboudumc	Nijmegen	765	3.0	675	88.2	90	11.8	19	2.5	
Erasmus MC	Rotterdam	2 636	10.4	2 331	88.4	305	11.6	13	0.5	
Maasstad Ziekenhuis	Rotterdam	780	3.1	724	92.8	56	7.2	8	1.0	
ETZ	Tilburg	1 174	4.6	1 093	93.1	81	6.9	19	1.6	
UMC Utrecht	Utrecht	1 749	6.9	1 556	89.0	193	11.0	65	3.7	
Isala – Sophia	Zwolle	509	2.0	472	92.7	37	7.3	20	3.9	
Total		25 306	100.0	22 465	88.8	2 841	11.2	525	2.1	
Paediatric										
EKZ, AMC-UvA	Amsterdam	71	27.5	71	100.0	0	0.0	1	1.4	
BKZ, UMCG	Groningen	28	10.9	28	100.0	0	0.0	0	0.0	
Erasmus MC – Sophia	Rotterdam	82	31.8	80	97.6	2	2.4	0	0.0	
WKZ, UMC Utrecht	Utrecht	77	29.8	76	98.7	1	1.3	2	2.6	
Total		258	100.0	255	98.8	3	1.2	3	1.2	

*Opt out: never gave permission to collect clinical information.

AMC-UvA, Academic Medical Center of the University of Amsterdam; ATHENA, AIDS Therapy Evaluation in the Netherlands; BKZ, Beatrix Kinderziekenhuis; EKZ, Emma Kinderziekenhuis; ETZ, Elisabeth-TweeSteden Ziekenhuis; HMC, Haaglanden Medisch Centrum; LUMC, Leids Universitair Medisch Centrum; MCL, Medisch Centrum Leeuwarden; MST, Medisch Spectrum Twente; MUMC+, Maastricht UMC+; SHM, *Stichting HIV Monitoring*; UMCG, Universitair Medisch Centrum Groningen; UMC Utrecht, Universitair Medisch Centrum Utrecht; WKZ, Wilhelmina Kinderziekenhuis.

The ATHENA cohort does not dictate scheduled study visits, examinations or blood work; that is, the frequency and type of visits, examinations and laboratory measurements depend on both the participant and physician.

Consequently, the cohort reflects routine HIV care, and follow-up time in the cohort is equal to follow-up time in HIV care in the Netherlands. If participants move from one HIV treatment centre to another, this transfer

is registered, and follow-up continues at the new centre. Likewise, children who transfer from paediatric to adult HIV care remain in follow-up. Participant registration and data collection are organised on a national level. When transferring to a new treatment centre within the Netherlands—in case of transfer from paediatric to adult care, or transfer to another treatment centre—the participants' study identifier is retained, and data collection is continued without interruption.

Key epidemiological data are collected from all HIV-positive people on registration at SHM. For national HIV surveillance, SHM reports these statistics to the *Centrum voor Infectieziektebestrijding (CIb; Centre for Infectious Disease Control)* of the *Rijksinstituut voor Volksgezondheid en Milieu (RIVM; National Institute for Public Health and the Environment)*. Through the RIVM-CIb, SHM also contributes to European HIV surveillance by the European Centre for Disease Prevention and Control (ECDC).⁶

After registration at SHM and enrolment in ATHENA, clinical and laboratory data from all adults and children are prospectively collected as long as the patients remain in care in a Dutch HIV treatment centre. The date of HIV diagnosis is usually retrieved from the letter of referral from the general practitioner or sexually transmitted infections clinic, or from health records in the HIV treatment centre, and can be self-reported on entry to care if there is no documentation available. All reported HIV tests, test dates and test outcomes (including the last negative HIV tests) are captured in the cohort. The data collection process is dynamic and has evolved over the years, with additions and removals of data items based on novel insights and clinical and epidemiological requirements. While the standard data collection protocol is already comprehensive, specific protocols exist for pregnant women, children and hepatitis B (HBV) and hepatitis C (HCV) virus coinfection. A complete overview of the items that are collected can be found online.⁷

On enrolment, the following information is collected: demographics, history of HIV infection (including the possibility of a primary infection), most likely route of HIV acquisition, smoking, alcohol and drug use. At each visit, the following information is collected: body weight and height, blood pressure, Centers for Disease Control and Prevention classification for HIV infection - Category B (CDC-B) and Centers for Disease Control and Prevention classification for HIV infection - Category C (CDC-C) events,⁸ antiretroviral therapy, adverse events (when resulting in a change of antiretroviral treatment or when specified in the protocol⁷), non-AIDS comorbidities (particularly diabetes mellitus, cardiovascular disease, chronic kidney disease and non-AIDS malignancies), comedication and participant's participation in clinical trials or studies. All available laboratory results are collected at each visit: virology, immunology, chemistry, haematology and results on viral coinfections or sexually transmitted diseases. HIV genome sequences and HCV and HBV genotypes are collected when available.

