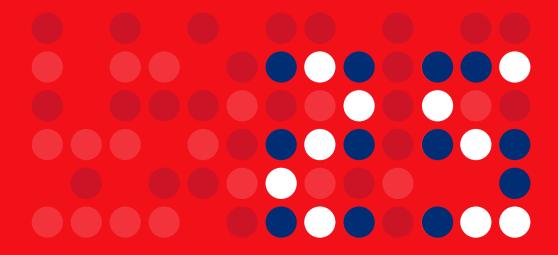


Human Immunodeficiency Virus (HIV) Infection in the Netherlands

HIV Monitoring Report

2025

Chapter 11: The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2024



11. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2024

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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/inject drugs (PWUD/PWID) was initiated in 1985 and discontinued in 2016.

In 2024, the cohort celebrated the milestone of 40 years of follow-up. 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 [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.

Collaborating institutes and funding

Within the ACS, the following institutes collaborated in 2024 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): Department of Medical Microbiology and Infection prevention,
 Laboratory of Experimental Virology (LEV), Experimental Immunology,
 Laboratory for Viral Immune Pathogenesis, and Internal Medicine (Department
 of Infectious Disease)
- Stichting hiv monitoring (SHM)



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 (*Rijksinstituut voor Volksgezondheid en Milieu - Centrum voor Infectieziektenbestrijding, 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 study protocol for the MSM cohort was approved by the Amsterdam UMC medical ethics committee in 2022.

The Amsterdam Cohort Studies (ACS)

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

In 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. During the 40-year follow-up period, minor changes in the inclusion criteria for ACS were introduced, mainly concerning HIV status and age. 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 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). Currently, eligible for enrolment are individuals of at least 16 years old, who were assigned male sex at birth and who have not undergone gender reassignment surgery, live in the Amsterdam area or are involved in MSM-related activities in Amsterdam, and who have had sex with at least one man in the preceding six months.

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.

All (sexual) behavioural data are collected by questionnaires, coordinated by the GGD Amsterdam, and clinical data (for PWH) are provided by SHM. Every 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.

As of 31 December 2024, 3,024 MSM have been included in the ACS since its initiation in 1984. These MSM contributed a total of 70,270 cohort visits at the GGD Amsterdam. Of these 3,024 MSM, 608 were living with HIV at entry into the study and 267 seroconverted for HIV during follow-up.

At 31 December 2024, 664 HIV-negative participants and 42 participants with HIV were in follow-up (meaning that they had at least one study visit in 2023 or 2024). Of these, 645 HIV-negative participants and 38 participants with HIV had at least one visit in 2024. 33 newly enrolled in the cohort in 2024, all MSM without HIV with a median age of 35 years at enrolment. After 2 years without any HIV seroconversions, two MSM seroconverted in 2024.

In this chapter, we report on the MSM actively participating in the ACS in 2024:

- The median age was 47 years at their last cohort visit in 2024;
- The majority was born in the Netherlands (84%) and a resident of Amsterdam (79%);
- 80% of the MSM had a college/university degree.



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

Between 1984 and 2016, a total of 1,661 PWUD had been included in the ACS of whom 1,303 had at least two cohort visits (the maximum number of visits was 78).¹ 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 reports², and publications.¹3·5

ACS biobank

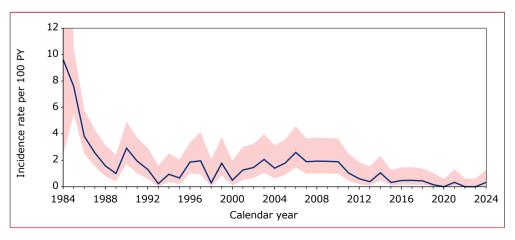
The ACS biobank, at the Amsterdam UMC, location AMC, stores all samples (plasma/serum, peripheral blood mononuclear cells) taken in the context of the ACS study. In addition to samples taken at routine ACS study visits, the biobank also contains samples collected for sub-studies and affiliated studies embedded in the ACS. Over the past 40 years, more than 350,000 samples have been stored for ongoing and future research.

