Special reports

7. The Amsterdam Cohort Studies on HIV infection – Annual Report 2011

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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 2011, the cohorts reached 27 years of follow-up. The initial aim of the ACS was to investigate the prevalence and incidence of, and risk factors for, HIV-1 infection and AIDS, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 27 years, these aims have remained mostly the same, although the emphasis of the studies has changed. Early on, the primary focus was to elucidate the epidemiology of HIV-1 infection, whilst more in-depth studies were performed later 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.

De Amsterdamse Cohort Studies (ACS) naar HIV en AIDS zijn gestart kort nadat de eerste gevallen van AIDS in Nederland werden gediagnosticeerd. Sinds oktober 1984 worden mannen die seks hebben met mannen (MSM) gevolgd in een prospectieve cohortstudie. Een tweede cohort onder drugsgebruikers startte in 1985. In 2011 bestonden de ACS 27 jaar. Het oorspronkelijke doel van de ACS was het onderzoeken van de prevalentie en incidentie van, en de risicofactoren voor HIV-1-infectie en AIDS en van het ontstaan en natuurlijk beloop van de HIV-1-infectie en het evalueren van de effecten van interventies. In de afgelopen 27 jaar zijn deze doelen min of meer gelijk gebleven maar is de nadruk van de studies wel verschoven. In het begin lag de focus vooral op het verkrijgen van inzicht in de epidemiologie van HIV-1. Later zijn meer verdiepende studies uitgevoerd naar met name de pathogenese van HIV-1. In de laatste paar jaar zijn eveneens de epidemiologie en het natuurlijk beloop van andere bloedoverdraagbare en seksueel overdraagbare aandoeningen (soa's) onder deelnemers aan de ACS bestudeerd.

Vanaf de beginfase heeft het onderzoek in de ACS zich onderscheiden door een multidisciplinaire aanpak (epidemiologie, sociale wetenschappen, virologie, immunologie en klinische geneeskunde). Deze unieke aanpak is erg productief gebleken en heeft in belangrijke mate inzicht en kennis verschaft over de verschillende aspecten van HIV-1. Deze expertise heeft direct bijgedragen aan de vooruitgang en verbetering van de preventie, diagnose en behandeling van HIV.

As of 31 December 2011, 2473 men who have sex with men (MSM) and 1658 (injecting) drug users (DU) were included in the Amsterdam Cohort Studies (ACS). Every 3 to 6 months, participants have completed a standardized questionnaire designed to obtain information regarding medical history, sexual and drug use behaviour, underlying cognitions, health care use, depression, psychological disorders, and demographics. In addition, they have undergone 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. 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 approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the DU cohort) is obtained for every participant.

Of the 2473 MSM, 614 were HIV-positive at study entry, and 228 seroconverted during follow-up. For the 1658 DU, 322 were HIV-positive at study entry, and 98 seroconverted during follow-up. By 31 December 2011, 353 MSM and 466 DU had died, and several other participants were asked to leave the study or left at their own request. In total, the Public Health Service of Amsterdam was visited 50,493 times by MSM and 26,554 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 are the Public Health Service of Amsterdam (PHSA) (Cluster Infectious Diseases, Department of Research), the Academic Medical Center (AMC) of the University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine, and the International Antiviral Therapy Evaluation Center) and the Jan van Goyen Medical Center (Department of Internal Medicine). Until 2007, collection of blood cells was performed at the Sanquin Blood Supply Foundation, but this activity has since moved to the Department of Experimental Immunology at the AMC. However, the Sanquin Blood Supply Foundation is still affiliated with the ACS. Also, many collaborations exist between the ACS and other research groups both within and outside of the Netherlands.

The ACS is a collaboration between the Public Health Service of Amsterdam, the Academic Medical Center of the University of Amsterdam, the Sanquin Blood Supply Foundation, the University Medical Center Utrecht, and the Jan van Goyen Medical Center. The ACS is part of

Stichting HIV Monitoring (SHM) (the Netherlands HIV monitoring foundation) and is financially supported by the Centre for Infectious Disease Control of the Netherlands National Institute for Public Health and the Environment.

