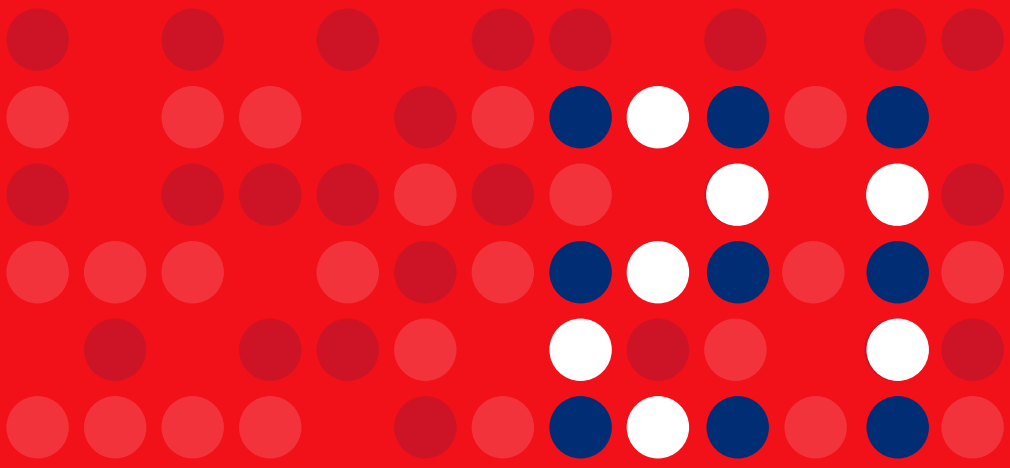
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2021

Chapter 8: The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2020



8. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2020

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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 (PWID) was initiated in 1985. In 2019, the cohorts reached 35 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 35 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 the past decade, research on the epidemiology of other blood-borne and sexually-transmitted infections (STIs), and their interaction with HIV, has also become an important component of the ACS research programme.

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, and other infections such as 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, different institutes collaborate to bring together data and biological sample collections, and to conduct research. These include the Public Health Service of Amsterdam (*Gemeentelijke Gezondheidsdienst Amsterdam*, GGD Amsterdam): Department of Infectious Diseases, Research and Prevention; the Amsterdam University Medical Centres (Academic Medical Centre [AMC] site): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease); the Emma Kinderziekenhuis (paediatric

HIV treatment centre); stichting hiv monitoring (SHM); MC Jan van Goyen: Department of Internal Medicine; and the HIV Focus Centrum (DC Klinieken Lairesse). From the start, Sanquin Blood Supply Foundation has been involved in the ACS and, since 2007, has provided financial support for the biobank of viable peripheral blood mononuclear cells (PBMC) at the AMC's Department of Experimental Immunology. 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 was approved by the AMC medical ethics committee in 2007 for the MSM cohort, and in 2009 for the PWID cohort.

The ACS in 2020

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

As of 31 December 2020, 2,901 MSM were included in the ACS. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding medical history, sexual behaviour and drug 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. Of the 2,901 MSM, 607 were HIV-positive at entry into the study and 263 seroconverted for HIV during follow up. In total, the GGD Amsterdam has been visited 63,154 times by MSM since 1984.

In 1984-85, men who had had sexual contact with a man in the preceding six months were enrolled, independent of their HIV status. In the period 1985-88, HIV-negative 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 preceding six months. In 1988-98, the cohort also included MSM living with HIV. In 1995–2004, 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, HIV-negative men 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 additional efforts to recruit young HIV-negative MSM (aged 30 years or younger).

HIV-seroconverters within the ACS remained in the cohort until 1999, when follow up of a selection of MSM living 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. All behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

In 2020, which was affected by the COVID-19 pandemic, 699 HIV-negative and 50 MSM living with HIV were active participants at the GGD Amsterdam; in other words, they visited the cohort at least once in 2019 or 2020. All 50 MSM living with HIV filled out behavioural questionnaires. In 2020, two new HIV-negative MSM, who were 28.7 and 48.4 years of age at inclusion, were recruited. The median age of the total group of MSM in active follow up was 44.5 (interquartile range [IQR] 34.0-55.9) years at their last cohort visit. The majority were born in the Netherlands and were residents of Amsterdam (83.4% and 88.8%, respectively). In total, 77.2% of the participants had a college degree or higher.

