

The Amsterdam Cohort Studies on HIV infection

Annual Report 2007

Introduction

The Amsterdam Cohort Study (ACS) on Human Immunodeficiency Virus (HIV) Infection and AIDS among homosexual men was initiated in 1984, followed shortly by the Amsterdam Cohort Study among Drug Users in 1985. The ACS, a collaboration of the Public Health Service Amsterdam (PHSA), the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation, and the University Medical Center Utrecht (UMCU), is part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment.

Until 31 December 2007, 2349 homosexual men (HM) and 1666 (injecting) drug users (DU) have been included in the ACS. Every 3 to 6 months, participants complete a standardized questionnaire designed to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognition, health care use, depression, psychological disorders, and demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, HIV-negative drug users as well), and blood is drawn for biologic and immunologic tests and storage.

Of the 2349 HM, 571 were HIV-positive at study entry, and 198 seroconverted during follow-up. For the 1666 DU, 323 were HIV-positive at study entry, and 96 seroconverted during follow-up. By 31 December 2006, 331 HM and 405 DU had died; several other participants were requested to leave the study or left at their own request. About 90% of participants who visited the ACS during a given calendar year returned for a follow-up visit the next year. In total, homosexual men visited PHSA 46,910 times, and injecting drug users made 23,948 visits.

ACS Open*

The ACS data are very suitable for universities and research institutes to teach students in epidemiology, biomedicine, and social science how to analyze longitudinal data sets. The concurrence of epidemiological and biomedical data also enables researchers from various disciplines to practice statistical techniques like survival, multi-level, and repeated measurement analyses. For this purpose, a data set that includes social-scientific, demographic, clinical, and biomedical information obtained from the participants of the ACS during the past 20 years of follow-up is available at www.amsterdamcohortstudies.org

*This project 'The opening up of the Amsterdam Cohort Studies (ACS Open)', has been funded by grant number 91104002 from MaGW and ZonMw.

The cohorts in 2007

Homosexual men

In 2007, 551 HM were followed at the PHSA of Amsterdam. Forty-nine of them were newly recruited in 2007. From 2005, recruitment was open for HM of all ages with at least one sexual partner in the preceding 6 months. Of the HM followed in 2007, 499 men were HIV-negative, and 52 men were HIV-positive. The HIV-positive men, of whom 36 were HIV seroconverters, were followed according to the HIV onderzoek onder positieven (HOP) protocol, which was initiated in October 2003 for HM who seroconverted or were HIV-positive at the time of entry into the study in the cohort of young HM after 1999.

Another 7 HIV-positive men were included in the HOP, but were exclusively followed in an HIV treatment centre outside the PHSA. From June 2006, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants were invited to participate in the ACS. By the end of 2007, 11 HIV discordant and 2 HIV-positive concordant couples had been included in this partner study.

In 2007, 226 HIV-positive HM who were recruited as part of the ACS before 1999 were seen at the Jan van Goyen Clinic or at one of the 22 other HIV treatment centres in the Netherlands. Sixty of them were HIV seroconverters. Plasma and cells from 54 of the 122 HIV-positive HM in active follow-up at the Jan van Goyen clinic in 2007 were stored. Of these, 33 were HIV seroconverters. The remaining 21 had been defined as 1) a slow or non-progressor or matched fast progressor in 1996; 2) HIV-positive for more than 10 years with a CD4 count greater than 400 cells/mm³ after 10 years of follow-up after a HIV-positive result without effective therapy.

Drug users

In 2007, 432 drug users were followed at the PHSA of Amsterdam: 61 were young drug users (aged 30 years or less) and recruited after 2000. In 2007, six new drug users were included because of the possibility that they had received hepatitis C treatment within the cohort (see below Dutch-C study). The cohort remained open to drug users less than 30 years of age who had used cocaine, heroin, or amphetamines at least 3 times a week in the 2 months preceding enrolment. Of the 432 DU followed in 2007, 64 were HIV-positive, of whom 24 seroconverted during follow-up in the ACS.

In 2005, within the DU cohort, a feasibility study was started to evaluate the possibility of hepatitis C virus (HCV) testing and treatment combined with methadone programs. As part of this project (the Dutch-C study), in 2007 15 HCV mono-infected DU in the cohort had initiated HCV therapy, resulting in a total group of 35 DU on HCV therapy.

