

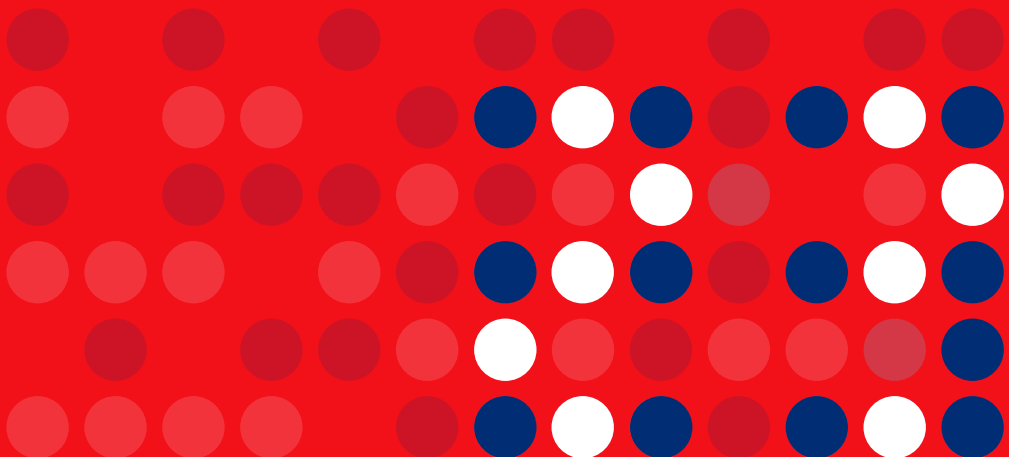
Human Immunodeficiency Virus (HIV)  
Infection in the Netherlands



# HIV Monitoring Report

# 2023

**Chapter 8: The Amsterdam Cohort Studies (ACS)  
on HIV infection: annual report 2022**



## 8. The Amsterdam Cohort Studies (ACS) on HIV infection: annual report 2022

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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.

In 2022, the cohorts reached 38 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 38 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 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.

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.



### Collaborating institutes and funding

Within the ACS, the following different institutes collaborate 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, Research and Prevention;
- **Amsterdam University Medical Centres, location Academic Medical Centre (AMC)** (Amsterdam UMC): Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Disease);
- **Emma Kinderziekenhuis** (Paediatric HIV treatment centre);
- **Stichting HIV Monitoring** (HIV Monitoring Foundation, SHM);
- **MC Jan van Goyen** Department of Internal Medicine; and
- **HIV Focus Centrum** (DC Klinieken Lairese)

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 Amsterdam UMC medical ethics committee in 2022 for the MSM cohort, and in 2009 for the PWID cohort.

### ACS in 2022

#### 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 in the study. From 2005 to 2022 men without HIV of all age groups were 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, continued 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 2022, 2,950 MSM have been included in the ACS since its initiation in 1984. Every three to six months, participants complete a standardised questionnaire designed to obtain data regarding: medical history, (sexual) behaviour and substance use, underlying psychosocial determinants, health care use, signs of depression and other psychological disorders, and demographics. In total, the GGD Amsterdam has been visited 67,636 times by MSM since 1984. Moreover, blood is collected for diagnostic tests and storage at the ACS biobank. Of the 2,950 MSM, 607 were living with HIV at entry into the study and 265 seroconverted for HIV during follow-up.



In 2022, the cohort had 615 active participants: 578 MSM without HIV and 37 MSM with HIV.

Active participation is defined as having had at least one study visit in the year 2021 or 2022. The total group of MSM in active follow-up had the following characteristics:

- 30 newly enrolled MSM without HIV, with a median age at inclusion of 32 years [interquartile range (IQR)=25-37];
- The median age was 46 years (IQR=35-53) at their last cohort visit in 2022;
- The majority was born in the Netherlands and was a resident of Amsterdam (83.7% and 89.4%, respectively);
- 78.4% had a college degree or higher.

