

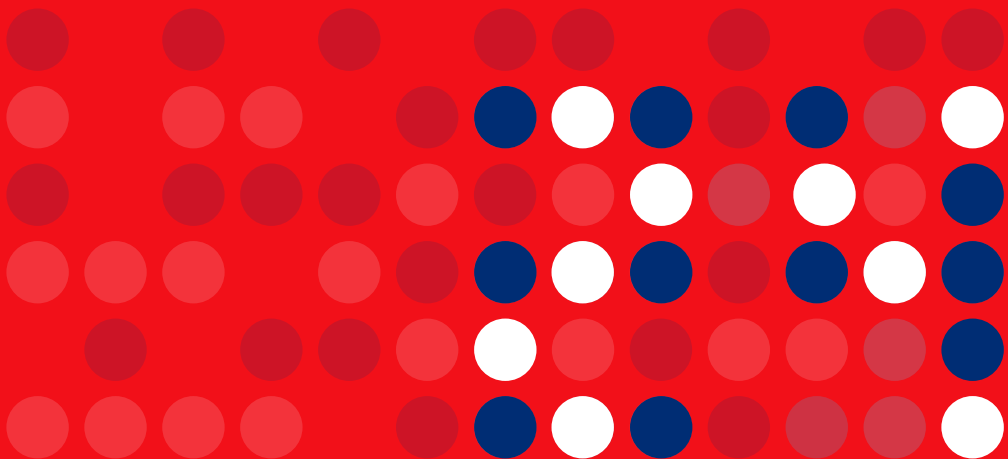
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands



HIV Monitoring Report

2024

**Chapter 10: The Amsterdam Cohort Studies (ACS)
on HIV infection: annual report 2023**



10. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2023

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Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS 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 people who use/used (injecting) drugs (PWUD/PWID) was initiated in 1985 and discontinued in 2016.

From the outset, research in the ACS has taken a multidisciplinary approach, integrating epidemiology, social science, virology, immunology, and clinical medicine in one study team. This unique collaboration has been highly productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection, as well as other infections such as STI [e.g., viral hepatitis B and C (HBV and HCV) and human papillomavirus (HPV)]. This expertise, in turn, has contributed directly to advances in prevention, diagnosis, and management of these infections.

In 2023, the cohort reached 39 years of follow-up. The initial aim of the ACS was to investigate the prevalence and incidence of HIV-1 infection and AIDS, the associated risk factors, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 39 years, the emphasis changed to accommodating changing knowledge gaps and needs. 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 infection³. In the past years, investigating the epidemiology, determinants, course of infections and pathogenesis of HIV, sexually transmitted (STI), blood-borne and other infections, and to evaluate the effect of interventions have become an important component of the ACS research programme.



Collaborating institutes and funding

Within the ACS, the following different institutes collaborated in 2023 to bring together data and biological sample collections, and to conduct research:

- **Public Health Service of Amsterdam** (*Gemeentelijke Gezondheidsdienst Amsterdam*, GGD Amsterdam): Department of Infectious Diseases
- **Amsterdam University Medical Centers, location Academic Medical Center (AMC)** (Amsterdam UMC): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease);
- **Stichting HIV Monitoring** (HIV Monitoring Foundation, SHM);

In previous years, Sanquin Blood Supply Foundation, Medical Center Jan van Goyen, and the HIV Focus Center of the DC-Clinics also contributed to sample and data collection, still being used in current research projects.

In addition, there are numerous collaborations between the ACS and other research groups, both within and outside the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control Netherlands of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu*, RIVM-CIb).

Ethics statement

The ACS has been conducted in accordance with the ethical principles set out in the Helsinki declaration. Participation in the ACS is voluntary and written informed consent is obtained from each participant. The most recent version for the MSM cohort was approved by the Amsterdam UMC medical ethics committee in 2022; for the (closed) PWID cohort, in 2009.

The Amsterdam Cohort Studies (ACS)

The cohort of men who have sex with men (MSM)

Between 1984 and 1985, men who had had sexual contact with at least one other man in the preceding six months were enrolled, independent of their HIV status. In the first 6 months of the recruitment period, 750 MSM, of which one-third with HIV, were enrolled. From 1985 to 1988, men without HIV 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 preceding six months. Between 1988 and 1998, MSM with HIV were also enrolled because of the cohort involvement in HIV treatment trials. From 1995 to 2004, only men aged 30 years or younger, with at least one male sexual partner in the previous six months, could be included the study. Since 2005, men without HIV of all age groups have been eligible to

participate in the ACS if they live in, or are closely connected to the city of Amsterdam and have had at least one male sexual partner in the preceding six months. In line with the advice issued by the International Scientific Advisory Committee in 2013, the cohort continues to strive to recruit young MSM (aged 30 years or younger). From 2022 onwards, we aim to actively follow 825 MSM (750 without HIV and 75 with HIV). Individuals of at least 16 years old, who were assigned male sex at birth and not having undergone gender reassignment surgery, live in the Amsterdam area or are involved in MSM-related activities in Amsterdam, and having had sex with at least one man in the preceding six months are eligible for enrolment. Active recruitment campaigns (e.g., online advertisements, promotional activities in gay venues in Amsterdam) are organized approximately once every two years.