The cohort of people who use/used injecting drugs (PWID)

As of 31 December 2016, 1,680 PWID were included in the ACS and contributed 28,194 visits. In 2014, the cohort was closed to new participants. Regular follow up of PWID continued until February 2016. All PWID who had ever participated in the ACS were then invited for an end-of-study interview and follow up was successfully ended in July 2016. Of the 1,680 PWID, 323 were HIV-positive at entry, and 99 seroconverted during follow up. The last HIV seroconversion was seen in 2012. By 31 December 2016, 576 deaths had been confirmed among PWID. The median age of the PWID who visited the ACS in 2016 was 55 (IQR 49-59) years, 8.1% had attained a high level of education, and 63.4% were born in the Netherlands.

ACS biobank

The ACS visits, together with data collected from several subgroup studies and affiliated studies embedded in the ACS, have resulted in a large collection of stored samples. The ACS biobank includes plasma/serum and PBMC samples collected

within the context of the ACS cohorts. It also contains samples collected during the Primo-SHM study (a national randomised study, which started in 2003, comparing the effects of early, temporary antiviral therapy with that of no therapy among patients who presented with primary HIV-1 infection at the AMC HIV outpatient clinic, and ACS seroconverters). These samples are stored at the Amsterdam University Medical Centres (AUMC), location AMC. At present, biological samples are still being collected prospectively for Primo-SHM participants visiting the AUMC, location AMC clinic, until one year after they have recommenced therapy. The ACS biobank also contains plasma and PBMC samples that were collected from HIV-positive and HIV-exposed children at the Emma Kinderziekenhuis in the AUMC, location AMC, before 2008. All stored samples are available for ACS research.

Subgroup studies and affiliated studies

AGE$_h$IV cohort study

The AGE$_h$IV cohort study (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) was started in October 2010. The aim of the study is to assess the prevalence and incidence of a broad range of comorbidities, along with known risk factors for these comorbidities, in individuals living with HIV aged 45 years and older, and to determine the extent to which comorbidities, their risk factors and their relation to quality of life differ between HIV-positive and HIV-negative groups.

Participants undergo a comprehensive assessment for comorbidities and complete a questionnaire at intake, as well as research follow-up questionnaires every subsequent two years. In total, 598 HIV-1-positive participants, and 550 HIV-negative individuals, completed a baseline visit between October 2010 and September 2012. HIV-1-positive participants were included through the AUMC, location AMC, HIV outpatient clinic, and HIV-negative participants from similar risk groups through the STI clinic at the GGD Amsterdam (486), or the ACS (64). All participants were aged 45 years or older and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. In 2020, the fifth round (2019-20) was concluded; 376 HIV-positive and 437 HIV-negative participants had a fifth visit. Due to the COVID-19 pandemic, the sixth round of the AGE$_h$IV study did not start in 2020.

In 2020, a two-year COVID-19 sub-study was started in this cohort. Participants were invited to complete a short online questionnaire and provide a blood sample for the measurement of SAR-CoV-2 antibodies. The first round of this sub-study

took place in September-October 2020, and the next rounds are scheduled for 2021 and 2022. In the first round of the sub-study 548 people participated (312 HIV-negative and 236 HIV-positive participants). Analyses are underway.

H2M cohort studies

From 2010 to 2013, the H2M (HIV and human papillomavirus [HPV] in MSM) cohort study was conducted in a subset of the HIV-negative (n=459) and HIV-positive (n=40) active participants in the ACS, and also among patients of the STI clinic of GGD Amsterdam and MC Jan van Goyen. The aim of the Aidsfonds-supported study was to compare the prevalence, incidence, and clearance of HPV infections associated with high-risk (hr) of anal cancer between HIV-negative and HIV-positive MSM.

Since September 2014, the collection of anal and genital swabs has been resumed in all consenting ACS participants. The key aim of this second study (the H2M3 study), which builds on the H2M study, is to examine long-term incidence and clearance of anal and penile hrHPV infections. As assays to determine HPV infection status are very costly, samples have been collected and stored, but not yet analysed. In 2020, collection of anal and penile swabs from ACS participants continued. Swabs have been stored at the laboratory of the Public Health Service of Amsterdam for future studies.