Primo-cohort

In addition to the cohorts mentioned above, the ACS is now also including patients who present with primary HIV-1 infection at the PHSA or at the outpatient clinic of the AMC. A portion of these patients are enrolled in the so-called primo-SHM study, a randomized study on the effect of early quadruple antiviral therapy as compared to no therapy. By the end of 2006, 139 patients were already included

as primary-infection patients. In 2007, 33 new patients with acute HIV-1 infection were enrolled in the study. Specimens of blood are collected from these patients for storage of plasma and peripheral blood mononuclear cells (PBMC). Sampling is more frequent early after entry into the study. For the ACS, follow-up of individuals randomized to the no-treatment arm is discontinued 1 year after the start of highly active antiretroviral therapy (HAART) caused by a CD4+ T cell decline to <350 cells/ul blood. Similarly, follow-up is discontinued 1 year after reinitiation of HAART for individuals who have to reinitiate therapy because of a CD4 decline to <350 cells/ul blood after scheduled interruption of the first HAART regimen begun during the primary infection phase.

HIV incidence

Nine homosexual men and one drug user had a first positive test for HIV in 2007 after a previous negative test. The drug user had a first positive test in 2007, but a last negative test in 2003, and therefore the HIV-seroconversion date is assigned to 2005 (midpoint between both dates). The incidence of HIV is approximately 1.2 per 100 person-years among HM and less than 1 per 100 person-years among DU. Figures 1 and 2 show the yearly HIV incidence rates for homosexual men and drug users since the start of the ACS through 2007.

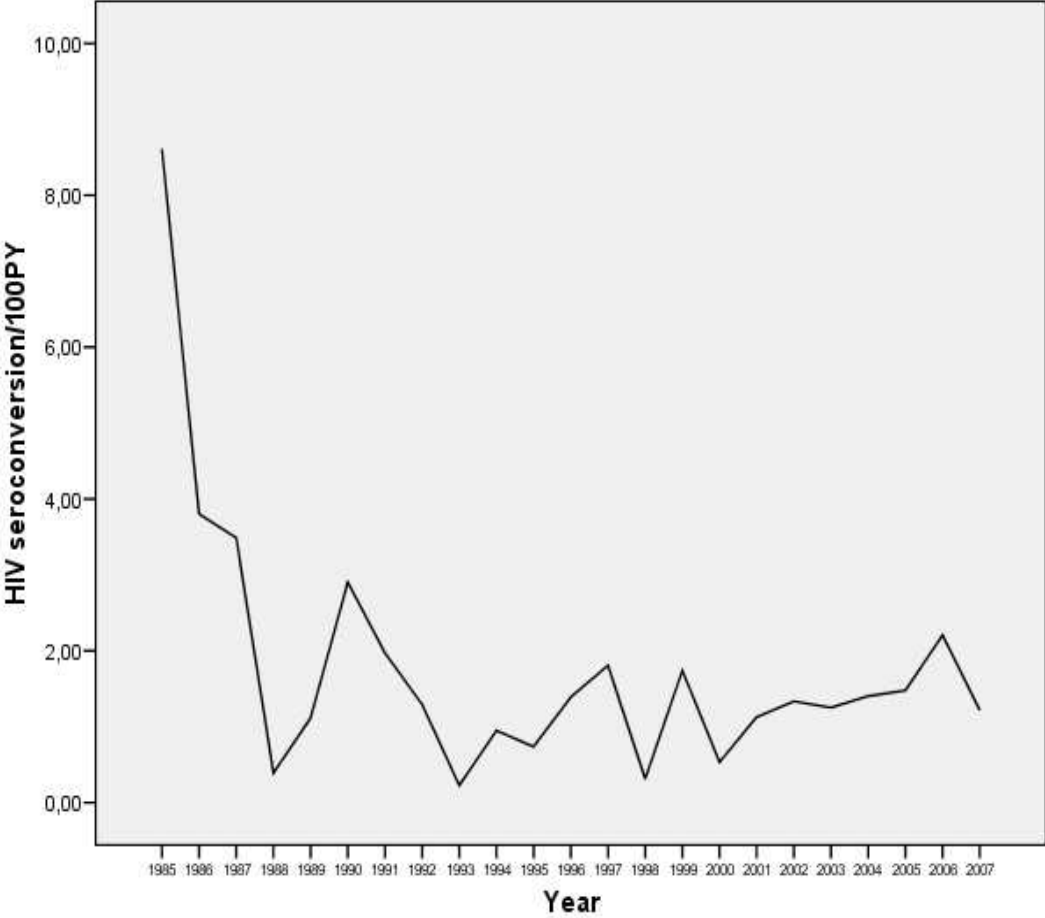


Figure 1: Yearly HIV incidence per calendar year in the ACS among homosexual men (HM)

