The Amsterdam Cohort Studies on HIV infection: annual report 2014

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Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were 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 drug users (DU) was initiated in 1985. In 2014, the cohorts reached 30 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 30 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 recent years, the focus has shifted to also include the epidemiology and natural history of other blood-borne and sexually transmitted infections (STI) among the participants in the ACS.

From the beginning, research in the ACS has taken a multidisciplinary approach (epidemiology, social science, virology, immunology and clinical medicine). This unique collaboration has been very productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection. This expertise has contributed directly to advances in prevention, diagnosis, and management of HIV infection.

As of 31 December 2014, 2,649 MSM and 1,680 injecting and non-injecting drug users were included in the ACS. Every three to six months, participants complete a standardised questionnaire designed to obtain information regarding medical history, sexual and drug use behaviour, underlying psychosocial determinants, healthcare use, depression, psychological disorders, and demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, also HIV-negative drug users), and blood is collected for diagnostic tests and storage. The ACS have been conducted in accordance with the ethical principles set out in the declaration of Helsinki, and participation in the ACS is voluntary; written informed consent (the most recent version was approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the DU cohort) is obtained from each participant.

Of the 2,649 MSM, 606 were HIV-positive at entry into the study, and 246 seroconverted during follow up. Of the 1,680 DU, 323 were HIV-positive at entry, and 99 seroconverted during follow up. By 31 December 2014, 562 DU had died, and several other participants had

been asked to leave the study or had left at their own request. In total, the Public Health Service of Amsterdam (Gemeentelijke Gezondheidsdienst Amsterdam; GGD Amsterdam) was visited 54,811 times by MSM and 27,777 times by DU.

Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together the data and biological sample collections and to conduct research. These include the GGD Amsterdam (Infectious Diseases Cluster, Department of Research), the Academic Medical Center (AMC) of the University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, Internal Medicine, Division of Infectious Diseases, HIV treatment centre, Emma Kinderziekenhuis), University Medical Center Utrecht (UMCU, Department of Immunology), Stichting HIV Monitoring (SHM), the Jan van Goyen Medical Centre (Department of Internal Medicine) and the HIV Focus Centre (DC Klinieken) Amsterdam. From the start, Sanquin Blood Supply Foundation has been involved in the ACS and, until 2007, research in the ACS was conducted by the Department of Clinical Viro-Immunology at Sanquin Research. Sanquin financially supports the maintenance of the biobank of viable peripheral blood mononuclear cells (PBMC) at the Department of Experimental Immunology at the AMC. In addition, there are numerous collaborations between the ACS and other research groups both within and outside of the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu, CIb-RIVM).

The ACS in 2014

The cohort of men having sex with men

Until 1995, 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 previous six months. During the period 1995–2004, only HIV-negative men aged ≤30 years with at least one male sexual partner in the previous six months could enter the study. Since 2005, recruitment has been open to HIV-negative MSM of all ages with at least one sexual partner in the preceding six months. HIV-seroconverters within the ACS remained in the cohort until 1999, when follow up of a selection of HIV-positive MSM was transferred to the Jan van Goyen Medical Center. In 2003, the 'HIV Onderzoek onder Positieven' (HOP) protocol (HIV Research in Positive Individuals) was initiated. Individuals with a recent HIV infection at study entry at the GGD Amsterdam and HIV seroconverters within the cohort return for follow up at the GGD Amsterdam or at an HIV treatment centre. 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 2014, 613 HIV-negative, and 47 HIV-positive MSM were in active follow up within the ACS (6-monthly visits to the GGD Amsterdam for STI testing, including HIV, and filling in behavioural questionnaires, according to the HOP protocol for HIV-positive individuals and HIV-negative protocol for HIV-negative individuals). The median age of the MSM was 40.5 years (interquartile range [IQR] 34.9-46.5), 7.6% were non-Dutch, and 79.8% had attained a high level of education. The majority of the participants (84.8%) were residents of

Amsterdam. Additional efforts to expand the HIV-negative cohort resulted in 97 newly recruited HIV-negative participants in 2014.

Apart from the HIV-positive MSM visiting the GGD Amsterdam, two groups of HIV-positive MSM are also followed outside the GGD Amsterdam:
1) The HIV-positive MSM who were transferred from the GGD Amsterdam to the Jan van Goyen Medical Centre in Amsterdam in 1999. In 2014, 17 were still being followed at the Jan van Goyen Medical Centre and 109 at the HIV Focus Centrun in Amsterdam. Behavioural questionnaires were filled in by 25 MSM.
2) HIV-positive MSM who were included into the HOP protocol, but not visiting the GGD Amsterdam. In 2014, 38 MSM were followed in an HIV treatment centre other than the Jan van Goyen Medical Centre or HIV Focus Centrum and filled in a behavioural questionnaire.