Furthermore, additional liver diagnostic information (fibroscan, liver pathology and radiology), and additional information concerning HBV and HCV coinfection (HBV vaccination, hepatocellular carcinoma screening, diagnosis and treatment, and virological response to antiviral treatment) are collected. During pregnancy, obstetric and pregnancy-related data are also collected. If applicable, the cause of death is classified by the physician, using the Coding of Death format.⁹

For children, additional information is collected at enrolment and subsequent visits: nationality, country of birth, HIV status of both parents, HIV status of their siblings, perinatal information, head circumference, puberty stage, Centers for Disease Control and Prevention classification for HIV infection - Category A (CDC-A) events,⁸ vaccinations, information regarding psychological, locomotor and puberty development, additional treatment, care and education. Additional laboratory results collected for children comprise HIV DNA and additional viral infections.

Patient and public involvement

The community of people living with HIV in the Netherlands, represented by the Dutch Association of People Living with HIV (*HIV Vereniging*), together with health-care providers and policy makers was closely involved in the establishment and setting-up of the ATHENA cohort in 1997 to monitor the effectiveness of providing early access to life-saving PI containing combination therapy by the Minister of Health. The involvement of the Dutch Association of People Living with HIV continues to the present, with the association being represented on both SHM's Governing Board and Scientific Advisory Board. Findings from the ATHENA cohort are published annually in the HIV Monitoring Report, which is publicly accessible through our website (<https://www.hiv-monitoring.nl/english/research/monitoringreports/>). Each year, the Dutch Association of People Living with HIV, together with other stakeholders, are asked for input on a press release by SHM in which key findings from the annual report are publicly disseminated.

FINDINGS TO DATE

Since 2001,¹ the ATHENA cohort provides a comprehensive overview of the trends over time in the HIV epidemic in the Netherlands including the impact of antiretroviral treatment (<https://www.hiv-monitoring.nl/english/research/monitoringreports/>). Furthermore, it has advanced our knowledge of HIV-associated comorbidities and coinfections, as well as insight on the spread and prevention of HIV. In addition, a complete and up-to-date list of scientific publications is available online (<https://www.hiv-monitoring.nl/english/research/publications/>).

Participant characteristics

On 1 January 2017, 19 035 HIV-1-positive participants were known to be in HIV care: 18 824 were aged 18 years or older

and 211 were below 18 years of age (table 2). The remaining 6001 participants were no longer in care because they had died (n=2776; 46%), were lost to care (n=1734; 29%) or had moved abroad (n=1491; 25%).²

The HIV epidemic in the Netherlands

The ATHENA cohort has generated many insights into the evolution of the Dutch HIV epidemic over time, including information on diagnosed, and estimates of as yet undiagnosed HIV infections, HIV transmission and transmission risk groups. For example, from the 1990s onwards, the annual number of new HIV diagnoses among men who have sex with men (MSM) increased from approximately 400 to well over 800 by 2009. However, since then, the registered number of new diagnoses has steadily declined, and in 2016, the estimated number of new HIV diagnoses among MSM was 545. Moreover, in the heterosexual population, the number of new diagnoses has declined to between 200 and 250 per year.² Although the overall rate of late presentation has also been declining,¹⁰ targeted programmes to reduce late HIV diagnoses remain needed for all risk groups and should be prioritised for heterosexual males and females, migrants from South and Southeast Asia and sub-Saharan Africa, people over 50 years of age and certain regions in the Netherlands.¹¹

Based on the ATHENA cohort and the ECDC HIV Modelling Tool,^{12 13} there were an estimated 1000 new HIV infections each year between 2000 and 2010, which subsequently decreased to 500 in 2016. In MSM, the number of new HIV infections reached a peak of approximately 900 around 2007, and then decreased to approximately 400 in 2016. The estimated number of people living with undiagnosed HIV has also decreased since 2000, although this decrease was less pronounced among MSM.² Studies combining modelling and phylogenetic analysis have shown that HIV transmission among MSM can be averted if men undergo annual HIV testing and, if found to be HIV positive, immediately initiate cART, or, if found to be HIV-negative, half of these men who are perceived to be at high-risk for HIV acquisition initiate pre-exposure antiretroviral prophylaxis.¹⁴