ACS in 2024: 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 11.1). Between 1985 and 1993 HIV incidence declined significantly, then stabilized between 1993 and 1996, before rising again in the period 1996 to 2009. Since 2009, the HIV incidence decreased again. After two years of zero seroconversions, two participants seroconverted in 2024.





PrEP use

354/664 (53%) participants without HIV reported PrEP use in 2024. Of these, 185 (53.1%) obtained PrEP through the national PrEP program at the Centre of Sexual Health, 143 (40.4%) through their GP, 9 (2.5%) through an Internal Medicine specialist or another physician and 14 (4.0%) obtained their pills through informal routes (e.g. cross-border clinics, sexual or social networks, self-prescribed or online offered pills).

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 is in accordance with the standard care offered by the Centre of Sexual Health Amsterdam. Chlamydia and gonorrhoea were tested with nuleic acid amplification techniques using urine samples and pharyngeal and rectal swabs. Syphilis was screened for by *Treponema pallidum* haemagglutination assay.

In 2024, STI data were available from the Centre of Sexual Health Amsterdam for 671 MSM (with 1,649 visits including extra STI visits) participating in the ACS. Of these, 154 (23.0%) had at least one positive bacterial STI test (94 (14.0%) gonorrhoea, 75 (11.2%) chlamydia and 21 (3.1%) syphilis). For MSM with and without HIV, 11 out of 38 (28.9%), and 143 out of 633 (22.6%), MSM had at least one positive bacterial STI test, respectively.

Until August 2024, participants using PTEP were screened for STIs 3-monthly, whereas other participants were screened 6-monthly, according to national PTEP guidelines. Following the revised national PTEP guidelines, STI screening is now offered 6-monthly to both PTEP-users and those not using PTEP. Trends of any bacterial STI incidence among MSM without HIV, and stratified for PTEP use and no PTEP use, between 2009 and 2024 are shown in figure 11.2 and 11.3. The annual incidence rate of any bacterial STI for MSM without HIV increased over time (Figure 11.2). MSM who used PTEP in the preceding 6 months were diagnosed with STIs more often than MSM who did not (Figure 11.3).

Figure 11.2: Any bacterial STI incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM) without HIV with at least two study visits, 2009–2024.

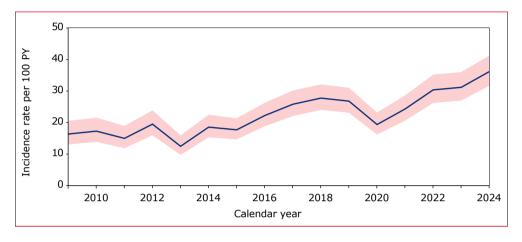
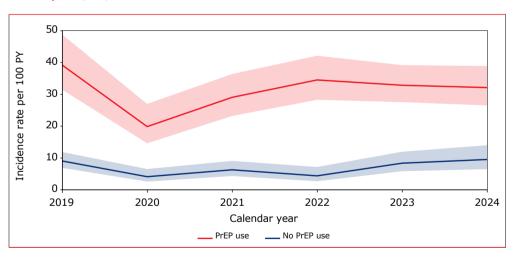


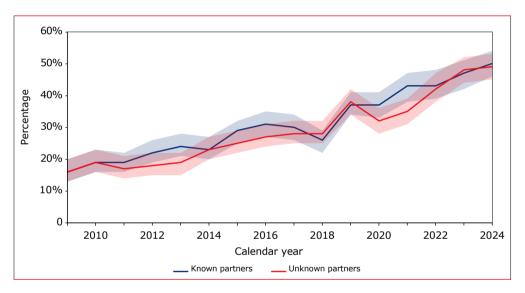
Figure 11.3: Any bacterial STI incidence per calendar year in the Amsterdam Cohort Studies (ACS) stratified by PrEP use in the preceding 6 months, among men who have sex with men (MSM) without HIV with at least two study visits, 2009-2024.



Sexual behaviour

Condomless anal sex with a casual partner was reported by 320 of 664 (48%) MSM without HIV in 2024. Trends in recent (i.e., in preceding 6 months) condomless anal sex among MSM without HIV continued to show an increase from 2009 onwards (Figure 11.4). Among 354 MSM using PrEP in 2024, 267 (75.4%) reported recent condomless anal sex in 2024. Among 291 MSM not using PrEP in 2024, 53 (18.2%) reported recent condomless anal sex.