The cohort of drug users
In 2014, DU included in the ACS were divided into two groups, in line with the advice issued by the scientific advisory board in 2013. Group 1 consists of DU visiting the GGD Amsterdam once a year to complete questionnaires without testing and blood sampling. In 2014, there were 224 DU in active follow up in this group. Group 2, the focus group, consists of DU who are 1) HIV positive; 2) hepatitis C (HCV) seroconverters; 3) multiple-exposed, non-infected with HIV and HCV, and 4) a random control group. This group visited the GGD Amsterdam twice a year for testing and blood sampling and to fill out questionnaires, as in the years before. In 2014, 89 DU were in active follow up in this focus group. The cohort has been closed since January 2014. Therefore, no new participants were recruited in 2014. The median age of the DU was 52.3 years (IQR 45.9-56.6), 12.5% were non-Dutch, and 6.5% had attained a high level of education. Two hundred and thirty-eight (96.0%) were residents of Amsterdam.

Subgroup studies and affiliated studies

AGEhiV Cohort Study
The AGEhiV Cohort Study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health, and 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 co-morbidities and known risk factors for these co-morbidities in HIV-infected patients aged ≥45 years, and to determine the extent to which co-morbidities, their risk factors and their relation to quality of life differ between HIV-infected and uninfected groups. Participants undergo a comprehensive assessment for co-morbidities and fill in a questionnaire at intake and 2 years afterwards.

In total, 598 HIV-1-infected participants and 550 HIV-uninfected individuals completed a baseline visit between October 2010 and September 2012. HIV-1-infected participants were included through the AMC HIV outpatient clinic and HIV-uninfected participants from the same HIV exposure groups were included through the STI clinic of the GGD Amsterdam (n=486) or the ACS (n=64). All participants were aged ≥45 years and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. By the end of 2014, the

first follow up had been completed, and 498 HIV-1-infected participants and 482 HIV-uninfected individuals had returned for their second visit.

ACS biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies, have resulted in a large collection of stored samples.

The ACS biobank includes plasma and peripheral blood mononuclear cell samples collected within the context of the Primo-SHM study (a national randomised study on the effects of early temporary antiviral therapy as compared to no therapy among patients who presented with primary HIV-1 infection at the AMC outpatient clinic and ACS seroconverters). These samples are stored at the AMC. At present, the biological samples are still being collected prospectively for Primo-SHM participants visiting the AMC clinic until one year after they have recommenced therapy.

The ACS biobank also includes plasma and PBMC samples that were collected from both HIV-infected and HIV-exposed children at the Emma Kinderziekenhuis in the AMC until 2008. These are also stored at the AMC. Currently, no new samples are being collected within the ACS setting. All stored samples are available for ACS research.

The HIV epidemic

HIV incidence

6 MSM participating in the ACS seroconverted for HIV in 2014. The observed HIV incidence among MSM has remained relatively stable in recent years and was 1.07 per 100 person years in 2014. The HIV incidence in drug users has been stable since 2008, with less than one case per 100 person years. As follow up was restricted to a selection of DU in 2014 and inclusion of new DU stopped, the yearly observed incidence of DU can only be presented until 2013. Figures 9.1 and 9.2 show the yearly observed HIV incidence rates for MSM and DU from the start of the ACS through 2014 and 2013, respectively.

Transmission of therapy-resistant HIV strains

In 2014, surveillance of transmission of drug-resistant HIV-1 strains was performed for six MSM seroconverters who had their first visit after being found to be HIV-positive in 2014, and for two MSM who were seropositive at study entry. None of the individuals were infected with a virus harbouring resistance-associated mutations in the protease and reverse transcriptase genes. In all individuals, naturally occurring sequence variation was found in the protease gene. HIV-1 subtypes were determined by phylogenetic analysis: seven individuals harboured subtype B HIV-1 strains; one had a mosaic virus containing subtype A and unknown sequences.

Highly active antiretroviral therapy (HAART) uptake

Of all 211 HIV-positive MSM from the ACS visiting the HIV Focus Centrum, the Jan van Goyen Medical Centre or one of the other HIV treatment centres in the Netherlands in 2014,

treatment data were available for 205 men. Of these, 199 (97%) received some form of antiretroviral therapy. Of the 204 MSM for whom viral load results were available in 2014, 197 (87%) had a viral load of <50 copies/ml (assays M2000rt). Of the 29 HIV-positive DU who visited the GGD Amsterdam in 2014 and for whom treatment data were available, 26 (90%) received some combination of antiretroviral therapy. Of the 29 DU for whom viral load results were available, 27 (93%) had an undetectable viral load (≤150 copies/ml [assay: M2000rt]) at their latest visit.

