The Amsterdam Cohort Studies on HIV infection
Annual Report 2008

Introduction

The Amsterdam Cohort Study (ACS) on Human Immunodeficiency Virus (HIV) infection and AIDS among homosexual men (HM) was initiated in 1984, followed shortly by the Amsterdam Cohort Study among drug users (DU) 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, the University Medical Center Utrecht (UMCU), and the Jan van Goyen Clinic, are part of the Netherlands HIV Monitoring Foundation and are financially supported by the Centre for Infectious Disease control of the Netherlands National Institute for Public Health and the Environment.

As of 31 December 2008, 2383 homosexual men and 1647 (injecting) drug users were included in the ACS. It should be noted that the number of drug users is lower than noted in the previous report because 18 drug users who were enrolled in the ACS in 2007 when they started HCV treatment did not meet the inclusion criteria for enrolment in the ACS, they have been excluded in the 2008 report. Every 3 to 6 months, participants complete a standardized questionnaire designed to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognitions, 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 diagnostic tests and storage.

Of the 2383 HM, 585 were HIV-positive at study entry, and 208 seroconverted during follow-up. For the 1647 DU, 322 were HIV-positive at study entry, and 96 seroconverted during follow-up. By 31 December 2008, 335 HM and 411 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, the PHSA was visited 47.524 times by HM and 25.131 times by DU.

ACS Open*

Over the past 25 years large amounts of social-scientific, demographic, clinical, and biomedical data have been obtained from the participants of the ACS by the different participating research groups. In 2005, the ACS Open projected group, composed of data managers and scientists from all participating research groups, started to combine the data sets and build an easily accessible multidisciplinary database comprising all longitudinally obtained epidemiological, social-scientific, and biomedical information and containing data about the availability of stored samples in the repositories. In

2009/2010, these data sets will be available for scientists in the participating research groups and their collaborators.

The ACS data are very suitable for use by universities and research institutes to teach epidemiological, biomedical, and social scientific students 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, multilevel, and repeated measurement analysis. For this purpose, a data set that includes social-scientific, demographic, clinical, and biomedical information obtained from the participants of the ACS over the past 25 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 MaGW and ZonMw (grant number 91104002).

The cohorts in 2008

Homosexual men

In 2008, 532 HM were followed at the PHSA of Amsterdam. Twenty-eight of them were newly recruited in 2008. 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 2008, 481 men were HIV-negative, and 51 men were HIV-positive. The HIV-positive men, of whom 38 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 study entry into the cohort of young HM after 1999.

Another 12 HIV-positive men were included in the HOP in 2008, of whom 6 were exclusively followed in an HIV treatment centre outside the PHSA. By the end of 2008, 34 HIV-positive men were still in active follow-up in an HIV treatment centre outside the PHSA. From June 2006 onwards, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants have also been invited to participate in the ACS. By the end of 2008, 12 HIV discordant and 2 HIV-positive concordant couples were included in this partner study, of which 7 couples were still in active follow up.

In 2008, 208 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-eight of them were HIV seroconverters. Plasma and cells from 57 of the 125 HIV-positive HM in active follow-up at the Jan van Goyen clinic in 2008 were stored. Of these, 35 were HIV seroconverters, and the remaining 22 were defined as 1) slow or non progressor or matched fast progressor in 1996; 2) were HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/µl after 10 years of follow-up after a HIV-positive result without effective therapy.

Drug users

In 2008, 390 drug users were followed at the PHSA of Amsterdam. Fifty-five were young drug users aged 30 years or less; were recruited after 2000; and had used cocaine, heroin, or amphetamines at

least 3 times a week in the 2 months preceding enrolment. Of the 390 DU followed in 2008, 35 were HIV-positive, and 19 seroconverted for HIV 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 2008 15 HCV mono-infected DU had initiated HCV therapy, resulting in a total group of 50 DU treated for HCV.