AMPrEP project in H-TEAM

The Amsterdam pre-exposure prophylaxis (AMPrEP) project was a prospective, longitudinal, open-label demonstration study, conducted in 2015-20. The aim was to assess the uptake and acceptability of daily, versus event-driven, pre-exposure prophylaxis (PrEP) among MSM and trans people at increased risk of HIV infection, as part of a comprehensive HIV-reduction package offered at a large centre for sexual health.

In total, 374 MSM and two trans persons were enrolled between August 2015 and May 2016 at GGD Amsterdam's centre of sexual health, including 35 ACS participants who chose to participate in the AMPrEP project. Participants were asked to attend a follow-up visit one month after their PrEP initiation visit, and return every three months thereafter. At every visit, participants filled out questionnaires on risk behaviour, adherence, and general wellbeing, and were screened for STIs and HIV. AMPrEP follow-up was completed on 1 December 2020. By then, all participants still in care and willing to continue PrEP were included in the national PrEP pilot at a centre for sexual health of their choice.

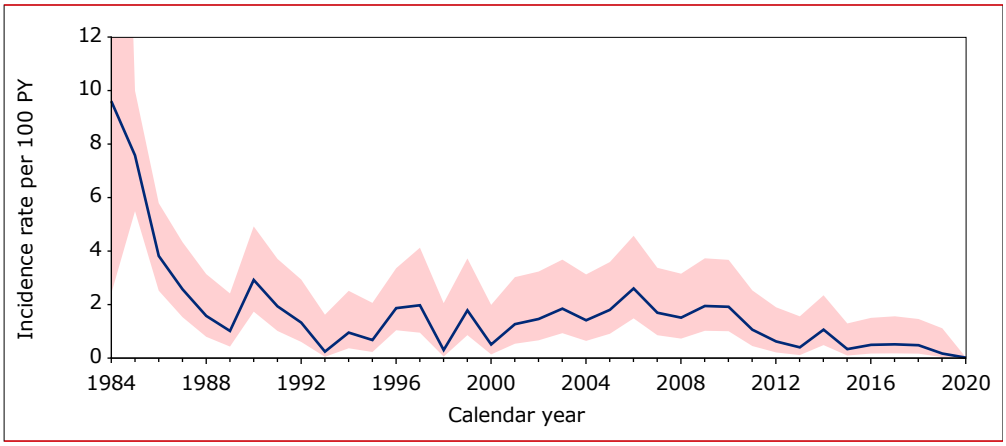
The AMPrEP project was part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic[a].

The HIV epidemic

HIV incidence

The observed HIV incidence rate among MSM participating in the ACS has changed over time. In 1985-93, it declined significantly, it then stabilised in 1993-96, before rising in 1996-2009. From 2009 onwards, the HIV incidence decreased significantly. In 2020, none of the MSM participating in the ACS seroconverted for HIV. *Figure 8.1* shows the yearly-observed HIV incidence rate for MSM from the start of the ACS through 2020.

Figure 8.1: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2020.*



Transmission of therapy-resistant HIV strains

In 2020, there was no surveillance conducted of transmitted, drug-resistant HIV-1 strains.