Response to cART

In the early 2000s, ATHENA generated additional evidence that cART was efficacious for the treatment of HIV and provided insight into CD4 cell count and viral load dynamics in both treated and untreated HIV infection.^{15–17} In recent years, initiation of cART following an HIV diagnosis has been taking place increasingly earlier and irrespective of CD4 cell count. By 2016, the median CD4 cell count at start of cART had increased to 410 cells/mm³, and the majority of people starting cART did so within 1 month of diagnosis (figure 2). At the same time, the time spent on a first-line regimen is increasing, and both short-term and long-term virological suppression rates are high and continue to improve. Since 2000, the annual proportion of individuals on cART with a viral load >200 copies/mL has decreased to approximately 3%. Consequently, earlier diagnosis in

combination with immediate treatment and very low rates of virological failure on treatment have contributed to a substantial decrease in the annual number of new HIV diagnoses among MSM in the Netherlands, despite an increase in risk behaviour.^{18 19}

Among adults who do experience virological failure, the rate of acquired drug resistance remains low and continues to decline over time.^{2 20} The overall prevalence of transmitted resistance remains low over time, in line with European surveillance data.²¹

Trends in morbidity and mortality over time

Since cART became available, AIDS-related deaths have decreased dramatically and life-expectancy has improved substantially.^{22 23} Moreover, data from the cohort led to the Netherlands becoming one of the first countries where HIV-positive people could get life insurance.²⁴ The limited and decreasing number of individuals who still die of AIDS each year mainly consist of those presenting late for care.

As a result of both increased life expectancy in people living with HIV, as well as an increase in age at HIV diagnosis, the HIV-positive population in the Netherlands is ageing (figure 3). Modelling studies have provided insight into the expected disease burden resulting from this age shift. By 2030, an estimated 73% of the HIV-positive population in the Netherlands will be aged 50 years or older, and 84% of HIV-positive people are expected to have at least one non-communicable disease (up from 29% in 2010).²⁵ Consequently, the annual cardiovascular disease incidence and costs are predicted to increase between 2015 and 2030. However, traditional cardiovascular disease prevention interventions can optimise cardiovascular health and avert future costs, particularly if targeting high-risk individuals.²⁶

Continuum of care

The Netherlands is well on its way to reaching the UNAIDS 90-90-90 targets for 2020,²⁷ and Amsterdam is among the first cities to have reached and exceeded these targets.²⁸ In 2016, an estimated 89% of all people living with HIV in the Netherlands were diagnosed and linked to care, 92% of these people were on cART and 95% of those on cART had a suppressed viral load (figure 4). Although time from acquiring HIV to reaching viral suppression has declined over time, further decline continues to be challenged mainly by the duration of undiagnosed HIV infection.^{2 29}

Pregnant women, children and adolescents

The combination of opt-out HIV screening and use of cART in HIV-positive pregnant women has reduced the risk of mother-to-child transmission to <1% in the Netherlands.² At the same time, an increasing number of children who acquired HIV through vertical transmission are being adopted from sub-Saharan Africa by Dutch parents. In general, paediatric HIV care has resulted in favourable treatment outcomes, and viral suppression among children has improved substantially over time.³⁰ Of note, however, is that adolescents and young adults are particularly vulnerable to virological failure, especially around and shortly

Table 2 The ATHENA cohort: participant characteristics of the 19 035 HIV-1-positive people in HIV care by 1 January 2017