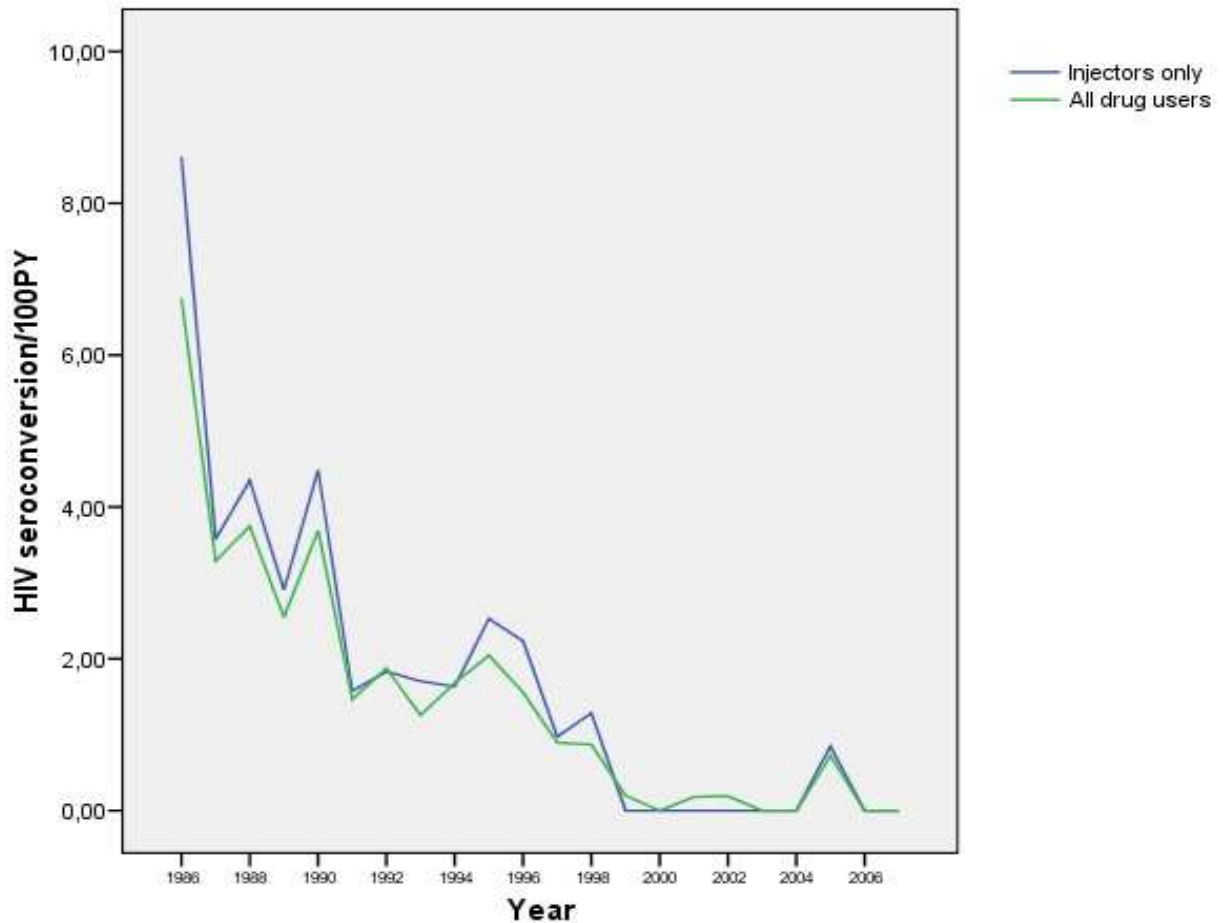


Figure 2: Yearly HIV incidence per calendar year in the ACS among drug users (DU)

Transmission of therapy resistant HIV strains

Of 10 HIV seroconverters with a first positive test result within the ACS in 2007 (9 HM, 1 DU), a sequence could be obtained for 8. Of these, no one was found to be infected with a drug-resistant strain.

HAART uptake

For the 243 HIV-positive HM (226 of whom were recruited before 1999 and 17 after 1999) who visited the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2007, all received **some** form of antiretroviral therapy. Of 202 HM with a known viral load, it was less than 50 copies/ml (assays: bDNA, M2000rt) for 189 men (94%).