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 2008, 172 patients were already included as patients with primary infection. In 2008, 23 new patients with acute HIV-1 infection were enrolled in the study, of which 16 participated in the randomised controlled trial. Blood is collected from all of these patients for storage of plasma and peripheral blood mononuclear cells (PBMC), and sampling is more frequent early after entry into the study. Follow-up of individuals who are randomized to the no-treatment arm is discontinued 1 year after they have to start HAART because of a CD4+ T cell decline <350 cells/µl. Similarly, follow-up of individuals who have to reinitiate HAART because of a CD4 decline (<350 cells/µl blood) after scheduled interruption of the first HAART regimen initiated during the primary infection phase is discontinued 1 year after therapy re-initiation.

HIV incidence

Eight homosexual men and no drug user had a first HIV-positive test in 2008 after a previous HIV-negative test. HIV incidence in 2008 was 2.01 per 100 person-years among HM, and has slowly increased since 1996. Among DU, the HIV incidence was less than 1 per 100 person-years. Figures 1 and 2 show the yearly observed HIV incidence rates for homosexual men and drug users from the start of the ACS through 2008.

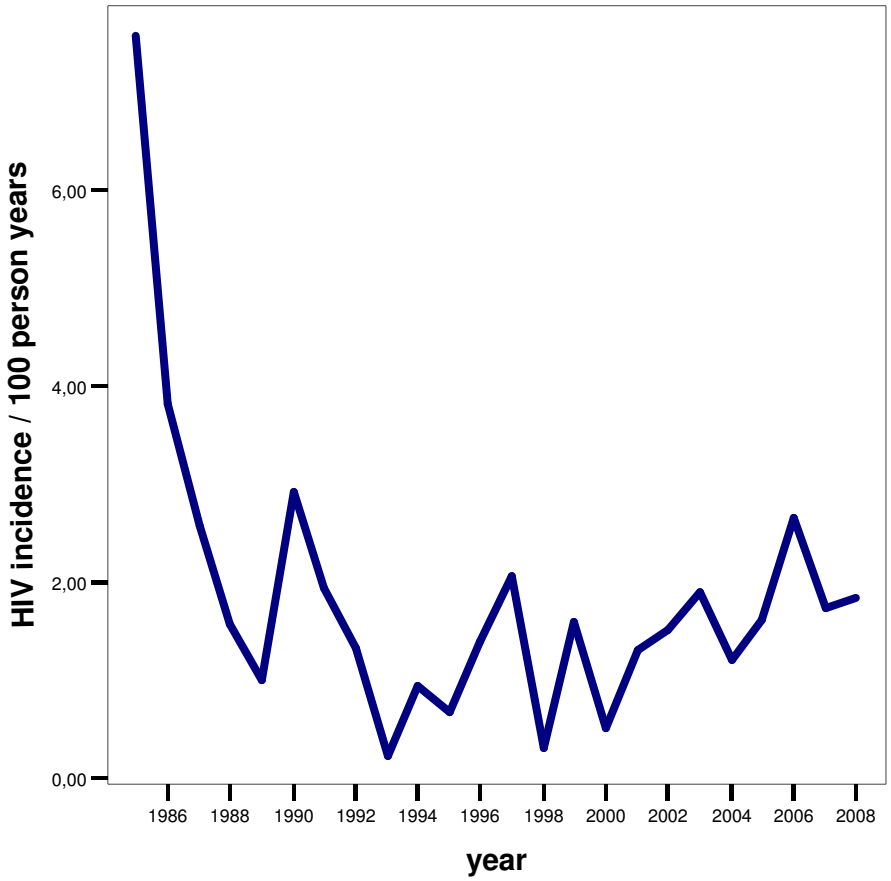

Figure 1: Yearly HIV incidence per calendar year in the ACS among homosexual men, 1984-2008