	Men who have sex with men		Heterosexual		Injecting drug use		Blood or blood products		Other/unknown		Total	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=11 928	n=2377	n=3104	n=84	n=151	n=89	n=795	n=283	n=15 475	n=3560		
Current age in years												
0-12	0	0	0	0	0	0	57	77	57	77	57	77
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	7.2%	27.2%	7.2%	27.2%	7.2%	27.2%
13-17	4	0	1	0	1	2	43	26	43	26	48	29
	0.0%	0.0%	0.0%	0.0%	0.7%	2.2%	5.4%	9.2%	5.4%	9.2%	6.3%	4.0%
18-24	199	16	37	0	3	1	46	41	46	41	264	79
	1.7%	0.7%	1.2%	0.0%	2.0%	1.1%	5.8%	14.5%	5.8%	14.5%	17.1%	2.2%
25-34	1432	221	497	2	18	10	87	32	87	32	1762	541
	12.0%	9.3%	16.0%	2.4%	11.9%	11.2%	10.9%	11.3%	10.9%	11.3%	11.4%	15.2%
35-44	2547	488	1017	10	24	22	115	38	115	38	3210	1087
	21.4%	20.5%	32.8%	11.9%	15.9%	24.7%	14.5%	13.4%	14.5%	13.4%	20.7%	30.5%
45-54	4131	853	955	34	55	29	214	37	214	37	5345	1055
	34.6%	35.9%	30.8%	40.5%	36.4%	32.6%	26.9%	13.1%	26.9%	13.1%	34.5%	29.6%
55-64	2548	538	415	34	26	16	142	26	142	26	3333	491
	21.4%	22.6%	13.4%	40.5%	17.2%	18.0%	17.9%	9.2%	17.9%	9.2%	21.5%	13.8%
65-74	929	222	144	4	22	6	73	5	73	5	1259	159
	7.8%	9.3%	4.6%	4.8%	14.6%	6.7%	9.2%	1.8%	9.2%	1.8%	8.1%	4.5%
≥75	138	39	38	0	2	3	18	1	18	1	197	42
	1.2%	1.6%	1.2%	0.0%	1.3%	3.4%	2.3%	0.4%	2.3%	0.4%	1.3%	1.2%
Current age 50 years or older												
No	6132	1150	2085	17	69	53	449	232	449	232	7874	2387
	51.4%	48.4%	67.2%	20.2%	45.7%	59.6%	56.5%	82.0%	56.5%	82.0%	50.9%	67.1%
Yes	5796	1227	1019	67	82	36	346	51	346	51	7601	1173
	48.6%	51.6%	32.8%	79.8%	54.3%	40.4%	43.5%	18.0%	43.5%	18.0%	49.1%	32.9%
Current age 60 years or older												
No	9899	1911	2776	68	117	75	648	267	648	267	12 755	3186
	83.0%	80.4%	89.4%	81.0%	77.5%	84.3%	81.5%	94.3%	81.5%	94.3%	82.4%	89.5%
Yes	2029	466	328	16	34	14	147	16	147	16	2720	374
	17.0%	19.6%	10.6%	19.0%	22.5%	15.7%	18.5%	5.7%	18.5%	5.7%	17.6%	10.5%
Region of origin												
Netherlands	8669	1136	913	41	97	17	360	102	360	102	10 394	1073
	72.7%	47.8%	29.4%	48.8%	64.2%	19.1%	45.3%	36.0%	45.3%	36.0%	67.2%	30.1%
Sub-Saharan Africa	164	636	1304	0	29	38	225	105	225	105	1058	1447
	1.4%	26.8%	42.0%	0.0%	19.2%	42.7%	28.3%	37.1%	28.3%	37.1%	6.8%	40.6%
Western Europe	744	80	71	27	3	3	31	25	31	25	882	126
	6.2%	3.4%	2.3%	33.1%	2.0%	3.4%	3.9%	8.8%	3.9%	8.8%	5.7%	3.5%
South America	749	209	307	1	3	9	37	13	37	13	1009	330
	6.3%	8.8%	9.9%	1.2%	2.0%	10.1%	4.7%	4.6%	4.7%	4.6%	6.5%	9.3%

Continued

Table 2 Continued

	Men who have sex with men		Heterosexual		Injecting drug use		Blood or blood products		Other/unknown		Total	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=11 928	n=2377	n=3104	n=84	n=151	n=89	n=795	n=283	n=15 475	n=3560		
Caribbean	453 3.8%	121 5.1%	162 5.2%	1 1.2%	4 2.6%	4 4.5%	35 4.4%	1 0.4%	618 4.0%	168 4.7%		
South and Southeast Asia	355 3.0%	39 1.6%	207 6.7%	1 1.2%	6 4.0%	11 12.4%	27 3.4%	8 2.8%	436 2.8%	227 6.4%		
Other	748 6.3%	149 6.3%	131 4.2%	13 15.5%	9 6.0%	7 7.9%	75 9.4%	26 9.2%	1020 6.6%	177 5.0%		
Unknown	46 0.4%	7 0.3%	9 0.3%	0 0.0%	0 0.0%	0 0.0%	5 0.6%	3 1.1%	58 0.4%	12 0.3%		
Years aware of HIV infection												
<1	473 4.0%	92 3.9%	87 2.8%	0 0.0%	7 4.6%	0 0.0%	32 4.0%	7 2.5%	605 3.9%	94 2.6%		
1–2	1107 9.3%	211 8.9%	226 7.3%	0 0.0%	8 5.3%	4 4.5%	75 9.4%	18 6.4%	1403 9.1%	248 7.0%		
3–4	1336 11.2%	224 9.4%	227 7.3%	3 3.6%	14 9.3%	2 2.2%	65 8.2%	28 9.9%	1641 10.6%	260 7.3%		
5–10	3505 29.4%	624 26.3%	720 23.2%	3 3.6%	21 13.9%	20 22.5%	191 24.0%	75 26.5%	4359 28.2%	818 23.0%		
10–20	3818 32.0%	1025 43.1%	1502 48.4%	21 25.0%	48 31.8%	42 47.2%	321 40.4%	106 37.5%	5297 34.2%	1671 46.9%		
>20	1683 14.1%	197 8.3%	330 10.6%	57 67.9%	51 33.8%	21 23.6%	99 12.5%	44 15.5%	2146 13.9%	452 12.7%		
Unknown	6 0.1%	4 0.2%	12 0.4%	0 0.0%	2 1.3%	0 0.0%	12 1.5%	5 1.8%	24 0.2%	17 0.5%		
Current CD4 count in cells/mm ³ , median/IQR range												
670	571	670	590	737	558	550	750	680	650	680		
510–870	410–790	490–870	370–832	544–980	370–750	400–790	530–1050	480–854	480–854	490–880		
Current CD8 count in cells/mm ³ , median/IQR range												
860	840	770	886	890	800	840	740	780	860	780		
640–1180	600–1177	573–1050	671–1125	635–1290	530–1100	590–1170	480–1000	630–1180	630–1180	573–1050		
Current HIV RNA <200 copies/mL												
No	503	144	209	7	7	52	24	282	720	282		
Yes	10 904	2137	2755	67	140	689	239	14063	14063	3217		
Current HIV RNA <100 copies/mL	91.4%	89.9%	88.8%	79.8%	92.7%	86.5%	86.7%	84.5%	90.9%	90.4%		
No	605	170	243	5	7	61	23	857	857	244		
Yes	5.1%	7.2%	7.8%	6.0%	4.6%	7.9%	7.7%	8.1%	5.5%	6.9%		