Of the 64 HIV-positive DU who visited the PHSA of Amsterdam in 2007, 40 (59%) received any combination of antiretroviral therapy. Of these, 33 (83%) had an undetectable viral load (less than 150 copies/ml (assay: m2000rt)) at their latest visit. Of 18 HIV-positive drug users not receiving HAART, 6 (33%) had an undetectable viral load.

In 2007, adherence was determined amongst 100 HIV-positive DU attending the ACS and reporting HAART use between January 1999 and August 2007. Full adherence (defined as taking more than 95% of medication in the past 6 months) was reported in 87.8% of visits. (Lambers et al., submitted).

Risk behaviour HM

In 2007, 558 HM (551 participants visiting the APHS and 7 HIV-positive men followed outside the APHS) filled in the behavioural questionnaire at least once. Of the 499 HIV-negative HM, 51.7% reported unprotected anal intercourse (UAI) in the past 6 months. Of the 59 HIV-positive HM, 23.3% reported UAI in the past 6 months.

Like the HIV incidence, trends in unprotected anal intercourse (UAI) amongst young (<36 years of age) HIV-negative HM participating in the ACS have remained relatively stable in recent years.

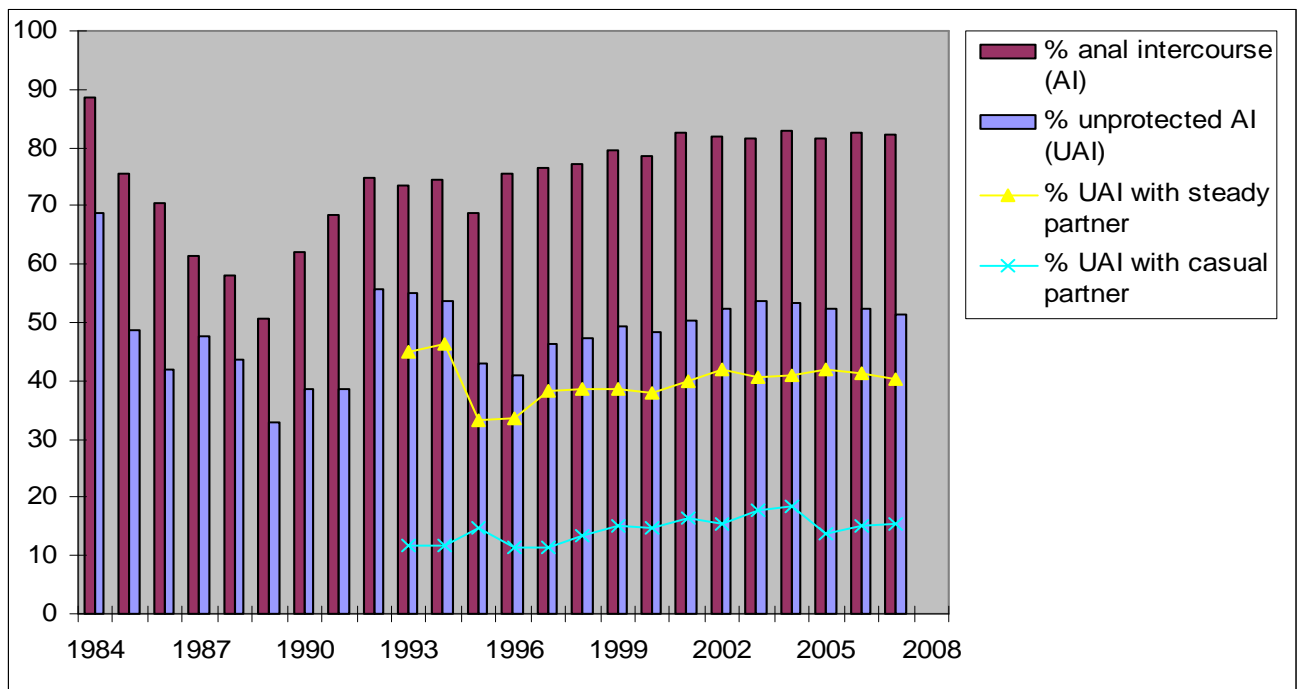


Figure 3: Trends in unprotected anal intercourse in the past six months amongst young HIV-negative HM (age at entry <30 and current age <36) from the Amsterdam Cohort Study 1984-2007

Risk behaviour DU

In the cohort of HIV-negative DU, reports of both injecting drugs and borrowing needles significantly declined over the period 1985-2007 (Lindenburg et al, AIDS 2006 + update 2006). Reports of sexual risk behaviour and sexually transmitted infections (STI) at follow-up visits decreased before 1996, but not after 1996 (see figure 4). This trend has not changed in recent years.