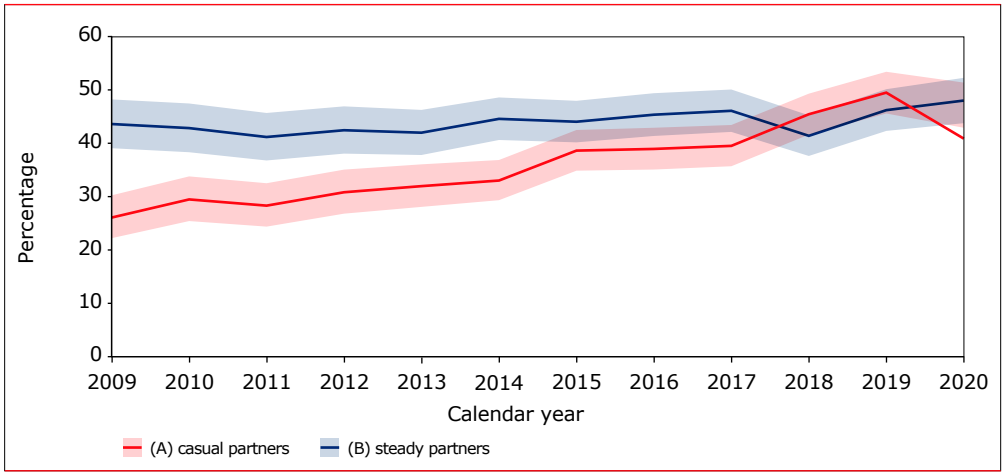
Risk behaviour of MSM in ACS

Condomless anal sex (CAS) with a steady or casual partner was reported by 207/453 (45.7%) and 150/453 (33.1%) HIV-negative MSM, respectively, during their cohort visit in 2020. Trends in CAS among HIV-negative MSM participating in the ACS, continued to show a gradual increase from 2009 onwards (*Figure 8.2*). Use of PrEP

a *www.hteam.nl*

has also increased since 2015. In 2020, 210/684 (30.7%) HIV-negative MSM actively participating in the ACS reported PrEP use in the preceding six months. CAS with a steady or casual partner was reported by 95 (45.2%) and 170 (81.0%) PrEP-using MSM, respectively. Among non-PrEP-using MSM, those figures were 166 (48.1%) and 98 (26.8%), respectively.

Figure 8.2: Trend in the proportion of condomless anal sex (CAS) with: (A) casual partners, and (B) steady partners, among HIV-negative men who have sex with men (MSM) in the Amsterdam Cohort Studies (ACS), 2009-2020.



STI screening among MSM in ACS

Since October 2008, all MSM participating in the ACS have been routinely screened for bacterial STIs during their cohort visits. This conforms with the standard care offered by the GGD STI clinics. Chlamydia and gonorrhoea were detected by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Syphilis was detected by Treponema pallidum haemagglutination assay (TPHA). In 2020, 42/533 (7.8%) MSM in the ACS tested positive for one of the bacterial STIs at least once during a cohort visit. For HIV-negative and HIV-positive MSM, these figures were 36/498 (7.2%) and 6/35 (17.1%), respectively. Since the STI testing frequency differs between PrEP-using (quarter-annually) and non-PrEP-using participants (semi-annually), STI incidence rates of these groups cannot be compared and, therefore, are not reported. In general, the incidence rate of a bacterial STI significantly increased between 2009-20.

Impact of COVID-19 on ACS

In 2020, the COVID-19 pandemic was a global public health threat. It also affected ACS data collection. In line with government measures to reduce the spread of COVID-19, the ACS was closed during periods of lockdown, from March to May 2020 and after December 15 2020. The only participants allowed to visit the cohort were those who a) had been warned by a partner that they may have contracted an STI, b) had run out of PrEP pills, or c) had STD symptoms. These criteria have led to selection bias. Moreover, sexual behaviour changed during the COVID-19 restrictions; the majority of participants (73%) reported fewer casual sex partners and 11% stopped using PrEP. Before the COVID-19 pandemic, 78% reported sexual contact with a casual sex partner; this figure dropped to 38% during the pandemic[1]. These behavioural changes may have affected STI transmission.

ACS 2020 research highlight

HIV-negative men who have sex with men (MSM) have an altered T-cell phenotype and bioenergy metabolism

CD8+ T-cell responses are crucial for our immune defence against viruses. However, continued antigen exposure, due to recurrent or chronic infections, induces T-cell exhaustion and senescence, affecting T-cell functionality. We have previously reported that higher levels of T-cell activation, exhaustion, and terminal differentiation are found in MSM, compared to blood donors. In Kruize et al., the bioenergy metabolism of T-cells in MSM was also impaired. Immunological and metabolic changes are associated with high-risk behaviour and cytomegalovirus (CMV) infection. This indicates that the higher antigen exposure in this group of MSM is likely to induce immunological changes in the T-cell population[2].

Immune activation correlates with, and predicts CXCR4 coreceptor tropism switch in HIV-1 infection

Coreceptor switching of HIV (from CCR5 to CXCR4 using HIV) is strongly associated with accelerated disease progression. We investigated the relationship between immunological factors and HIV coreceptor switching in a) a cross-sectional study in HIV-1 subtype C (HIV-1C)-infected patients, and b) in a longitudinal HIV-1 subtype B (HIV-1B) seroconverter cohort (ACS). In Connell et al., T-cell activation preceded and independently predicted X4-coreceptor switching providing novel insights into HIV-1 pathogenesis[3].