Continued

Table 2 Continued

	Men who have sex with men		Heterosexual		Injecting drug use		Blood or blood products		Other/unknown		Total	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=11 928	n=2377	n=3104	n=84	n=151	n=89	n=795	n=283	n=15 475	n=3560		
Yes	10802 90.6%	2111 88.8%	2721 87.7%	69 82.1%	140 92.7%	78 87.6%	680 85.5%	240 84.8%	13926 90.0%	3142 88.2%		
Ever AIDS	2125 17.8%	714 30.0%	676 21.8%	35 41.7%	50 33.1%	24 27.0%	278 35.0%	81 28.6%	3248 21.0%	816 22.9%		
AIDS at diagnosis	1129 9.5%	509 21.4%	395 12.7%	6 7.1%	31 20.5%	12 13.5%	196 24.7%	43 15.2%	1883 12.2%	456 12.8%		
Current HIV treatment	11 642 97.6%	2307 97.1%	3013 97.1%	84 100.0%	146 96.7%	89 100.0%	773 97.2%	278 98.2%	15 088 97.5%	3464 97.3%		
Currently not on combination antiretroviral therapy	18 0.2%	2 0.1%	2 0.1%	0 0.0%	0 0.0%	0 0.0%	1 0.1%	2 0.7%	21 0.1%	4 0.1%		
Not started	268 2.2%	68 2.9%	89 2.9%	0 0.0%	5 3.3%	0 0.0%	21 2.6%	3 1.1%	366 2.4%	92 2.6%		

ATHENA, AIDS Therapy Evaluation in the Netherlands.