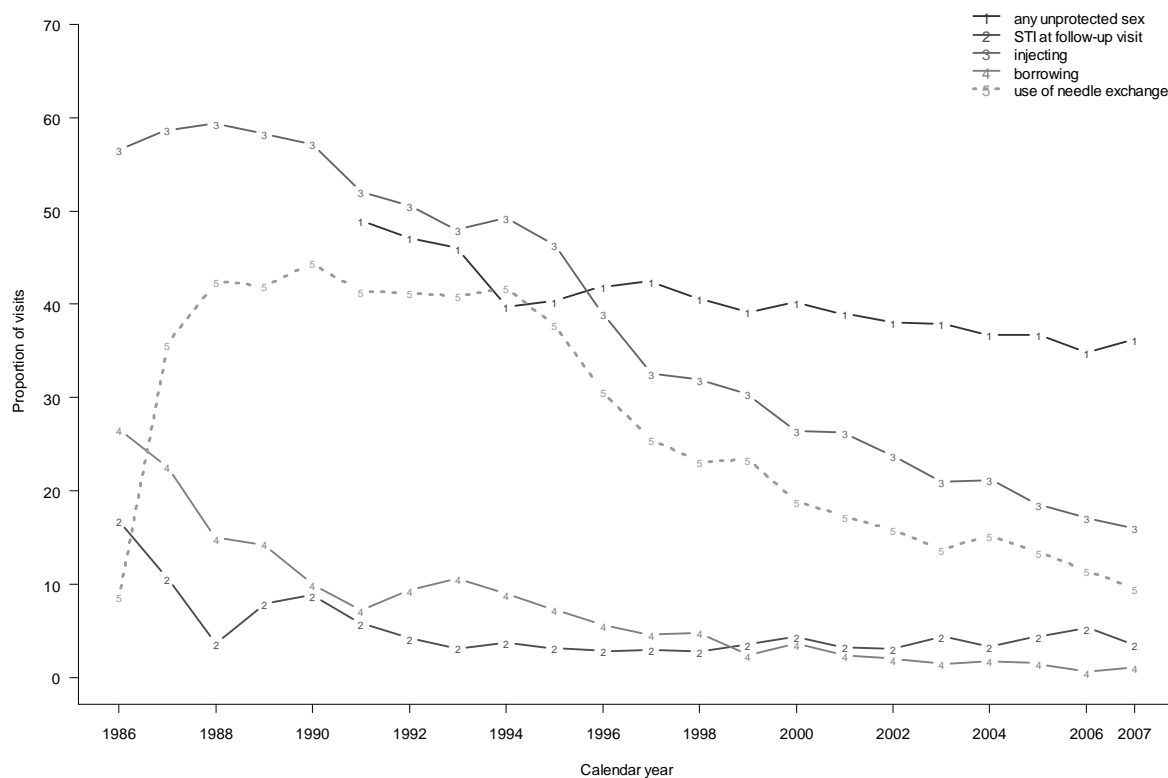


Figure 4. Proportion of visits per calendar year at which injecting drugs and sexual risk behaviour was reported among 1315 DU who were HIV-negative on ACS entry, 1986-2007.

Herpes Simplex Virus (HSV)-1 and HSV-2 prevalence among homosexual men

Between 1984 and 2003 seroprevalence of HSV-1 and HSV-2 was determined amongst 1847 HIV-positive and HIV-negative HM. Of these men, 1207 (65%) were HSV-1 antibody positive, whilst 759 of the 1847 (41%) were HSV-2 antibody-positive. Of the total group, 558 (30%) were positive for both. HSV-1 and HSV-2 prevalence decreased over calendar time among HIV-negative HM, but remained stable in those who were HIV-positive. The association between HIV infection and HSV-2 became stronger over time. (Smit et al., 2007)

Incidence of hepatitis C (HCV), hepatitis B (HBV) and HIV among injecting drug users

HIV, HBV, and HCV incidences were determined among 960 ever-injecting DU (IDU) between 1985 and 2002. These data were used to model patterns of incidence for all three viruses with use of flexible curves. Differences between the three separate incidence curves over calendar time were calculated.

Figure 5 shows that there was a difference in the incidence of new infections each year for HIV, HBV, and HCV. The decline in incidence over time followed the same trend for all three viruses, probably due to a decline in injecting behavior. However, for HBV this decline started later, which might have been due to sexual transmission or a difference in transmissibility of HBV.