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

Between 1984-2016, 1,680 PWUD/PWID were included and followed in the ACS, who contributed 28,194 visits. Study enrolment and data collection continued until 2014 and February 2016, respectively. An end-of-study interview was offered to those who had ever participated in the ACS. Median age of the PWUD/PWID cohort was 55 (IQR=49-59) years in 2016, 8.1% had attained a high level of education, and 63.4% were born in the Netherlands. Of the 1,680 PWUD/PWID, 323 were living with HIV at entry, and 99 HIV seroconverted during follow-up. The last HIV seroconversion was seen in 2012. In total, 576 deaths had been confirmed among PWID.

### **ACS biobank**

The ACS biobank stores all samples [plasma/serum, peripheral blood mononuclear cells (PBMC)] 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<sub>n</sub>IV cohort study**

The AGE<sub>n</sub>IV 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<sub>n</sub>IV 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.

In total, 598 participants with HIV-1 and 550 individuals without HIV were enrolled between October 2010 and September 2012. People with HIV-1 were included through the Amsterdam UMC, location AMC, HIV outpatient clinic, and participants without HIV from similar risk groups engaged via the Centre of Sexual Health Amsterdam (n=486) and the ACS (n=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 2021, the sixth study round was started, and during 2022, 206 participants without HIV came for a sixth round visit. The sixth round will be completed in 2023.

In 2020, a two-year COVID-19 sub-study was initiated within the AGE<sub>h</sub>IV cohort, with as main aim to assess whether the risk for SARS-CoV-2 infection, the immune response to natural infection and to vaccination, and the disease burden (including mental health) differed between participants with and those without HIV. Five consecutive 6-monthly visits were conducted between September 2020 and October 2022. During each visit, participants completed a questionnaire and provided a blood sample to measure SARS-CoV-2 immune responses. Additionally, in the four to 13 weeks after their last dose of the primary COVID-19 vaccination, participants were invited for an additional blood draw to measure SARS-CoV-2 vaccine immune responses. In total, 567 participants (241 participants with HIV-1 and 326 participants without HIV) were included in this COVID-19 sub-study, of whom 441 (195 with and 246 without HIV) participated in the additional post-vaccination blood draw<sup>a</sup>. This sub-study has now been completed. Three papers have been published and a fourth is in preparation; the results are discussed below.

In the first paper using data collected within the AGE<sub>h</sub>IV COVID-19 sub-study, B-cell and T-cell responses to SARS-CoV-2 vaccines among 195 participants with HIV-1 and 246 controls without HIV were compared. Participants with HIV-1 showed strong immune responses, similar to controls, with no significant differences in key markers. Factors like prior SARS-CoV-2 infection, mRNA vaccine type, and demographics influenced vaccine response, but HIV status did not, offering reassurance about vaccine effectiveness in participants with HIV-1 with access and a good response to HIV treatment (Verburgh-2023-Microbiol Spectr). In the second paper, the impact of social distancing on health-related quality of

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<sup>a</sup> The first manuscript on the cumulative SARS-CoV-2 incidence in this cohort was published in December 2021: <https://academic.oup.com/ijid/article/225/11/1937/6470931>; (Verburgh et al., 2022)



life and depressive symptoms among 214 participants with HIV-1 and 285 controls without HIV was examined. The majority of both groups reported social distancing important and adhered to these measures. Irrespective of HIV status, concerns about contracting COVID-19 negatively affected participants' perceived current health and increased risk of depressive symptoms (Schaaf-2022-JAIDS). Lastly, in the third paper, the incidence of SARS-CoV-2 infection, risk factors and SARS-CoV-2 nucleocapsid antibody levels between 241 participants with HIV-1 (99.2% virally suppressed) and 326 participants without HIV were compared. The cumulative incidence of SARS-CoV-2 infection by April 2021 was similar in both groups (13.4% in HIV-positive and 11.6% in HIV-negative individuals). Younger age and African origin were associated with a higher risk of COVID-19 infection, but HIV status did not impact this risk. Moreover, among those with COVID-19 infection, HIV status did not affect antibody levels, with only self-reported fever being associated with higher antibody levels. To conclude, participants with HIV-1 with suppressed HIV-viremia and adequate CD4 counts, defined as  $\geq 500/\mu\text{L}$  and no clinically relevant immunodeficiency, had similar risk of SARS-CoV-2 acquisition and antibody levels with comparable controls (Verburgh-2022-J Infect Dis).