Men who seroconverted for HIV within the ACS remained in the cohort until 1999, when follow-up of a selection of MSM with HIV was transferred to the MC Jan van Goyen. In 2003, the 'HIV Research in Positive Individuals' (*Hiv Onderzoek onder Positieven*, HOP) protocol was initiated. Individuals with a recent HIV infection when entering the study at the GGD Amsterdam, and those who seroconverted for HIV during follow-up within the cohort, continue to return for study visits at the GGD Amsterdam, or at an HIV treatment centre. Blood samples from these participants are stored at the ACS Biobank long-term storage and analyses. All (sexual) behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

As of 31 December 2023, 2,989 MSM have been included in the ACS since its initiation in 1984. Of these 2,989 MSM, 607 were living with HIV at entry into the study and 264 seroconverted for HIV during follow-up. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding: medical history, (sexual) behaviour and substance use, uptake of prevention measures (including PrEP, doxyPEP, and condom use) underlying psychosocial determinants, health care use, signs of depression and other psychological disorders, and demographics. Moreover, blood is collected for diagnostic tests and storage at the ACS biobank. In total, the GGD Amsterdam has been visited 68,892 times by MSM since 1984.

In 2023, 682 participants were in follow-up (meaning that they had at least one study visit in the year 2022 or 2023), of whom 635 were actively participating through at least one visit in the year 2023.



In this chapter, we report on the MSM actively participating in the ACS in 2023:

- 38 newly enrolled in the cohort in 2023, of whom all 38 were MSM without HIV and no MSM with HIV; with a median age of 35 years at inclusion were enrolled;
- The median age was 45 years at their last cohort visit in 2023;
- The majority was born in the Netherlands (83%), and a resident of Amsterdam (80%), respectively;
- 85% of the MSM had a college degree or higher.

The cohort of people who use or inject drugs (PWUD/PWID) – discontinued

Between 1984-2016, a total of 1,661 PWUD had been included in the ACS of whom 1,303 had at least two cohort visits (maximum 78 visits)². Study enrolment and data collection continued until 2014 and February 2016, respectively. Data and samples from these participants of this cohort are still being used for research. For more details, we refer to previous monitoring reports¹ and a few publications^{2,4-6}.

ACS biobank

The ACS biobank stores all samples (plasma/serum, peripheral blood mononuclear cells) taken in the context of the ACS study, at the Amsterdam UMC, location AMC. In addition to samples taken at routine ACS study visits, it also includes samples collected for sub-studies and affiliated studies embedded in the ACS.

Subgroup studies and affiliated studies

AGE_nIV cohort study

The AGE_nIV cohort study is a collaboration between the Amsterdam UMC, location AMC, Departments of Infectious Diseases and Global Health, the Amsterdam Institute of Global Health and Development, the GGD Amsterdam, and SHM. The AGE_nIV study was started in October 2010 and aims to assess the prevalence and incidence of a broad range of comorbidities, along with known risk factors for these comorbidities, in people with HIV aged 45 years and over. It also strives to determine the extent to which comorbidities, their risk factors and their relation to quality of life, differ between groups of people with and without HIV. Participants undergo a comprehensive assessment for comorbidities and completed a questionnaire at intake. Every two years, participants complete follow-up research questionnaires, and attend the GGD for body measurements and to provide a blood sample. So far six such study rounds have been completed.