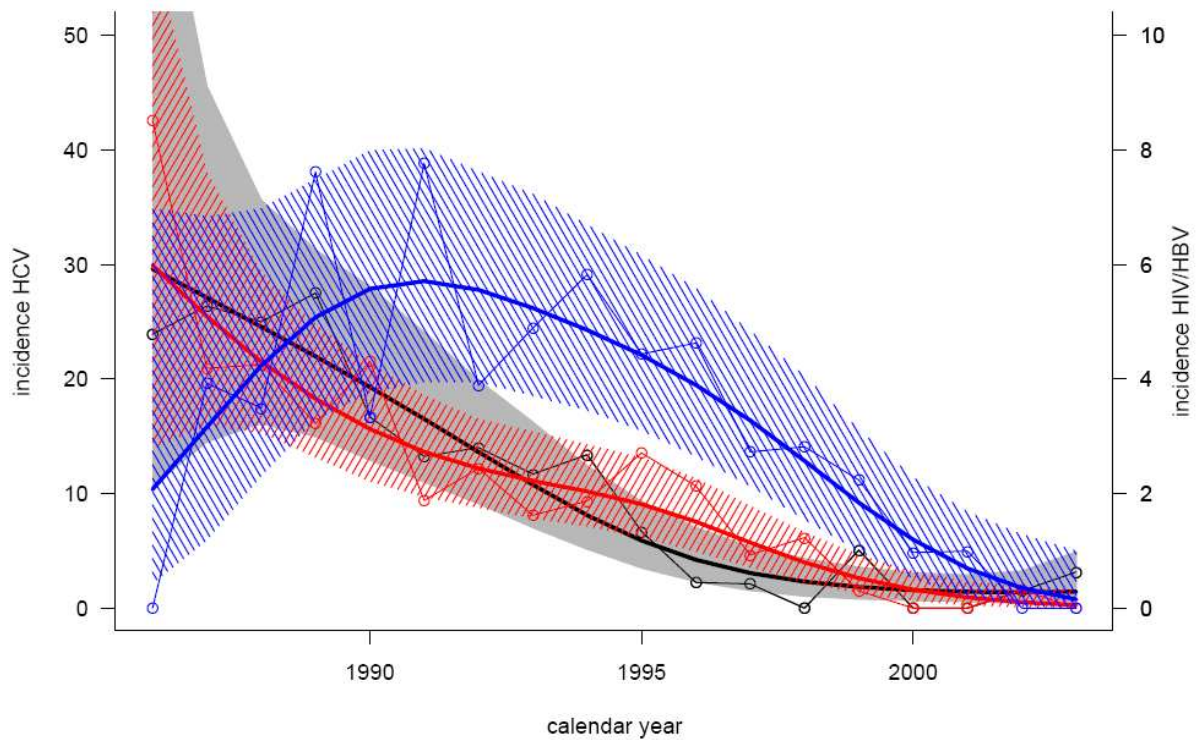


Figure 5: HIV (black), HBV (blue), HCV (red) incidence among IDU in Amsterdam, 1985 until 2002.

Steering committee: The politburo

In the 2007, the politburo met several times to consider proposals submitted for use of data and/or samples (serum/PBMCs): 22 from Sanquin, 5 from the AMC, 2 from the PHSA, 7 from the UMCU, and 2 from researchers not affiliated with the ACS. All requests were approved, some after revision.

Publications in 2007 that include ACS data

Dukers NHTM, Fennema HSA, van der Snoek EM, Krol A, Geskus RB, Pospiech M, Jurriaans S, van der Meijden WI, Coutinho RA, Prins M

HIV incidence and HIV testing behavior in men who have sex with men: using three incidence sources, The Netherlands, 1984-2005

AIDS 2007;21:491-9

Dorrucci M, Rezza G, Porter K, Phillips A, and the Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration

Temporal Trends in Post seroconversion CD4 Cell Count and HIV Load: The Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration, 1985-2002

Journal of Infectious Diseases 2007;195:525-34

Fidler S, Fox J, Touloumi G, Pantazis N, Porter K, Babiker A, Weber J, and the CASCADE Collaboration Slower CD4 cell decline following cessation of a 3-month course of HAART in Primary HIV infection

AIDS 2007 Jun 19;21(10):1283-91

Lampe FC, Porter K, Kaldor J, Law M, Kinloch-de Loes S, Phillips AN; on behalf of the CASCADE Collaboration

Does combination antiretroviral treatment initiated during acute HIV infection impact on subsequent off-treatment viral load? Comparison of the Quest trial results with CASCADE natural history study