### Primo-SHM Trial

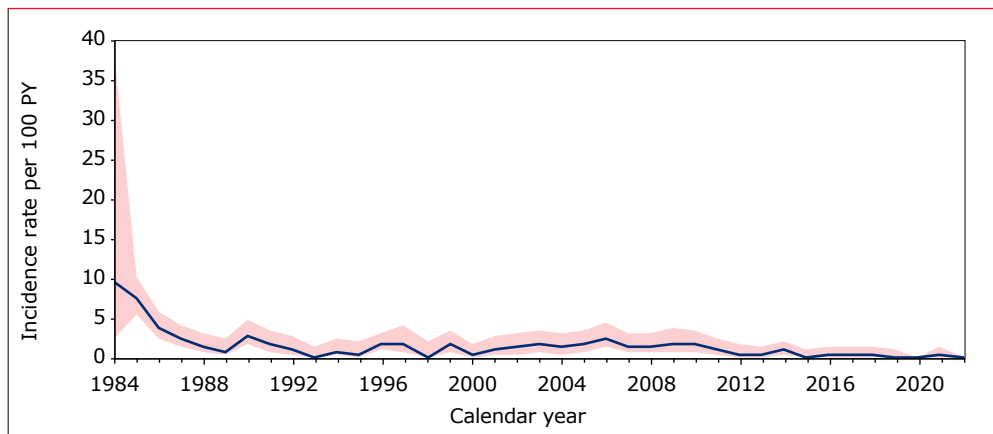
The Primo-SHM study is a national, randomised study that started in 2003. It compares the effects of early, temporary antiviral therapy with that of no therapy among (1) individuals presented with primary HIV-1 infection at the Amsterdam UMC HIV outpatient clinic, and (2) ACS participants who seroconverted for HIV during follow-up. Samples collected within the Primo-SHM study are stored at the ACS biobank at the Amsterdam UMC.

## ACS in 2022: HIV/STI and sexual behaviour among MSM

### HIV incidence

The estimated HIV incidence rate among MSM participating in the ACS has declined over time (*Figure 8.1*). 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, no MSM participating in the ACS seroconverted for HIV.

**Figure 8.1:** HIV incidence rate among men who have sex with men participating in the Amsterdam Cohort Studies (ACS), 1984–2022



### Sexual behaviour

Condomless anal sex with a steady and casual partner was reported by 176 out of 416 (42.3%) and 191 out of 292 (65.4%) MSM without HIV, respectively, during their cohort visit in 2022. Trends in recent (i.e., in preceding 6 months) condomless anal sex among MSM without HIV participating in the ACS continued to show an increase from 2009 onwards (*Figure 8.2*). More specifically, proportion of MSM reporting condomless anal sex showed a higher increase for casual partners than for steady partners in recent years. Use of PrEP has also increased since 2015. Data on recent PrEP use was available for 539 MSM without HIV actively participating in the ACS, of whom 199 (36.9%) reported PrEP use in the preceding six months. Of these 199 PrEP users, 80 (40.2%) obtained PrEP through the national PrEP program at the Centre of Sexual Health, 68 (34.2%) through their general practitioner; 18 (9.1%) through a PrEP study (e.g., *AmPrEP*, *DISCOVER*), 5 (2.5%) through an Internal Medicine specialist or another PrEP prescribing physician, and 5 (2.5%) obtained their pills through informal routes (e.g., *sexual or social networks, or online offered pills*). Of the remaining 23 PrEP users, data on PrEP uptake route were not available. Of the 199 MSM using PrEP, 174 (87.4%) reporting recent anal sex with either steady or casual partners (*Figure 8.3*). Among those, condomless anal sex with a steady and casual partner was reported by 74 (42.5%) and 138 (79.3%), respectively. Among the 379 MSM not using PrEP, 278 (81.2%) reported recent anal sex. Of these, 115 (41.4%) and 62 (22.3%) reported condomless anal sex with a steady and a casual partner, respectively.