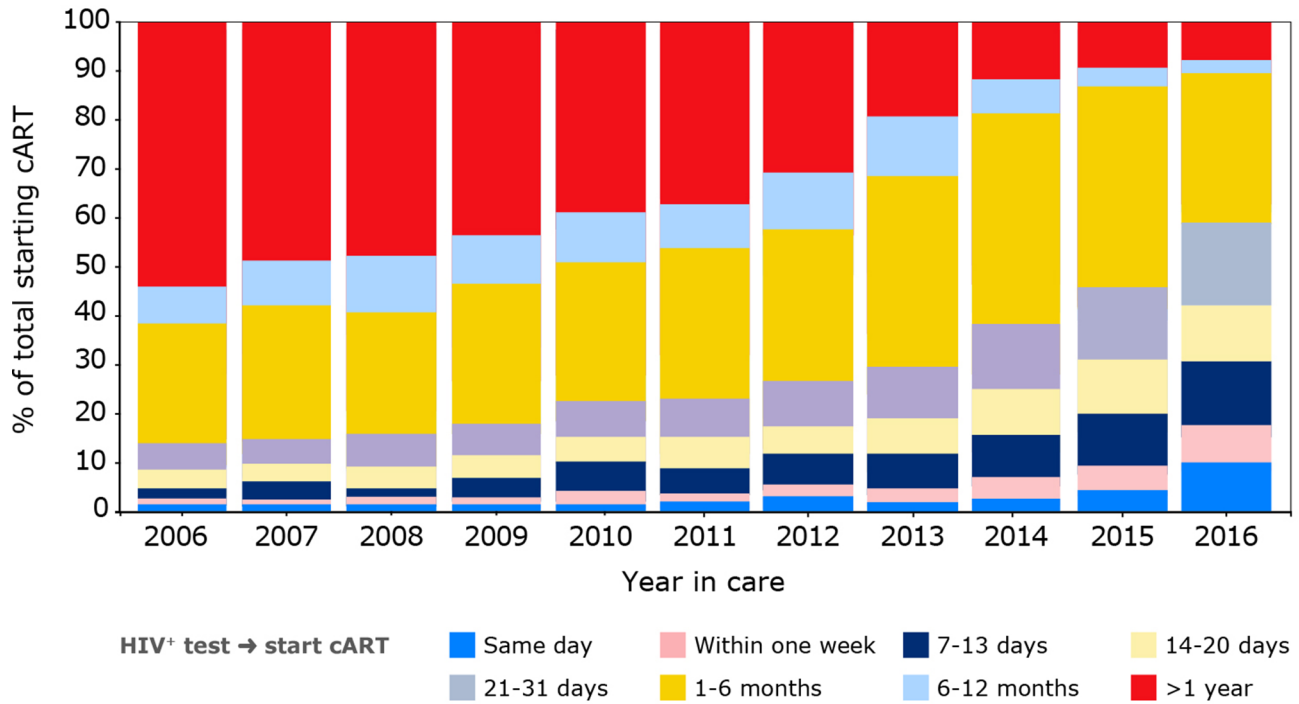


Figure 2 Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) among people initiating cART by year of entry into care.

after the moment of transition from paediatric to adult care.³¹

Viral hepatitis coinfection

HBV and HCV coinfections are relatively common among HIV-positive people and are closely monitored in the cohort.² However, phylogenetic analysis has shown limited overlap between HCV and HIV transmission networks,

which indicates a dynamic sexual network structure of Dutch HIV-positive MSM.³²

Up to 2016, an increase in the prevalence of active HCV (presence of detectable HCV RNA) was reported, especially among MSM. Since the introduction and reimbursement of direct-acting antiviral agents for HCV treatment in 2014, increasing numbers of HIV-positive people with both acute and chronic HCV coinfection have been treated for, and successfully cured of, HCV (ie, sustained virological response) (figure 5).^{2, 33} This has resulted in a rapidly declining number of coinfecting individuals in HIV care who still need to be cured of HCV.

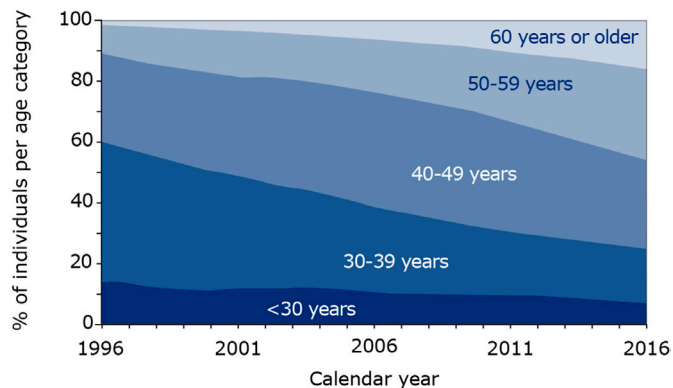


Figure 3 Increasing age distribution of the ATHENA cohort over time. Legend: this figure includes all HIV-1-positive people in clinical care. In 1996, 14% of the patients in care were younger than 30 years of age, whereas 11% were 50 years or older. In 2016, these proportions were 7% and 46%, respectively, while 16% of patients in care were 60 years of age or older. The proportion of patients in clinical care as of 31 December of each calendar year is shown according to those who were <30 years of age, 30–39 years, 40–49 years, 50–59 years and 60 years or older. ATHENA, AIDS Therapy Evaluation in the Netherlands.

STRENGTHS AND LIMITATIONS

The unique strength of the cohort is its completeness, both in terms of coverage (ie, 98% of all HIV-positive people in care in the Netherlands), as well as the quality and extensiveness of the data collection.³⁴ Furthermore, follow-up and data collection continues uninterrupted for children who transfer from paediatric to adult HIV care and for people who transfer to another HIV treatment centre within the Netherlands.

To improve data quality, SHM has developed a quality management system based on the principals of a plan–do–check–adjust cycle. New data collectors receive intensive training and follow a personal coaching programme. SHM also has an internal helpdesk that resolves questions from the data collectors. After collection, the data are automatically checked for inconsistencies and source-verified by the data management and quality control departments.