Human papillomavirus in MSM

The H2M (HIV and HPV in MSM) study is a successful collaboration between the CIb-RIVM, the GGD Amsterdam, the Jan van Goyen Medical Centre, HIV Focus Centrum, VU University Medical Center (VUmc), and the AMC. The study aims to compare the prevalence, incidence, and clearance of high-risk (hr) human papillomavirus (HPV) infections between HIV-negative and HIV-infected MSM.

The participants were recruited from three sites: the ACS (n=520; mostly HIV-negative), the STI clinic at the GGD Amsterdam (n=120; all HIV-infected), and the Jan van Goyen Medical Centre/ HIV Focus Centrum (n=160; all HIV-infected). Recruitment was carried out in 2010 and 2011, and participants were followed for 24 months. Participants provided self-collected swabs from the anus and penile shaft, as well as oral rinse-and-gargle specimens. These were tested for the presence of HPV DNA and, if positive, HPV types were determined. Serum was tested for L1 HPV antibodies.

During the two-year follow-up period, a high incidence of hrHPV infections was observed, and the incidence was significantly higher in HIV-infected compared to HIV-uninfected men; this was the case for both anal and penile infections. We did not find an effect of CD4 count (curent or nadir) on incidence or clearance.

The study is now being continued in two separate studies. In the HIV-infected population, potential predictors for high-grade anal intra-epithelial neoplasia are being examined. This study, the H2M2, is an Aids Fonds-supported project, and a collaboration between the GGD Amsterdam, the CIb-RIVM, and the AMC. In the HIV-negative population, long-term incidence and clearance of anal and penile infections are being examined (H2M3 study).

Risk behaviour of MSM in ACS

Information from the questionnaires completed by 613 HIV-negative MSM during cohort visits in 2014 showed higher proportions of unprotected anal intercourse (UAI) with steady partners (39.5%) compared to casual partners (25.2%). Trends in UAI among HIV-negative MSM who are participants in the ACS, especially UAI with casual partners, continue to show a gradual increase from 1996 onwards. (Figure 9.3)

Risk behaviour of DU in ACS

As follow up was restricted to a selection of DU in 2014 and inclusion of new DU stopped, trends in risk behaviour of DU can only be presented until 2013. In HIV-negative DU, reports of both injection and borrowing needles significantly declined over the period 1985-2013.

Reports of high-risk sexual behaviour at follow-up visits decreased before 1996, then remained relatively stable until 2005, and further decreased to approximately 22% in 2013. Reports of STI have remained relatively stable at approximately 1% in recent years (see Figure 9.4)

STI screening among MSM in ACS

Since October 2008, all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Cases of syphilis are detected by Treponema pallidum haemagglutination assay (TPHA). In 2014, a total of 668 MSM from the ACS were screened for STI. The overall prevalence of any STI was 9.2% (113/1,230).

ACS 2014 research highlights

The ability of the human immunodeficiency virus type 1 (HIV-1) to replicate in its target cells is influenced by numerous host factors that act at different steps of the viral replication cycle. On the one hand, HIV-1 exploits many host factors to successfully replicate, while on the other hand several host factors can potentially restrict viral replication. Recently, a new type of host factor was described that plays a more complex role in HIV-1 infection. These factors help HIV-1 to avoid innate recognition by limiting the production of viral nucleic acids and replication of the virus in its target cells.

The exonuclease TREX1 shields HIV-1 from recognition by innate immune receptors, thereby preventing a type I interferon response. We studied the role TREX1 in the clinical course of HIV-1 infection by analysing the effect of genetic variation in Trex1 on HIV-1 disease progression in the ACS. The single nucleotide polymorphism (SNP) rs3135941 in TREX1 was associated with accelerated disease progression, independent of the CCR5-Δ32 genotype and human leukocyte antigen (HLA) alleles. In vitro, the SNP rs3135941 in Trex1 was associated with increased HIV-1 replication in PBMCs, which might explain the association between this SNP and accelerated disease progression in HIV-1 infected individuals(181).