Figure 8.2: Trends in the proportion of condomless anal sex with (A) casual and (B) steady sexual partners among men who have sex with men without HIV participating the Amsterdam Cohort Studies (ACS), 2009–2022

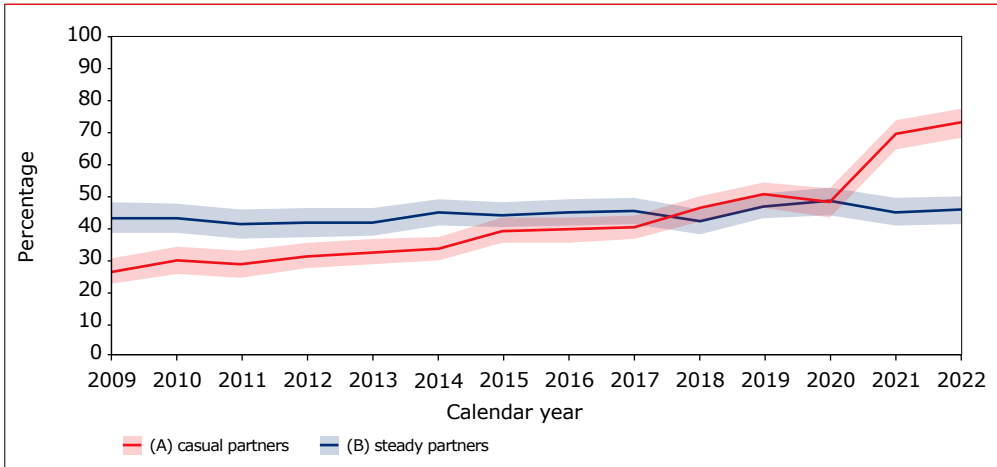
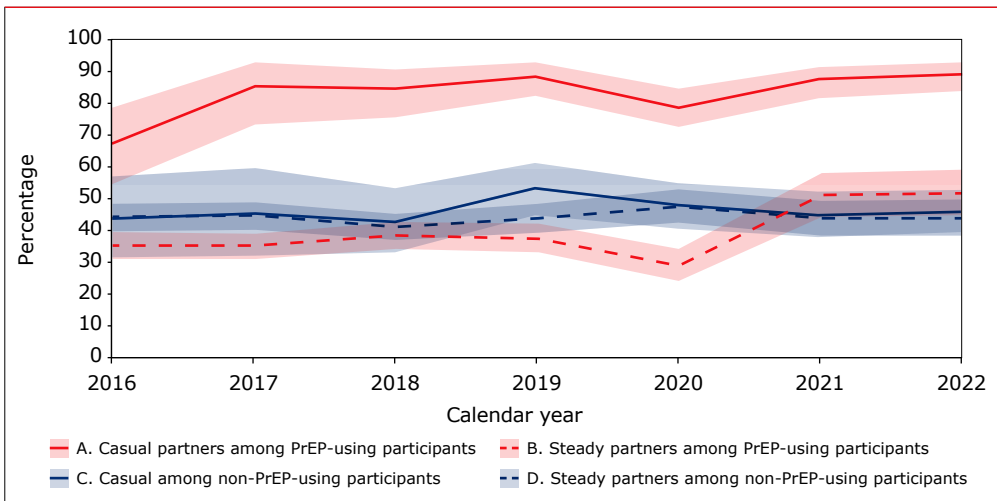


Figure 8.3: Trends in the proportion of condomless anal sex with casual and steady sexual partners among PrEP-using and non-PrEP-using men who have sex with men without HIV participating the Amsterdam Cohort Studies (ACS), 2016–2022



### 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.

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 cannot be compared and, therefore, are not reported here. In general, the incidence rate of a bacterial STI among MSM in the ACS significantly increased in the period 2009 to 2019. In 2022, STI data were available for 556 MSM actively participating in the ACS. Of these 556 MSM, 43 (7.7%) MSM had at least one positive bacterial STI test. For MSM with and without HIV, these figures were 3 out of 34 (8.9%), and 40 out of 522 (7.7%), respectively.