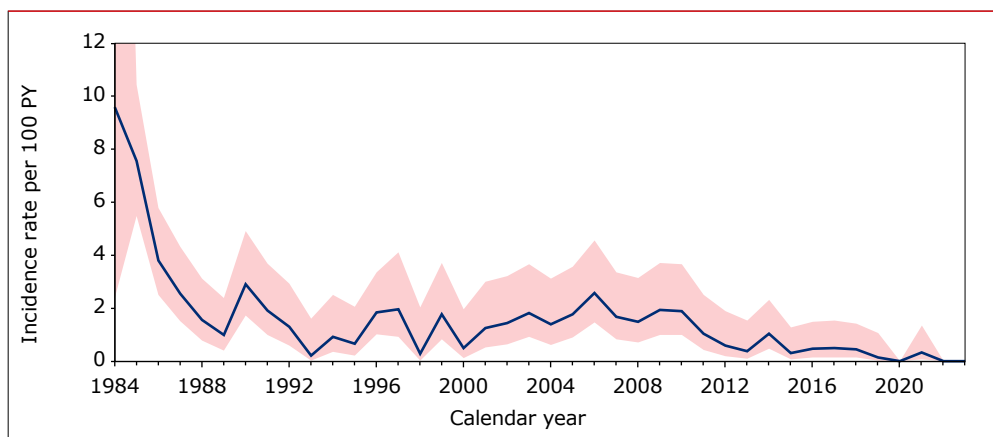
In total, 598 participants with HIV and 550 individuals without HIV were enrolled between October 2010 and September 2012. People with HIV (PWH) were included through the Amsterdam UMC, location AMC, HIV outpatient clinic, and participants without HIV but with similar sexual behaviour / drug use patterns via the Centre of Sexual Health Amsterdam (486) and the ACS (64). All participants were aged 45 years and over, and participants without HIV were as comparable as possible to participants with HIV with respect to age, gender, ethnicity, and risk behaviour. In 2023, the sixth round was completed, and the seventh round was started. In total, 410 participants without HIV had a sixth round visit.

ACS in 2023: HIV/STI and sexual behaviour among MSM

HIV incidence

The observed HIV incidence rate among MSM participating in the ACS has declined over time (*Figure 10.1*). Between 1985 and 1993 it declined significantly, then stabilised between 1993 and 1996, before rising in the period 1996 to 2009. Since 2009, the HIV incidence has decreased significantly. In 2022 and 2023, no MSM participating in the ACS seroconverted for HIV.

Figure 10.1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2023.





PrEP use

Use of PrEP has increased since 2015. Data on recent PrEP use was available for 490 MSM without HIV actively participating in the ACS in 2023, of whom 232 (47.3%) reported PrEP use in the preceding six months. Of these 232 PrEP users, 104 (44.8%) obtained PrEP through the national PrEP program at the Centre of Sexual Health, 99 (42.7%) through their GP; 13 (5.6%) through a PrEP study, 7 (3.0%) through an Internal Medicine specialist or a PrEP prescribing physician, and 6 (2.6%) obtained their pills through informal routes (e.g., *sexual or social networks, or online offered pills*); of the remaining 3 (1.3%) PrEP users, data on PrEP uptake route were not available.

STI screening

Since October 2008, all MSM participating in the ACS are routinely screened for bacterial STIs during their cohort visits (in addition to HIV testing). This conforms with the standard care offered by the Centre of Sexual Health Amsterdam. Chlamydia and gonorrhoea were detected by polymerase chain reaction techniques using urine samples and pharyngeal and rectal swabs. Syphilis was detected by *Treponema pallidum* haemagglutination assay.

In 2023, STI data were available from the Centre of Sexual Health Amsterdam for 639 MSM participating in the ACS. Of these 639 MSM, 129 (20.2 %) MSM had at least one positive bacterial STI test (79 (12.4%) gonorrhoea, 62 (9.7%) chlamydia and 13 (2.0%) syphilis). For MSM with and without HIV, 13 out of 37 (35.1%), and 116 out of 602 (19.3%), MSM had at least one positive bacterial STI test, respectively.

Following national PrEP guidelines, those who use PrEP are screened for STIs more often (i.e., 3-monthly) compared to those not using PrEP (i.e., 6-monthly). As the STI testing frequency differ between PrEP using and non-PrEP using participants, STI incidence rates are complex to compare between these groups and, therefore, are not reported here.

ACS 2023 research highlights

A genetic variation in fucosyltransferase 8 accelerates HIV-1 disease progression indicating a role for N-glycan fucosylation

Core fucosylation by fucosyltransferase 8 (FUT8) is an important posttranslational modification that impacts components of the immune system. Genetic variations in FUT8 can alter its function and could, therefore, play a role in the antiviral immune response and pathogenesis of HIV-1. This study analysed the effect of a single nucleotide polymorphism (SNP) in FUT8 on the clinical course of HIV-1 infection⁷. In the ACS, we observed that the presence of the minor allele of SNP rs4131564 in the FUT8 gene was associated with accelerated disease progression. Although we did not observe an effect of the SNP on T cell activation and functionality, this study underscoring a role for N-glycan fucosylation in HIV pathogenesis.