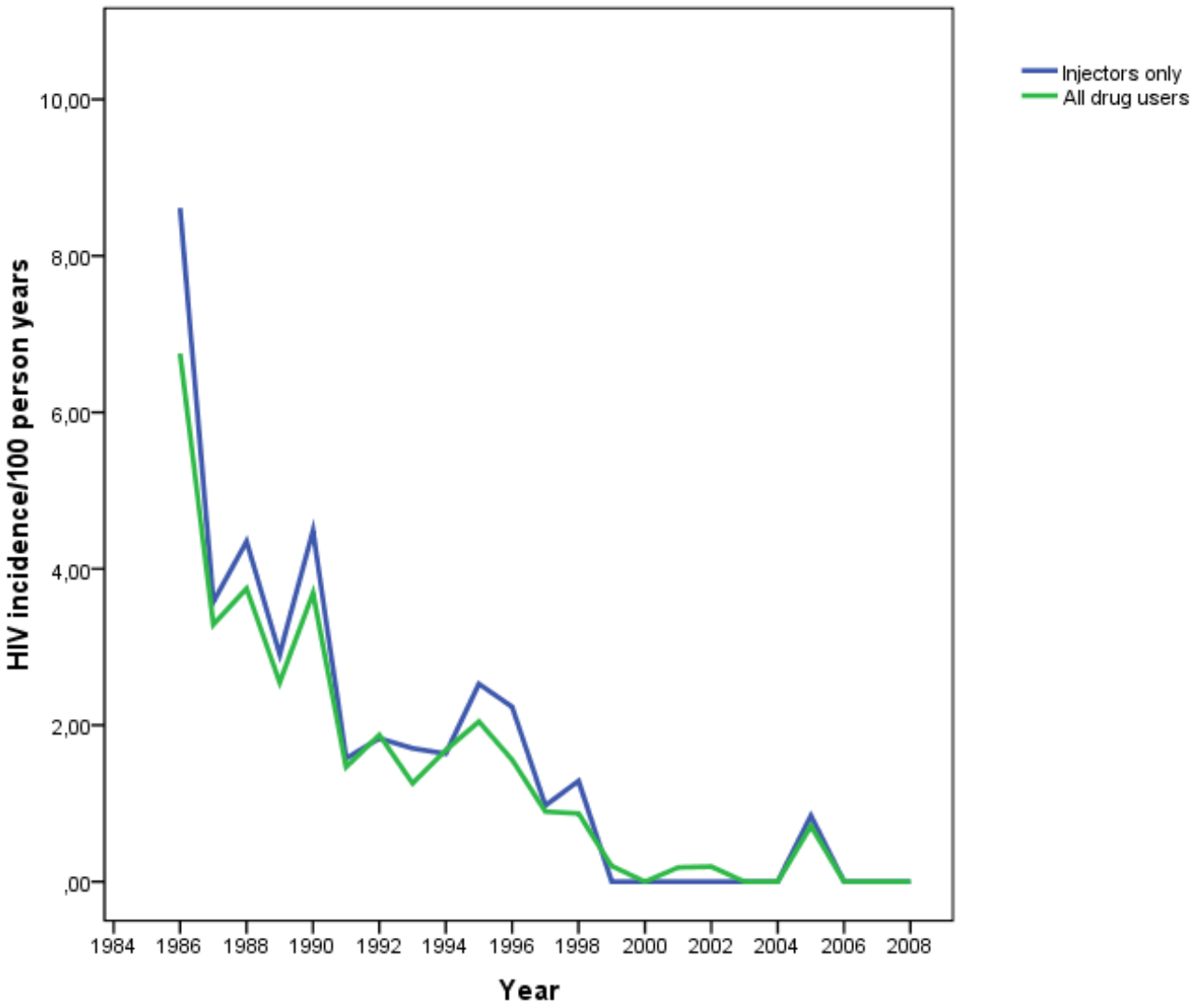

Figure 2: Yearly HIV incidence per calendar year in the ACS among drug users, 1986-2008

Transmission of therapy resistant HIV strains

Surveillance of transmission of drug-resistant HIV-1 strains was performed for 7 HM seroconverters, and 5 of the 6 seropositive HM at entry. In most individuals, only naturally occurring sequence variation was found, but in one of the seroconverters, sequences harboring resistance-associated mutations were found. A 41L mutation and a so-called 215-revertant (215L) were found.

HAART uptake

All 234 (208 who were recruited before 1999 and 26 after 1999) HIV-positive HM visiting the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2008 received any form of antiretroviral therapy. Of 192 HM for whom viral load results were available, 189 (98%) had a viral load of less than 50 copies/ml (assays: bDNA, M2000rt).