Figure 11.4: Proportion of men reporting condomless anal sex (CAS) with casual partners per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM) without HIV with at least two study visits, 2009–2024.



ACS 2024 research highlights

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 other factors, e.g. beliefs, attitude, subjective norms, and perception of risk, in relation to self-reported vaccination uptake⁶. 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.



Influenza-like illness symptoms due to endemic human coronavirus reinfections are not influenced by the length of the interval separating reinfections

Little is known about the disease following human coronavirus reinfections occurring several years after the previous infection, once humoral immunity has waned. To investigate this, disease symptoms were monitored during human coronavirus reinfection intervals in the Amsterdam Cohort Studies. Importantly, we found no influence of reinfection interval length on the disease manifestation. We found that after a long period with no infection by a human coronavirus, the absence of immune-boosting does not make people more ill when they eventually do catch the virus. We conclude that, once a human coronavirus has been fully adapted to its host and the vast majority of people having been infected at least once, there may not be an urgent need to repeatedly vaccinate the general immunocompetent population against that human coronavirus.

Polyfunctionality and breadth of HIV-1 antibodies are associated with delayed disease progression

Despite the availability of effective treatment, HIV-1 still causes significant mortality and morbidity across the globe. Alternative ways for protection or treatment against HIV-1 are needed. Antibody-mediated effector functions could potentially contribute to the effectiveness of novel approaches. However, we need more information on which antibody properties are associated with these potential beneficial functions of antibodies. Studying antibody responses during natural HIV-1 infection can provide guidance on this topic. We identified several antibody properties that were associated with reduced HIV-1 disease progression in the Amsterdam Cohort Studies of individuals with untreated HIV-1. High levels of IgG1 and low levels of IgG2 and IgG4, broad and polyfunctional antibodies and interaction with immune proteins FcyRs and C1q, were all associated with delayed disease progression. Subsequently, effective strategies against HIV-1 will likely require multiple different components. The antibody properties described in this study can contribute to a more detailed bio-molecular roadmap for antibody-based strategies for HIV-1 prevention, therapy and cure.

HIV-1 vaccine field

One of the main goals of the HIV-1 vaccine field is the generation of recombinant envelope glycoprotein (Env) immunogens that can elicit protective broadly neutralizing antibody (bNAb) responses. The first-generation recombinant HIV-1 Env immunogens consisted of unstable complexes that expose non-neutralizing antibody (non-NAb) epitopes, which are normally not exposed on infectious viral Env. It took several years of iterative design to generate soluble SOSIP trimers of native-like Env immunogens. The basis of these immunogens are HIV-1 Env

sequences from the Amsterdam Cohort Studies. The essential SOSIP modifications include the truncation of gp41 at position 664, a disulfide bond (501C-605C) to covalently link the gp120 and gp41 subunits, an Ile-to-Pro mutation (I559P) to prevent conformational transitions to the post-fusion state and an RRRRRR (R6) multibasic motif to enhance furin cleavage. The determination of these Env SOSIP trimer structures led to a plethora of further structure-based stabilizing mutations and novel Env trimer designs. Significantly, several of these native-like Env SOSIP trimers that are based on an Env sequence from the Amsterdam Cohort Studies, are currently being tested in phase I clinical vaccine trials.⁹⁻¹¹

Energy demanding RNA and protein metabolism drive dysfunctionality of HIV-specific T cell changes during chronic HIV infection

A small group of people with HIV (PWH) is able to control their infection without the need of antiviral therapy. In these so-called long-term non-progressors (LTNP), an effective CD8 T cell response is thought to maintain the immunological control of HIV. Here we studied the virus specific CD8 T cells from PWH from the Amsterdam Cohort Studies to gain molecular insights in CD8 T cell functionality in HIV infection. We observed that HIV-specific CD8 T cells from PWH who are unable to control their infection, show a functional impairment already during the asymptomatic phase of infection and differed from LTNP with regards to cytokine signaling and mitochondrial function. Targeting the mitochondria to improve the immune function, indeed showed an increase in IFNY release upon antigen stimulation. This indicates that treatment strategies to enhance the cellular metabolism and improve mitochondrial function may improve virus specific CD8 T cell responses and aid a controlling immune response in chronic infection.