The ACS in 2011

The cohort of men having sex with men

In 2011, 564 MSM were followed at the PHSA. Twenty-seven of them were newly recruited, and two died in 2011. From 2005, recruitment has been open for MSM of all ages with at least one sexual partner in the preceding 6 months. Of the MSM in active follow-up by the end of 2011 at the PHSA, 480 men were HIV-negative, and 84 men were HIV-positive. The HIV-positive men were followed at the PHSA or in an HIV treatment centre outside the PHSA according to the 'HIV Onderzoek onder Positieven' (HOP) protocol, which is comparable to the HIV-negative protocol. This protocol was initiated in October 2003 for MSM who seroconverted or who tested HIV-positive at entry into the study cohort of young MSM after 1999. Of the 84 MSM in active follow-up in 2011, 6 were newly included, 56 were HIV seroconverters, and 40 were being followed at an HIV treatment centre outside the PHSA. In 2006, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants were also invited to participate in the ACS. Thirteen HIV discordant and 3 HIV-positive concordant couples were included in this partner study, of which 5 couples were still in active follow-up in 2011.

In 2011, 152 HIV-positive MSM were in active follow-up at the Jan van Goyen clinic since 1999. Of these, 41 were HIV seroconverters, and 30 were defined as (1) slow or non-progressor or matched fast progressor in 1996 or (2) were HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/mm^3 after 10 years of follow-up following an HIV-positive result without effective therapy.

Since November 2008, all MSM followed at the PHSA have been routinely screened for STI. Furthermore, between July 2010 and July 2011 all these MSM were invited to participate in the H2M study. In this study MSM are additionally screened for Human Papillomavirus (HPV) during five consecutive 6-monthly visits to investigate the prevalence, incidence and clearance of anal, penile and oral HPV infections among HIV-negative and HIV-positive MSM (H2M study).

The cohort of drug users

In 2011, 327 drug users were followed at the PHSA. Of the 327 DU followed in 2011, 24 were HIV-positive at entry, 15 seroconverted for HIV during follow-up in the ACS. Inclusion criteria are individuals between 18 and 30 years who regularly use hard drugs in Amsterdam and individuals older than 30 years who started injecting hard drugs in the preceding 2 years in Amsterdam. Although the cohort is open and efforts were made to include new participants, nobody was recruited in 2011, which might be explained by the unpopularity of injecting drugs in Amsterdam.

In 2005, a feasibility study (the Dutch-C project) was started within the DU cohort to evaluate the possibility of hepatitis C virus (HCV) testing and treatment combined with methadone programs. This project is one of the first studies specifically designed as an intervention to increase HCV assessment and treatment in a well defined cohort of DU. Treatment for HCV in a multidisciplinary setting is still offered to drug users at the PHSA.

Sub and affiliated studies

Primo-SHM study

In addition to the cohorts previously described, from May 2003 until March 2010 the ACS also included 238 patients who presented with primary HIV-1 infection at the outpatient clinic of the AMC in the so-called "Primo-SHM study". The Primo-SHM study is a national randomized study on the effect of early temporary quadruple antiviral therapy as compared to no therapy. Some of these patients were seronegative men in the MSM cohort at the PHSA who seroconverted during follow-up. Some of them are also still followed with the HOP protocol of the ACS at the PHSA. All 466 samples that are collected within the Primo-SHM study are part of the ACS and stored at the Department of Experimental Immunology.

AGE$_h$IV Cohort Study

The Age$_h$iv Cohort Study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health and Amsterdam Institute of Global Health and Development, the PHSA, and the SHM, was started in November 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 and older 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. By the end of 2011, about 525 HIV-1-infected participants were included through the AMC HIV outpatient clinic, and 400 HIV-uninfected individuals belonging to the same HIV exposure groups were included through the STI clinic of the PHSA or the Amsterdam Cohort Studies. All participants are aged ≥45 years and are as comparable as possible with respect to age, gender, ethnicity and risk behaviour.