Noncanonical-NF- κ B activation and DDX3 inhibition reduces the HIV-1 reservoir by elimination of latently infected cells ex-vivo

HIV-1 continues to be a major global health challenge. Current HIV-1 treatments are effective but need lifelong adherence. An HIV-1 cure should eliminate the latent viral reservoir that persists in people living with HIV-1. Different methods have been investigated that focus on reactivation and subsequent elimination of the HIV-1 reservoir, and it is becoming clear that a combination of compounds with different mechanisms of actions might be more effective. In this study we targeted two host factors for the elimination of the viral reservoir: inhibitor of apoptosis proteins that control apoptosis and the DEAD-box helicase DDX3, facilitating HIV mRNA transport/translation⁸. We show in ex-vivo experiments using PBMC from ACS participants, that targeting of these host factors with SMAC mimetics and DDX3 inhibitors induce reversal of viral latency and eliminate HIV-1-infected cells.



Comprehensive harm reduction programs substantially reduce new HIV and viral hepatitis infections among PWID

Although the Netherlands, Canada and Australia were early adopters of harm reduction for PWID, their respective HIV and hepatitis C epidemics differ. This study⁵ using novel methodologies and data from three cities, Amsterdam, Vancouver and Melbourne, showed that dual engagement with needle and syringe exchange and opioid agonist therapy programs reduced the risk of HIV infection by 41% and the risk of hepatitis B and C infection by 76% and 72%, respectively, when compared to no or suboptimal engagement to these programs research. Study findings are also summarized and published in a policy brief⁹.

Mpox vaccination intention and uptake MSM participating in the ACS

In response to the 2022 mpox outbreak, vaccination was offered in the Netherlands to MSM at increased risk for mpox. Among the MSM participants of the ACS, we studied the intention to vaccinate, as well as e.g. beliefs, attitude, subjective norms, and perception of risk, in relation to self-reported vaccination uptake¹⁰. While this study found that the intention to vaccinate for mpox was high among MSM in the ACS, the high intent did not necessarily result in vaccine uptake. Mpox risk perception might have played a more pivotal role in getting vaccinated, which may be related to the evolution of vaccination eligibility criteria and accessibility to the vaccine.

Current and upcoming ACS research projects

Data collected within the ACS are used for multiple research projects at present. In the context of the COVID-19 pandemic, we are investigating the SARS-CoV-2 seroconversion among MSM participating in the ACS over time. Furthermore, data on alcohol and other substance use among these ACS participants have been analysed to estimate the frequency and its determinants of problematic and non-problematic substance use. We are updating estimates of HCV-infection incidence and spontaneous-clearance rates among the ACS participants, along with associated factors. Sexual behaviour including anal sex with casual and steady partners, in relation to both condom and PrEP use, is currently studied in greater detail. Regarding PrEP use, data on PrEP surfing, defined as using the PrEP status of sexual partners as HIV prevention strategy, are currently being analysed. Qualitative research to identify barriers and missed opportunities of PrEP-uptake, PrEP-care and PrEP-use among MSM with and without HIV and previous PrEP experience are ongoing. We are also planning to contribute to the mapping of the PrEP need, use, and care in Amsterdam; i.e. the PrEP cascade. More upcoming research is in preparation related to condom use and norms regarding condom use.

Furthermore, in the context of pandemic preparedness, the ACS team is working on a project to identify how *findable, accessible, interchangeable* and *reusable* (i.e. *FAIR*) the ACS data are, in order to make improvements in this where possible. Moreover, the ethical and legal barriers to starting (sub)studies within the ACS are examined, in order to arrive at a roadmap to quickly start a research project on an emerging disease.

Steering committee

In 2023 the steering committee gathered on five occasions. Seven proposals for use of ACS data or samples (serum/PBMC) were submitted to the committee: three from Experimental Immunology (Amsterdam UMC, location AMC), three from Medical Microbiology and Infection Prevention (Amsterdam UMC, location AMC), and one from the GGD Amsterdam. One proposal was an international collaboration with a group of Ulm University in Germany. Three proposals were collaborations within the ACS between the GGD and MMI Amsterdam UMC. The ACS reviewed the proposal and suggested minor revisions in some cases, after which all requests were approved.

Publications in 2023 that included ACS data

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1. Liza N. Coyer, Sex, drugs, PrEP and STI: Trends among men who have sex with men. 13 January 2023
2. Joanna Kaczorowska. Colonization, transmission and long-term dynamics of anelloviruses in humans. 13 April 2023
3. Cormac M. Kinsella. Computational discovery of viruses and their hosts. 11 September 2023
4. Silvia Achia Nieuwenburg - Early syphilis infection among men who have sex with men. 22 December 2023

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Amsterdam Cohort Studies (ACS) participants

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