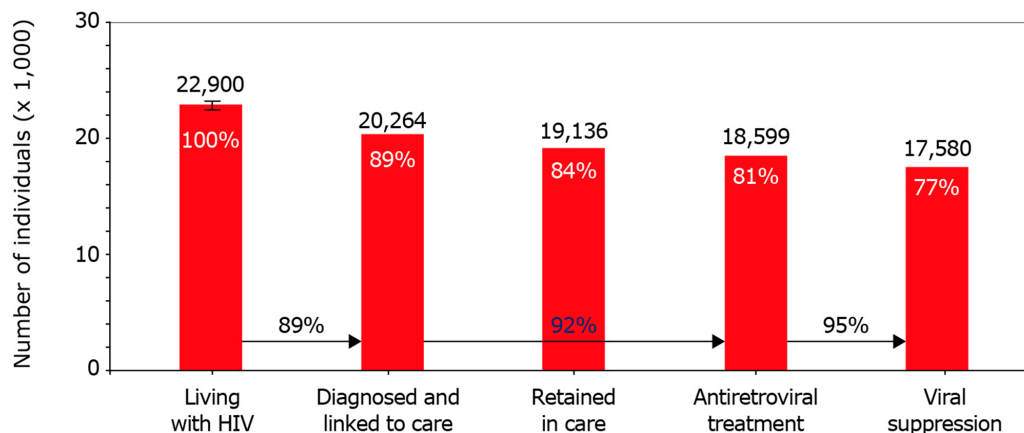


Figure 4 Continuum of HIV care for the total estimated HIV-positive population in the Netherlands in 2016.

SHM has become an integral part of HIV care and works closely with all the HIV-treating physicians and the *Nederlandse Vereniging van HIV Behandelaren* (Dutch Association of HIV-Treating Physicians). Additionally, SHM has contributed to the development of care indicators and provides these statistics for the *Zichtbare Zorg* (Visible Care) programme,³⁵ which is run by the Public Health Inspection Agency and was commissioned by the Ministry of

Health, Welfare and Sport to allow comparison of quality of healthcare.

Another main strength is the participation of SHM and the ATHENA cohort in regional, national and international scientific research collaborations. There is close collaboration with the Academic Medical Center of the University of Amsterdam, the Public Health Service Amsterdam through the Amsterdam Cohort Studies