HIV-infected and HIV-exposed children

At the Emma Children's Hospital in the AMC, both HIV-infected and HIV-exposed children are in follow-up. Data from both groups are collected by the SHM, and collaborators in the Departments of Obstetrics and Gynecology and Experimental Immunology at the AMC analyse factors involved in neonatal HIV-1 transmission. The children infected with HIV-1 are included in the Paediatric Amsterdam Cohort on HIV-1 (PEACH). The HIV-exposed children are studied in the context of the European Collaborative Study on Mother-to-Child Transmission (MTCT) of HIV (ECS), an ongoing birth cohort study that recently merged with the Paediatric European Network for Treatment of AIDS (PENTA). All samples that are collected within the study until 2008 are part of the ACS and stored at the Department of Experimental Immunology.

The HIV epidemic

HIV incidence

Five MSM and no DU participating in the ACS seroconverted for HIV in 2011. The observed HIV incidence among MSM declined to 1.2 per 100 person-years in 2011.

Figure 7.1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2011.

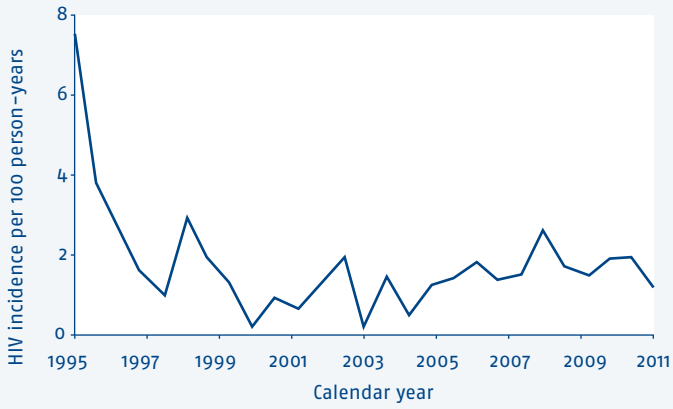
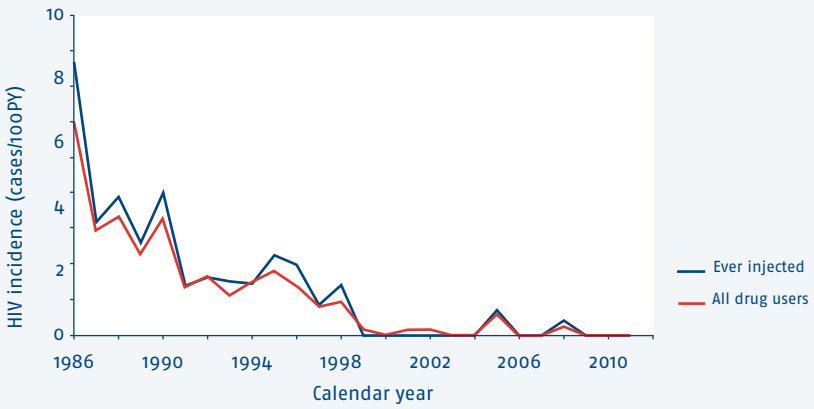


Figure 7.2: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among drug users, 1986–2011.



The HIV incidence in drug users has continued to decline and is now less than 1.0/100 person-years. *Figures 7.1* and *7.2* show the yearly observed HIV incidence rates for MSM and drug users from the start of the ACS through 2011.

Transmission of therapy-resistant HIV strains

Surveillance of transmission of drug-resistant HIV-1 strains was performed for seven MSM seroconverters and for four MSM who were seropositive at study entry in 2011. Two individuals were infected with virus harbouring resistance-associated mutations: a so-called 215-revertant (215E) mutation was found in one of the seroprevalent participants, and a virus carrying multiple protease (30N, 88D) and reverse transcriptase (41L, 215C) mutations was found in one of the seroconverters. In eight individuals only naturally occurring sequence variation was found, and no sequence could be obtained from one individual because of a low viral load. Phylogenetic analysis showed that all individuals harboured subtype B HIV-1 strains.