Of the 50 HIV-positive DU who visited the PHSA of Amsterdam in 2008 and for whom treatment data were available, 41 (79%) received any combination of antiretroviral therapy. Of these, 38 (93%) had an undetectable viral load (less than or equal to 150 copies/ml [assay: m2000rt]) at their latest visit. Of 9 HIV-positive DU not receiving HAART, 3 (33%) had an undetectable viral load.

Adherence was investigated amongst 102 HIV-positive DU who attended the ACS and reported HAART use between January 1999 and February 2009. Full adherence (defined as taking more than 95% of medication in the past 6 months) was reported in 88% of visits. (Lambers et al., submitted).

Risk behaviour HM

Of the 405 HIV-negative HM who filled in a questionnaire at least once up until July 2008, 56% reported unprotected anal intercourse (UAI) in the past 6 months. Like the HIV-incidence, trends in UAI among HIV-negative HM participating in the ACS have slowly increased since 1996.

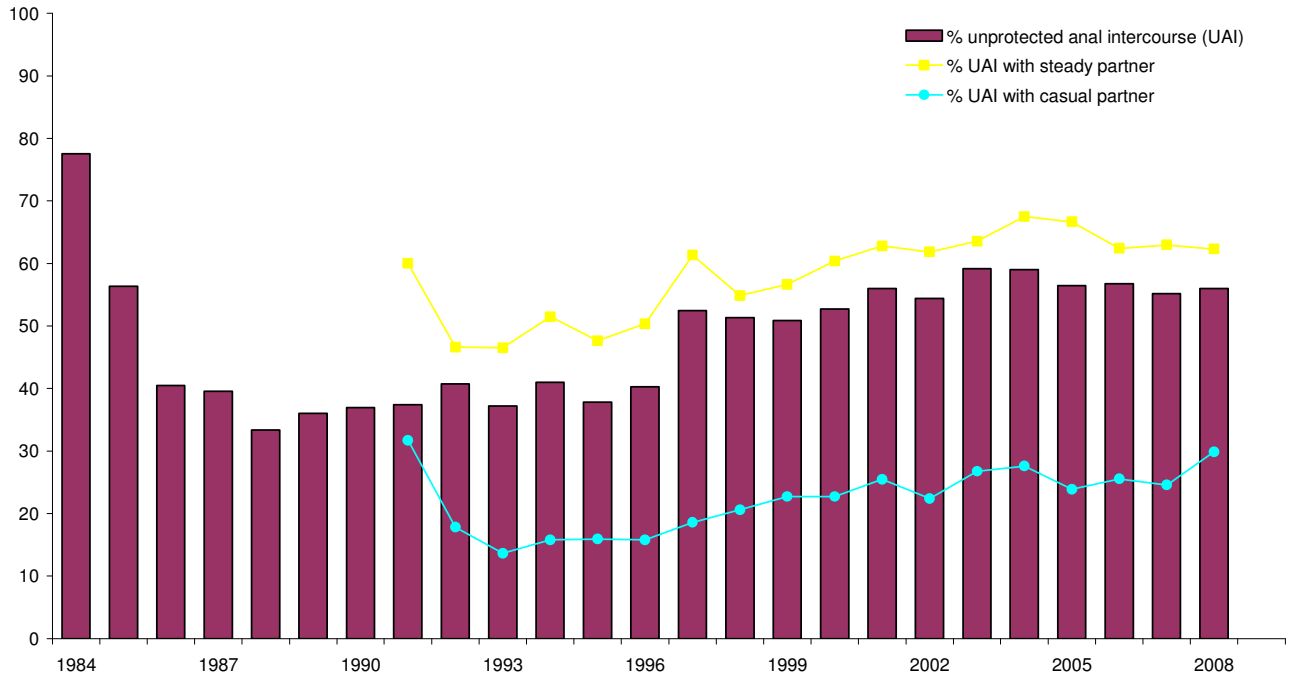

Figure 3: Trends in unprotected anal intercourse in the past 6 months among HIV-negative HM from the Amsterdam Cohort Study 1984-2008

Risk behaviour in DU

In the cohort of HIV-negative DU, reports of both injecting and borrowing needles significantly declined over the period 1985-2008 (Lindenburg et al, AIDS 2006 and update in 2008). Reports of sexual high risk behaviour and sexually transmitted infections at follow-up visits decreased before 1996, but remained relatively stable after 1996 (see figure 4).