The innate cytosolic DNA sensor IFI16 senses incomplete viral DNA transcripts in resting CD4+ T cells, resulting in a pro-inflammatory response that ultimately leads to the death of the abortively-infected resting CD4+ T cell. We analysed whether genetic variation in the IFI16 gene affects the clinical course of HIV-1 infection in the ACS population. We observed that SNP rs1417806 in IFI16 is associated with increased CD4+ T cell counts at set point and with a delayed HIV-1 disease progression (182). This suggests that IFI16 does affect HIV-1 pathogenesis, especially during the early phase of infection. Despite more than 30 years of intensive research, no HIV-1 vaccine candidate is capable of establishing strong and durable protective immunity. In particular, the induction of broadly-reactive neutralising antibodies is high on the wish list for an HIV-1 vaccine. Broadly reactive neutralising antibody activity against HIV-1 generally takes 2-4 years to develop in an HIV-1-infected patient. In the ACS there are two participants, infected via injecting drug use, who are so-called elite neutralisers and who had already developed broadly reactive neutralising activity in their first year post-seroconversion. It could be that virus strains infecting these elite neutralisers have unusually immunogenic broadly neutralising antibody epitopes. The characterisation of

envelope glycoproteins and the broadly neutralising antibodies from these elite neutralisers will be of great value in vaccine development to ultimately prevent HIV-1 infection(183).

Steering committee

In 2014, the steering committee met three times. Sixteen proposals for use of data and/or samples (serum/PBMC) were submitted to the steering committee: two from the AMC Experimental Immunology department, two from the AMC Experimental Immunology and Laboratory Experimental Virology together, ten from the AMC Medical Microbiology department, and two from the GGD Amsterdam. Thirteen requests were approved, some after revision, and three requests were denied. Three of the approved proposals were collaborations with groups outside the ACS, of which two were from abroad

Publications in 2014 that include ACS data

1. Booiman T, Kootstra NA. Polymorphism in IFI16 affects CD4(+) T-cell counts in HIV-1 infection. Int J Immunogenet 2014 Dec;41(6):518-20.

2. Booiman T, Setiawan LC, Kootstra NA. Genetic variation in Trex1 affects HIV-1 disease progression. AIDS 2014 Nov 13;28(17):2517-21.

3. de Vos AS, Prins M, Coutinho RA, van der Helm JJ, Kretzschmar ME. Treatment as prevention among injecting drug users; extrapolating from the Amsterdam cohort study. AIDS 2014 Mar 27;28(6):911-8.

4. Engsig FN, Zangerle R, Katsarou O, Dabis F, Reiss P, Gill J, Porter K, Sabin C, Riordan A, Fätkenheuer G, Gutiérrez F, Raffi F, Kirk O, Mary-Krause M, Stephan C, de Olalla PG, Guest J, Samji H, Castagna A, d'Arminio Monforte A, Skaletz-Rorowski A, Ramos J, Lapadula G, Mussini C, Force L, Meyer L, Lampe F, Boufassa F, Bucher HC, De Wit S, Burkholder GA, Teira R, Justice AC, Sterling TR, Crane HM, Gerstoft J, Grarup J, May M, Chêne G, Ingle SM, Sterne J, Obel N; for the Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery. Clin Infect Dis 2014 May;58(9):1312-21.

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7. Gijsbers EF, van Nuenen AC, de la Pena AT, Bowles EJ, Stewart-Jones GB, Schuitemaker H, Kootstra NA. Low level of HIV-1 evolution after transmission from mother to child. Sci Rep 2014 May 28;4:5079.

8. Grebely J, Dore GJ, Kim AY, Lloyd A, Shoukry NH, Prins M, Page K. The genetics of spontaneous clearance of hepatitis C virus infection: A complex topic with much to learn. Hepatology 2014 Apr 9 [Epub ahead of print].

9. Grebely J, Grady B, Hajarizadeh B, Page K and Dore GJ on behalf of the InC3 Study Group. Disease progression during advanced fibrosis: IL28B genotype or HCV RNA levels? Hepatology 2014; 59(4):1650-51.

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Theses in 2014 that include ACS data

Viviana Cobos Jiménez - 25 March 2014: HIV-1 infection in macrophages and genes involved throughout: Big eaters versus small invaders. Supervisor: Prof. T.B.H. Geijtenbeek (AMC); co-supervisor: Dr. N.A. Kootstra (AMC).

Jannie van der Helm - 26 September 2014: International epidemiological studies on HIV, HCV and STI. Supervisor: Prof. H.J.C. de Vries (AMC/GGD Amsterdam) and Prof. M. Prins (AMC/GGD Amsterdam); co-supervisor: Dr. R.B. Geskus (AMC/GGD Amsterdam).

Anneke de Vos - 28 October 2014: Heterogeneity in risk-behaviour matters; Modelling the spread of HIV and hepatitis C virus among injecting drug users. Supervisors: Prof. M.E.E. Kretzschmar (UMC Utrecht) and Prof. M. Prins (AMC/GGD Amsterdam)