Antiviral Therapy 2007;12(2):189-93

Van den Berg CHSB, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, Coutinho RA, Wolthers KC, Prins M

Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users European Journal of Epidemiology 2007, March 3

Witteveen E, van Ameijden EJ, Prins M, Schippers GM

Factors associated with the initiation of cocaine and heroin among problem drug users: reflections on interventions

Substance Use Misuse 2007;42(6):933-47

Van de Laar TJW, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA, van der Meer JT, Vries HJ, Mulder JW, Agtmael M, Jurriaans S, Wolthers KC, Coutinho RA

Increase in HCV Incidence among Men Who Have Sex with Men in Amsterdam Most Likely Caused by Sexual Transmission

Journal of Infectious Diseases 2007 Jul 15;196(2):230-8.

Van der Bij AK, Kolader ME, de Vries HJ, Prins M, Coutinho RA, Dukers NH
Condom use rather than serosorting explains differences in HIV incidence among men who have sex with men
Acquired Immune Deficiency Syndrome 2007 Aug 15;45(5):574-80

van den Berg CHSB, Smit C, van Brussel G, Coutinho R, Prins M
Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users
Addiction 2007;102:1454-62

Witteveen E, van Ameijden EJC, Prins M, Schippers GM
Unmet needs and barriers to healthcare utilization among young adult, problematic drug users: An exploratory study
Sucht 2007;53(3): 169-76

Smit C, Pfrommer C, Mindel A, Taylor J, Spaargaren J, Berkhout B, Coutinho R, Dukers NHTM
Rise in seroprevalence of herpes simplex virus type 1 among highly sexual active homosexual men and an increasing association between herpes simplex virus type 2 and HIV over time (1984-2003) European Journal of Epidemiology 2007 December; 22(12): 937–944.

Geskus RB, Prins M, Hubert J-B, Miedema F, Berkhout B, Rouzioux C, Delfraissy J-F, Meyer L
The HIV RNA setpoint theory revisited
Retrovirology 2007;Sep 21;4(1):65

Bhaskaran K, Mussini C, Antinori A, Walker AS, Dorrucchi M, Sabin C, Phillips A, Porter K, CASCADE Collaboration
Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy
Annals of Neurology 2007;Sept 25;

Kootstra NA, Navis M, Beugeling C, van Dort KA, Schuitemaker H.
The presence of the Trim5alpha escape mutation H87Q in the capsid of late stage HIV-1 variants is preceded by a prolonged asymptomatic infection phase.
AIDS. 2007;21(15):2015-23.

Navis M, Schellens I, van Baarle D, Borghans J, van Swieten P, Miedema F, Kootstra N, Schuitemaker H.
Viral replication capacity as a correlate of HLA B57/B5801-associated nonprogressive HIV-1 infection.

Journal of Immunology 2007;179(5):3133-43.

Choudhary SK, Vrisekoop N, Jansen CA, Otto SA, Schuitemaker H, Miedema F, Camerini D.
Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease.

Journal of Virology 2007 Aug;81(16):8838-42. Epub 2007 May 30.

Quakkelaar ED, van Alphen FP, Boeser-Nunnink BD, van Nuenen AC, Pantophlet R, Schuitemaker H.

Susceptibility of recently transmitted subtype B human immunodeficiency virus type 1 variants to broadly neutralizing antibodies.

Journal of Virology 2007;81(16):8533-42. Epub 2007 May 23.

Quakkelaar ED, Bunnik EM, van Alphen FP, Boeser-Nunnink BD, van Nuenen AC, Schuitemaker H.

Escape of human immunodeficiency virus type 1 from broadly neutralizing antibodies is not associated with a reduction of viral replicative capacity in vitro.

Virology. 2007;363(2):447-53. Epub 2007 Mar 13.

Bunnik EM, Quakkelaar ED, van Nuenen AC, Boeser-Nunnink B, Schuitemaker H.

Increased neutralization sensitivity of recently emerged CXCR4-using human immunodeficiency virus type 1 strains compared to coexisting CCR5-using variants from the same patient.

Journal of Virology 2007;81(2):525-31. Epub 2006 Nov 1.

Quakkelaar ED, Beaumont T, van Nuenen AC, van Alphen FP, Boeser-Nunnink BD, van 't Wout AB, Schuitemaker H.

T cell line passage can select for pre-existing neutralization-sensitive variants from the quasispecies of primary human immunodeficiency virus type-1 isolates.