SARS-CoV-2 research within the ACS

Seasonal coronavirus protective immunity is short-lasting

A key unsolved question in the current coronavirus disease 2019 (COVID-19) pandemic is the duration of acquired immunity. Insights from infections with the four seasonal human coronaviruses might reveal common characteristics applicable to all human coronaviruses. We monitored healthy individuals for more than 35 years. Edridge et al. found that reinfection with the same seasonal coronavirus occurred frequently at 12 months after infection[4].

Sexual behaviour and its determinants during COVID-19 restrictions among men who have sex with men (MSM) in Amsterdam

We investigated the impact of Dutch COVID-19 restrictions on sexual behaviour and HIV/sexually-transmitted infection (STI) rates among MSM participating in the ACS. ACS participants complete a questionnaire on sexual behaviour and are tested for HIV/STI biannually. They may also be tested at the STI clinic between study visits. On 29 May 2020, ACS participants were invited to complete an online questionnaire on health, COVID-19 risk perceptions, and sexual behaviour. Determinants of reporting casual sex partners (CSP) during COVID-19 restrictions were examined using logistic regression. Of 683 MSM, 353 (52%; median age 47 years; IQR 38-53 years) completed the questionnaire. The majority (73%) reported a reduction in the number of their CSP during COVID-19 restrictions. In total, 133 MSM (38%), reported CSP during COVID-19. In multivariable analysis, these men were associated with not having a college/university degree, being single, lower perceived importance of avoiding COVID-19, number of CSP before COVID-19, and current preexposure prophylaxis use (P, 0.05 for all). During COVID-19 restrictions, no HIV infections were diagnosed, and the STI positivity rate was 8%. Since COVID-19, the number of CSP has decreased among MSM, and there may have been a temporary reduction in HIV/STI transmission. Some MSM were not fully compliant to social distancing regulations and reported CSP, which was related to prior sexual behaviour and low perceived importance of avoiding COVID-19. For these men, it is important to maintain accessible HIV/STI-related testing and care during times of lockdown[1].

Current and upcoming ACS research projects

Currently, data collected within the ACS are used for multiple research projects. HCV-infection incidence and spontaneous-clearance rates, along with associated factors, are in the process of being estimated and identified.

Blood samples of ACS participants are among others being analysed for SARS-CoV-2 antibodies. Seroprevalence of SARS-CoV-2 antibodies and their determinants are to be determined.

Since 2019, PrEP has been widely available for eligible individuals. To optimise current PrEP eligibility criteria, uptake, and retention, data from ACS is being used. Previously, trials on prophylactic use of antibiotics before or after sex to prevent bacterial STIs have been conducted outside the ACS cohort. Currently, within the Netherlands, the option to take antibiotics in this way is not offered due to insufficient evidence on its efficacy and safety. Current informal use, intentions, and beliefs regarding prophylactic antibiotics among ACS participants are to be determined.

In trials, long-acting oral and injectable PrEP were found to be as safe and effective as the (short-acting oral) PrEP that is currently available in the Netherlands. Attitudes towards and intentions to switch to long-acting PrEP among ACS participants are to be determined.

Using qualitative research methods, the definition and aspects of sexual wellbeing are to be determined using data of, among others, ACS participants.

Steering committee

In 2020, the steering committee met five times (since April 2020, these have been online meetings). Seven proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: one from Experimental Immunology (AUMC), four from Laboratory of Experimental Virology (AUMC), and two from the GGD Amsterdam. Three of the proposals were collaborations with groups outside the ACS: one proposal from the RIVM, and one from Medical Microbiology (AUMC), both in collaboration with the GGD Amsterdam, and one was a collaboration with a diagnostic company. Six requests were approved after minor revisions recommended by the ACS steering committee. One proposal was initially rejected, but, following major revisions, the proposal was eventually approved (in 2021).

Publications in 2020 that included ACS data

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Femke Lambers – Changing perspectives. Hepatitis C virus infection in key population. *https://dare.uva.nl/search?identifier=a9983539-893c-47ec-832a-b4947d68640c*

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