### ACS 2022 research highlights

#### A highly virulent variant of HIV-1 circulating in the Netherlands

HIV-1 virulence is most commonly measured by the concentration of viral particles in blood plasma and the dynamics of CD4+ T cell decline in peripheral blood. Successful treatment with antiretroviral drugs suppresses viral load and interrupts the decline in CD4 counts that would otherwise lead to AIDS. Viral load dynamics and CD4 cell decline could however change with the emergence of a new viral variant(s). We screened for new viral variants and found a distinct, new subtype-B HIV-1 variant. Within two Dutch studies (the BEEHIVE project and the ATHENA project, among the participants also ACS with HIV-1), we identified 107 individuals with this distinct subtype-B viral variant, among 7,272 Dutch participants with HIV tested in total, and this variant was rarely found in countries outside the Netherlands. The variant is more virulent as participants with HIV carrying this variant experienced double the rate of CD4+ cell count declines than expected. Fortunately, upon HIV-1 treatment these individuals showed the same CD4 cell recovery as participants with HIV not carrying the more virulent variant of HIV-1 (Wymant-2022-Science).



### **Trends in sexual behaviour and STI after initiating PrEP in MSM from Amsterdam**

MSM who initiate PrEP may report increased condomless anal sex and number of partners, and, consequently, more often acquire STIs. Using data from the ACS, sexual behavior and STI incidence among MSM after PrEP-initiation were compared with controls not initiating PrEP. MSM who initiated PrEP between January 1, 2015 and December 31, 2019 were compared to MSM who did not use PrEP. This study found that 228 out of the 858 (26.6%) MSM initiated PrEP; and 198 out of 228 (86.8%) were matched to a control. Before PrEP-initiation, end-points increased over time in both groups, although not significantly. Among MSM who initiated PrEP, casual partner number as well as odds of condomless anal sex, receptive condomless anal sex and anal STI were higher post- than pre-PrEP-initiation. These differences were not found among the controls. These findings support frequent STI screening and counseling in MSM who use PrEP (Coyer-2022-AIDS Patient Care STDS).

### **Eligibility criteria vs. need for PrEP: a reappraisal among MSM in Amsterdam**

To reconsider PrEP eligibility criteria towards MSM with highest HIV-risk, PrEP need (in other words: risk of acquiring HIV infection) was assessed using ACS data from 2011-2017 for all MSM not using PrEP. Among 810 MSM, 22 HIV-infections and 436 anal STIs were diagnosed during follow-up. Chemsex, condomless anal sex with a casual partner and anal STI were significantly associated with the highest risk for acquiring HIV. Chemsex and condomless anal sex with a casual partner were also significantly associated with anal STI, as was younger age and group sex. This study shows that chemsex should be an additional PrEP eligibility criterion in order to further optimizing HIV prevention (De La Court-2022-Epidemiol Infect).

### **Current and upcoming ACS research projects**

Data collected within the ACS are used for multiple research projects at present. Estimates of HCV-infection incidence and spontaneous-clearance rates, along with associated factors, are in the process of being updated. Data on PrEP surfing, defined as using the PrEP status of sexual partners as HIV prevention strategy, are being collected and will be analysed thereafter. From May 2022, the first mpox cases were reported in Europe, and over half of those diagnosed with mpox in the Netherlands were found in Amsterdam. Since vaccine campaigns are commonly leveraged by high vaccine intention, ACS data are being used to assess the impact of intention to vaccinate and other factors on mpox vaccination uptake. Also, those who were vaccinated against mpox were invited for additional blood draw in order to assess the immune response post-vaccination. Moreover, data on alcohol and other substance use have been collected in the ACS over the preceding years. Analysis of these data have been initiated in order to estimate the frequency and its determinants of problematic and non-problematic substance use in the context

of the COVID-19 pandemic. Furthermore, qualitative data collection and analysis in order to identify barriers and missed opportunities of PrEP-uptake, PrEP-care and PrEP-use among MSM with HIV and previous PrEP experience are ongoing. Additionally, ACS participants can participate in a qualitative study on sexualized drug use (i.e., chemsex) among MSM, conducted by GGD Amsterdam.