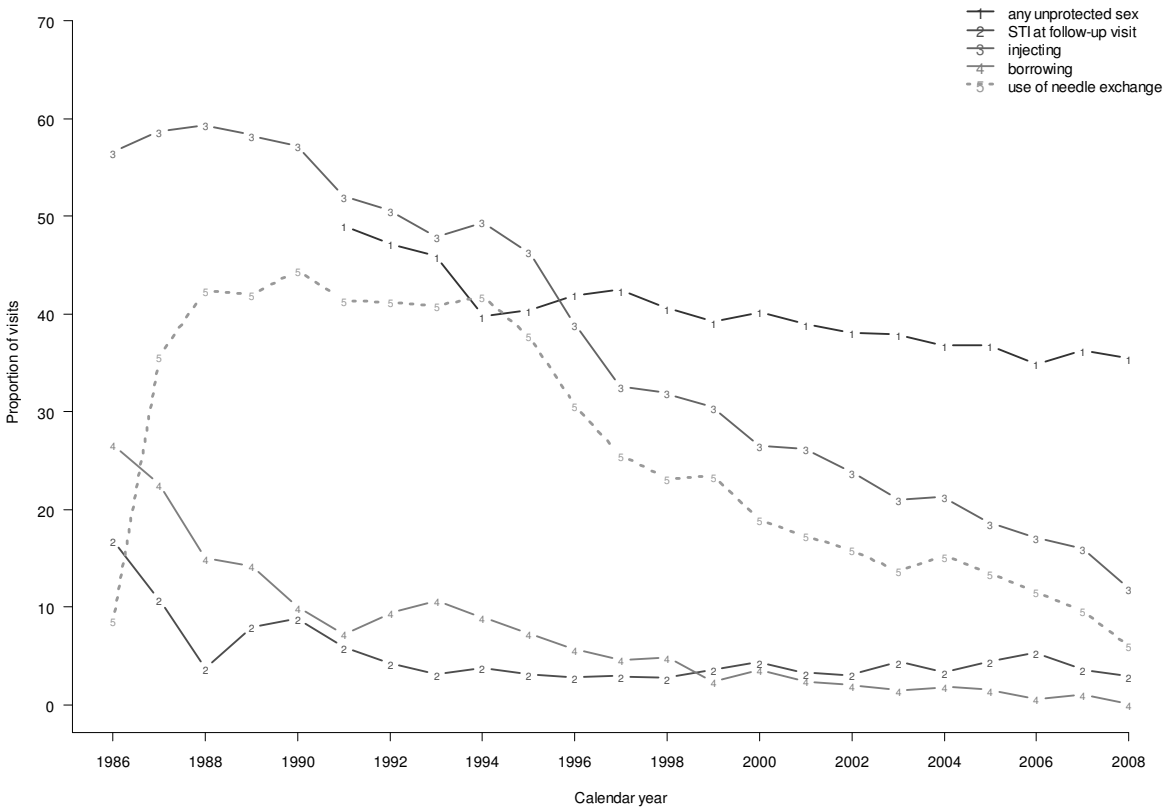

Figure 4. Proportion of visits per calendar year at which injecting and sexual high risk behaviour was reported among 1315 DU who were HIV-negative on ACS entry, 1986-2008.

HCV in drug users

Non-injecting drug users

Amongst self-declared never-injecting drug users, the HCV antibody prevalence at ACS entry was 6.3%. HCV strains that circulate among never-injectors phylogenetically cluster with those circulating among their injecting counterparts. Although this is all suggestive for underreporting of past injecting behaviour, household or sexual transmission of HCV from injectors to non-injectors cannot be ruled out. This stresses the need for HCV-testing among DU who report never injecting (van den Berg, 2009).