Current and upcoming ACS research projects

Data collected within the ACS are currently used for multiple research projects. As 2024 marked the 40th anniversary of the study, we are studying trends in HIV and STI incidence and sexual behaviour over 40 years of follow-up. Sexual behaviour, including anal sex with casual and steady partners, in relation to both condom and PrEP use, is currently being studied in greater detail. Trends and current norms and negotiation experiences regarding condom use are also being analysed.

Quantitative and qualitative studies on individual and contextual motives underlying choices of HIV prevention strategies (including condoms, PrEP, and viral load sorting) are ongoing, and conducted in collaboration with Maastricht University. Data on PrEP surfing, defined as using the PrEP status of sexual partners as HIV prevention strategy, are currently being analyzed. Data of ACS are also used in research into the mapping of the PrEP need, use and care in Amsterdam;



i.e. the PrEP cascade. More research is in preparation on doxyPEP, as well as on motivations for MSM to use long-acting PrEP modalities and preferences regarding implementation.

In the context of the COVID-19 pandemic, we are investigating 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 nonproblematic substance use.

Data Preparedness of the Amsterdam Cohort Studies

The ACS team supports the Open Science movement, and aims to improve the findability, accessibility, interoperability, and reusability (FAIR) of the ACS (meta) data. In 2024, to enhance the Open Science principles within the ACS, the "Data Preparedness of the Amsterdam Cohort Studies" project was undertaken. This project was funded by ZonMw under the "Stimuleringsimpuls FAIR-data voor Pandemische Paraatheid" program (grant number 10710032320005; € 50,000; 2024).

The evaluation of the FAIRness of the ACS (meta)data revealed that improvements could be made in all four aspects of FAIR: findability, accessibility, reusability and interoperability. Key improvement points include: (1) making metadata findable and accessible by making the metadata available in the National Health Catalogue, (2) publishing data request forms and the ACS data request process online, and (3) making the data dictionary accessible online again. This includes the launch of a new website for researchers: www.acsresearch.nl. Initial steps have been taken to implement these improvements. The evaluation of obstacles in requesting ACS data showed that a clearer understanding of participant consent over the years is needed. This would help to efficiently determine whether data requests can be processed, and for which participants and periods. Additionally, the evaluation revealed that the data request procedure was unclear for both internal and external researchers. The solution to this issue involved revising the data application form and developing a flowchart of the data request procedure, so researchers know wat to expect in advance.

As a continuation of the project, we aim to further implement the identified improvements regarding the findability, accessibility, interoperability, and reusability of the ACS (meta)data. A follow-up grant application has been submitted to NWO (Open Science Infrastructure | Open Science NL) for this purpose.

Steering committee

In 2024 the steering committee met four times. Ten proposals for use of ACS data or samples (serum/PBMC) were submitted to the committee: four from Experimental Immunology (EXIM, Amsterdam UMC, location AMC) and six from Medical Microbiology and Infection Prevention (MMI, Amsterdam UMC, location AMC). Two proposals were collaborations between EXIM Amsterdam UMC and Radboud MC. The ACS reviewed the proposals and suggested major revisions in some cases, after which all requests were approved.

Research Meetings

An internal ACS research meeting with Amsterdam UMC and GGD researchers was held on April 11th, 2024, during which six ACS researchers presented research findings.

Publications in 2024 that included ACS data

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PhD theses in 2024 that included ACS data

- Lisa van Pul. Host-control of HIV: balance between immunity and immunopathology. 2 February 2024
- Tom Caniels. Guided by glycoproteins: insights from antibody responses enable viral vaccine design. 11 March 2024
- Marloes Grobben. Polyfunctional antibodies in viral disease; Detecting, controlling and preventing infections with antiviral antibodies. 15 March 2024
- M. Ferdyansyah Sechan. New Insights into Protective Immunity against Endemic Human Coronaviruses. 9 September 2024
- Mitch Brinkkemper. Multivalent nanoparticle vaccine candidates against sarbecoviruses and HIV-1. 8 November 2024

Acknowledgements

Amsterdam Cohort Studies (ACS) participants

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