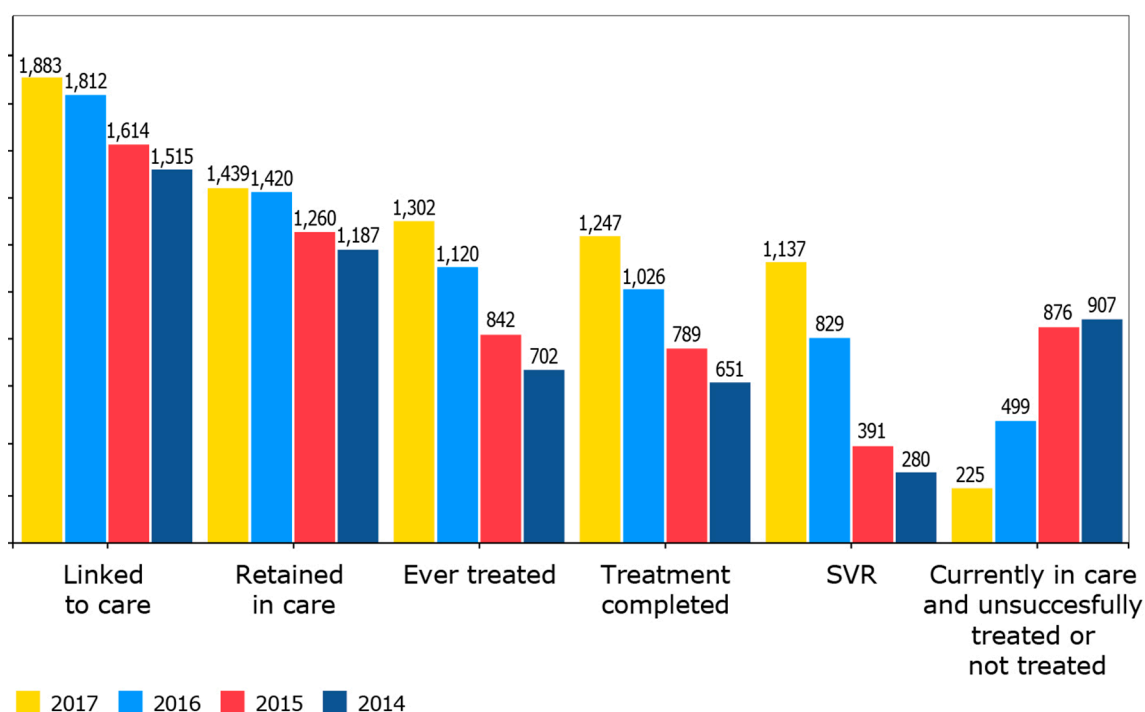


Figure 5 Hepatitis C continuum of care. Legend: out of a total of 1883 individuals linked to HIV care and diagnosed with HCV, 1439 individuals (76%) were retained in care, and of these 1439, 1302 (90%) had ever received treatment for HCV. Of the 1302 individuals treated for HCV, 1247 (96%) had completed HCV treatment and had data available to calculate their HCV treatment response. Overall, 1137 of the 1247 (91%) individuals who completed treatment had achieved an SVR. As a result, 302 of the 1439 individuals (21%) who were alive and in care as of 1 May 2017 in one of the Dutch HIV treatment centres remained untreated (n=137), not successfully treated (n=85), were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation (n=80). All 80 individuals in whom SVR could not yet be calculated due to insufficient time since treatment discontinuation had been treated with novel direct-acting antiviral agents combinations. For that reason, we extrapolated the observed direct-acting antiviral agents SVR rate of 97% and assumed that 97% of these 80 individuals (n=77) will eventually be successfully treated. This resulted in an estimated number of 302–77=225 individuals who remain untreated or unsuccessfully treated. SVR, sustained virological response (ie, HCV cure).

(ACS)³⁶; the MSM Observational Study of Acute Infection with Hepatitis C (MOSAIC)³²; Co-morbidity and Ageing with HIV (AGE_hIV) cohort study³⁷; EU-funded Co-morbidity in Relation to AIDS (COBRA) programme³⁸; and the HIV Transmission Elimination Amsterdam (H-TEAM) initiative.³⁹ ATHENA collaborates with other research groups and observational cohorts in western Europe, the USA and Canada. Data sharing and collaboration has taken place or is ongoing with the Collaboration of Observational HIV Epidemiological Research Europe (COHERE),⁴⁰ EuroSIDA,⁴¹ the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)⁴² within the Paediatric European Network for the Treatment of AIDS (PENTA), the European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCoord); A Collaboration on HIV-2 infection (ACHIEV_{2E})⁴³; Antiretroviral Therapy Cohort Collaboration (ART-CC)⁴⁴; Data collection on Adverse events of anti-HIV Drugs (D:A:D)⁴⁵; HIV Cohorts Analysed Using Structural Approaches to Longitudinal data (HIV-CAUSAL) Collaboration⁴⁶; Bridging the Evolution and Epidemiology of HIV in Europe (BEEHIVE)⁴⁷; HIV Resistance Response Database Initiative (RDI)^{48, 49}; and International epidemiology Databases to Evaluate AIDS (IeDEA).⁵⁰

A limitation of the cohort is that the data are based on medical records and not on scheduled data collection through questionnaires. While the data collection protocol is structured, the availability of the data depends on the frequency of patient visits and the completeness and detail of the notes in the medical record. Although this provides insight into routine HIV care in a 'real life' setting, some aspects of HIV care and disease progression might go unmeasured and therefore unnoticed. Data collection largely depends on information captured by the medical records of HIV physicians and HIV nurse consultants. This potentially limits obtaining more detailed data regarding less severe comorbid conditions and substance use, which may not be brought to the attention of the HIV physician. Furthermore, while the cohort captures 98% of all people in HIV care, we do not know well which (eg, migrants) and how many people do not enter HIV care. Another limitation is that HIV genotype sequence data are incomplete and not available from all cohort participants.

COLLABORATION

HIV physicians can review the data of their own treatment centre and compare these data with the full cohort through an online report builder. Statistical information or data for own research purposes can be requested by submitting a research proposal (<https://www.hiv-monitoring.nl/english/research/research-projects/>). For correspondence: hiv.monitoring@amc.uva.nl.

Acknowledgements The ATHENA national observational HIV cohort is not possible without the ongoing contribution of all HIV treating physicians, nurse consultants and staff at the diagnostic laboratories and facilities in the HIV treatment centres, along with the data collecting and monitoring staff both within and outside Stichting HIV Monitoring (listed under collaborators). We would like to extend our sincerest thanks and appreciation to representatives of the Dutch Association of People Living with HIV (HIV Vereniging) for being represented on SHM's Governing Board and Scientific Advisory Board.

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Funding The ATHENA cohort is managed by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment.

Competing interests None declared.

Patient consent Not required.

Ethics approval At initiation, the cohort was approved by the institutional review board of all participating centres. People entering HIV care receive written material about participation in the ATHENA cohort and are being informed by their treating physician of the purpose of collection of data, after which they can consent verbally or elect to opt-out. Data are pseudonymised before being provided to investigators and may be used for scientific purposes. A designated quality management coordinator safeguards compliance with the European General Data Protection Regulation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement HIV physicians can review the data of their own treatment centre and compare these data with the full cohort through an online report builder. Statistical information or data for own research purposes can be requested by submitting a research proposal (<https://www.hiv-monitoring.nl/english/research/research-projects/>). For correspondence: hiv.monitoring@amc.uva.nl.

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