Clinical course

DU co-infected with HCV and HIV remain at increased risk of dying from hepatitis/liver-related causes in the era of HAART, compared to HCV-mono-infected DU, suggesting that HIV continues to accelerate progression of HCV disease (Smit, 2008)

The rate of spontaneous viral clearance amongst DU from the ACS was 33% following acute infection; it was higher in women, DU without HIV, and those without an active hepatitis B infection. Multiple HCV infections were observed in 10 of 24 HCV-seroconverters with spontaneous viral clearance (11 re-infections; 3 super-infections) and in 13 of 35 HCV-seroconverters without viral clearance (20 super-infections). The incidence of HCV re-infection was at least similar to that of initial HCV infection.

Although partial immunity cannot be excluded, this will further complicate vaccine development. Harm reduction will remain dependent on precautionary measures preventing the further spread of HCV and on the treatment of those chronically infected (van de Laar, 2009).

Steering committee: The politburo

In the 2008, the “Politburo” met several times. Forty proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: 21 from AMC-Experimental Immunology, 8 from the AMC-Medical Microbiology, 1 from AMC-Internal Medicine, 2 from the PHSA, 5 from the UMCU, and 3 from researchers not affiliated with the ACS. All requests were approved, some after revision. One request was withdrawn after approval.

Publications in 2008 that include ACS data

Bezemer, D., F. de Wolf, M. C. Boerlijst, A. van Sighem, T. D. Hollingsworth, M. Prins, R. B. Geskus, L. Gras, R. A. Coutinho, and C. Fraser. 2008. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. Aids 22:1071-7.

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Navis, M., D. E. Matas, A. Rachinger, F. A. Koning, P. van Swieten, N. A. Kootstra, and H. Schuitemaker. 2008. Molecular evolution of human immunodeficiency virus type 1 upon transmission between human leukocyte antigen disparate donor-recipient pairs. PLoS One 3:e2422.

Navis, M., I. M. Schellens, P. van Swieten, J. A. Borghans, F. Miedema, N. A. Kootstra, D. van Baarle, and H. Schuitemaker. 2008. A nonprogressive clinical course in HIV-infected individuals expressing human leukocyte antigen B57/5801 is associated with preserved CD8+ T lymphocyte responsiveness to the HW9 epitope in Nef. J Infect Dis 197:871-9.

Pantazis, N., G. Touloumi, P. Vanhems, J. Gill, H. C. Bucher, and K. Porter. 2008. The effect of antiretroviral treatment of different durations in primary HIV infection. Aids 22:2441-50.

Pasternak, A. O., K. W. Adema, M. Bakker, S. Jurriaans, B. Berkhout, M. Cornelissen, and V. V. Lukashov. 2008. Highly sensitive methods based on seminested real-time reverse transcription-PCR for quantitation of human immunodeficiency virus type 1 unspliced and multiply spliced RNA and proviral DNA. J Clin Microbiol 46:2206-11.

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Tesselaar, K., and F. Miedema. 2008. Growth hormone resurrects adult human thymus during HIV-1 infection. J Clin Invest 118:844-7.

Touloumi, G., N. Pantazis, H. A. Stirnadel, A. S. Walker, F. Boufassa, P. Vanhems, and K. Porter. 2008. Rates and determinants of virologic and immunological response to HAART resumption after treatment interruption in HIV-1 clinical practice. J Acquir Immune Defic Syndr 49:492-8.

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Theses in 2008 that include ACS data

Buchholz A
Health-related Quality of Life and Psychosocial Functioning in Problem Drug Users.

Co-promotor Prof dr. GM Schippers
promotor Prof dr F Rist

van de Laar TJ.
Molecular Epidemiology of hepatitis C virus.
Co-promotor: Dr SM Bruisten, Dr M Prins
Promotor: Prof dr RA Coutinho

Witteveen E.
Knowledge gained through experience in young problem drug users. Reflections on interventions and change.
Co-promotor: Dr EJC van Ameijden
Promotor: Prof dr GM Schippers