### Steering committee

In 2022 the steering committee gathered on four occasions. On March 22, a meeting with Amsterdam UMC and GGD Amsterdam researchers was held to discuss the future of the ACS, and how ACS fits in the ongoing and future research lines of the research groups. Ten proposals for use of ACS data or samples (serum/PBMC) were submitted to the committee: three from Experimental Immunology (Amsterdam UMC, location AMC), four from Medical Microbiology and Infection Prevention (Amsterdam UMC, location AMC), and one from the GGD Amsterdam. Two proposals were a collaboration with a group outside the ACS; National Institute for Public Health and the Environment (RIVM) and UMC Utrecht in collaboration with the GGD Amsterdam. The ACS reviewed the proposal and suggested minor revisions in some cases, after which all requests were approved.

### Publications in 2022 that included ACS data

1. Romijnders KAGJ, de Groot L, Vervoort SCJM, Basten MGJ, van Welzen BJ, Kretzschmar ME, Reiss P, Davidovich U, Rozhnova G. The perceived impact of an HIV cure by people living with HIV and key populations vulnerable to HIV in the Netherlands: A qualitative study. *Journal of virus eradication*. Mar 2022. 8, p. 1-7
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7. Timmerman AL, Kaczorowska J, Deijs M, Bakker M, van der Hoek L. Control of Human Anelloviruses by Cytosine to Uracil Genome Editing. *mSphere.* 2022 Dec 21;7(6):e0050622. doi: 10.1128/msphere.00506-22. Epub 2022 Nov 14. PMID: 36374042; PMCID: PMC9769745.
8. Xiridou M, Heijne J, Adam P, Op de Coul E, Matser A, de Wit J, Wallinga J & van Benthem B (2022). How the Disruption in Sexually Transmitted Infection Care Due to the COVID-19 Pandemic Could Lead to Increased Sexually Transmitted Infection Transmission Among Men Who Have Sex With Men in The Netherlands: A Mathematical Modeling Study. *Sexually transmitted diseases*, 49(2), 145–153. <https://doi.org/10.1097/OLQ.0000000000001551>
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15. van Schooten J, Farokhi E, Schorcht A, van den Kerkhof TLGM, Gao H, van der Woude P, Burger JA, Meesters TGR, Bijl T, Ghalaiyini R, Turner HL, Dorning J, van Schaik BDC, van Kampen AHC, Labranche CC, Stanfield RL, Sok D, Montefiori DC, Burton DR, Seaman MS, Ozorowski G, Wilson IA, Sanders RW, Ward AB, van Gils MJ. Identification of IOMA-class neutralizing antibodies targeting the CD4-binding site on the HIV-1 envelope glycoprotein. *Nat Commun.* 2022 Aug 3;13(1):4515. doi: 10.1038/s41467-022-32208-0. PMID: 35922441
16. Kaczorowska J, Cicilionytė A, Wahdaty AF, Deijs M, Jebbink MF, Bakker M, van der Hoek L. Transmission of anelloviruses to HIV-1 infected children. *Front Microbiol.* 2022 Sep 16;13:951040. doi: 10.3389/fmicb.2022.951040. PMID: 36187966; PMCID: PMC9523257.
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### PhD theses in 2022 that included ACS data

1. Hanne M.L. Zimmermann, HIV prevention in the biomedical era: A psychosocial investigation among men who have sex with men, 9 February 2022
2. Eline van Dulm-Freriks, Antibiotic resistance in specific sociodemographic groups: Implications for public health, 21 January 2022
3. Anna Schorcht, HIV-1 vaccine candidates based on envelope glycoproteins from infected individuals in Amsterdam, 9 June 2022
4. Jelle van Schooten, Fine-mapping HIV-1 antibody responses to guide vaccine design, 9 September 2022
5. Marlies van Haaren, Antiviral monoclonal antibodies inform vaccine design, 14 September 2022