Virology. 2007;359(1):92-104. Epub 2006 Oct 18.

Bronke C, Jansen CA, Westerlaken GH, De Cuyper IM, Miedema F, Tesselaar K, van Baarle D.

Shift of CMV-specific CD4+ T-cells to the highly differentiated CD45RO-CD27-phenotype parallels loss of proliferative capacity and precedes progression to HIV-related CMV end-organ disease.

Clinical Immunology 2007;124(2):190-9. Epub 2007 Jun 6.

Tsegaye A, Ran L, Wolday D, Petros B, Dorigo W, Piriou E, Messele T, Sanders E, Tilahun T, Eshetu D, Schuitemaker H, Coutinho RA, Miedema F, Borghans J, van Baarle D.

HIV-1 Subtype C gag-specific T-cell responses in relation to human leukocyte antigens in a diverse population of HIV-infected Ethiopians.

Journal of Acquired Immune Deficiency Syndrome 2007;45(4):389-400.

Tsegaye A, Ran L, Wolday D, Petros B, Nanlohy NM, Meles H, Girma M, Hailu E, Borghans J, Miedema F, van Baarle D.

Stable pattern of HIV-1 subtype C Gag-specific T-cell responses coincides with slow rate of CD4 T-cell decline in HIV-infected Ethiopians.

AIDS. 2007;21(3):369-72.

Casula M, Vrisekoop N, Wit FW, de Baar MP, de Ronde A, Miedema F, Reiss P.

Mitochondrial DNA decline in T cells of HIV-1 seroconverters may be dependent on immune activation.

Journal of Infectious Diseases 2007;196(3):371-6. Epub 2007 Jun 15.

Gras L, Kesselring AM, Griffin JT, van Sighem AI, Fraser C, Ghani AC, Miedema F, Reiss P, Lange JM, de Wolf F; ATHENA, Netherlands National Observational Cohort Study.

CD4 cell counts of 800 cells/mm³ or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm³ or greater.

Journal of Acquired Immune Deficiency Syndrome 2007;45(2):183-92.

Cornelissen M, Jurriaans S, Kozaczynska K, Prins JM, Hamidjaja RA, Zorgdrager F, Bakker M, Back N, van der Kuyl AC

Routine HIV-1 genotyping as a tool to identify dual infections

AIDS 2007;21:807-811

Gali Y, Berkhout B, Vanham G, Bakker M, Back N, Ariën KK

Survey of the temporal changes in HIV-1 replicative fitness in the Amsterdam Cohort

Virology 2007;364:140-146

van der Hoek L, Pollakis G, Lukashov VV, Jebbink MF, Jeeninga RE, Bakker M, Dukers N, Jurriaans S, Paxton WA, Back N, Berkhout B

Characterization of an HIV-1 group M variant that is distinct from the known subtypes

AIDS Research and Human Retroviruses 2007;23:466-470

van der Kuyl AC, van den Burg R, Zorgdrager F, Groot F, Berkhout B, Cornelissen M

Sialoadhesin (CD169) expression in CD14⁺ cells is upregulated early after HIV-1 infection and increases during disease progression

PLoS ONE 2007;2:e257

van der Kuyl AC, Cornelissen M

Identifying HIV-1 dual infections

Retrovirology 2007;4:67

van Montfort T, Nabatov AA, Geijtenbeek TBH, Pollakis G, Paxton WA
Efficient capture of antibody neutralized HIV-1 by cells expressing DC-SIGN and transfer to CD4+
T lymphocytes
Journal of Immunology 2007;178:3177-3185

Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP.
Variation in HIV-1 set-point viral load: epidemiological analysis and an
evolutionary hypothesis.
Proceedings of the National Academy of Sciences U S A. 2007 Oct 30;104(44):17441-6. Epub
2007 Oct 22 .

Theses in 2007 that include ACS data

Akke K. van der Bij
Epidemiology of re-emerging sexually transmitted infections
19 januari 2007
Promotor: Roel Coutinho
Co-promotor: Nicole Dukers

Colette Smit
25 years of HIV: Trends in mortality, HIV coinfections, and HIV-related risk behaviour
10 april 2007
Promotor: Roel Coutinho
Co-promotor: Maria Prins

Marloes Naarding
Inhibition of mother to child transmission of HIV-1 during breastfeeding
9 March 2007
Promotor: Ben Berkhout
Co-promotor: Bill Paxton

Esther Quakkelaar
Antibody neutralization of HIV-1
March 23 2007
Promotor: Hanneke Schuitemaker