In the cohort of drug users, no seroconversions or seropositive entries appeared.

Highly active antiretroviral therapy (HAART) uptake

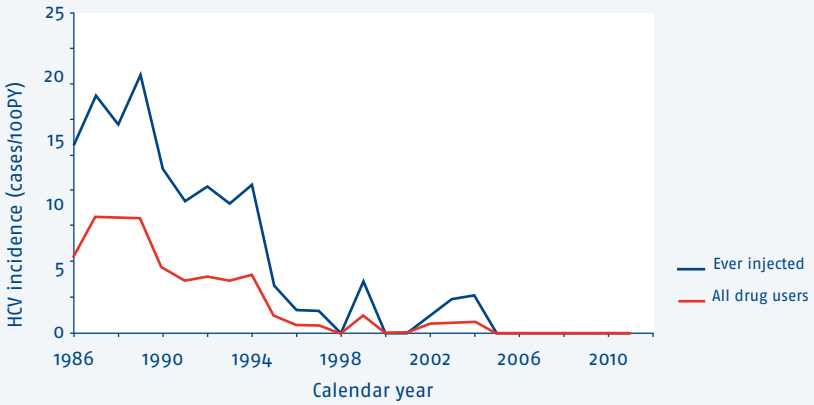
Of all 193 HIV-positive MSM visiting the Jan van Goyen Clinic or one of the other HIV treatment centers in the Netherlands according to the ACS protocols in 2011 and for whom treatment data were available, 185 (96%) received some form of antiretroviral therapy. Of 192 MSM for whom viral load results were available in 2011, 158 (82%) had a viral load of less than 50 copies/ml (assays: M2000rt).

Of the 30 HIV-positive DU who visited the PHSA in 2011 and for whom treatment data were available, 29 (97%) received some combination of antiretroviral therapy. Of the 30 DU, 28 (93%) had an undetectable viral load (less than or equal to 150 copies/ml [assay: M2000rt]) at their latest visit.

HCV incidence in drug users

In 2011 the HCV incidence was updated for the DU cohort. The HCV incidence in the total group and among injectors has strongly declined over the years to 0/100 person years since 2005 (see *Figure 7.3*).

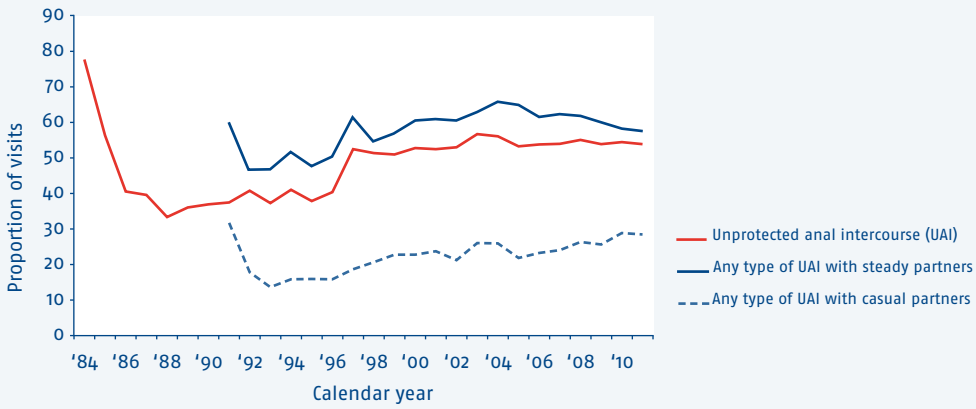
Figure 7.3: HCV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among drug users, 1986–2011



Risk behaviour of MSM

Information from the 895 questionnaires filled in by 479 HIV-negative MSM during cohort visits in 2011 resulted in 457 reports (54%) of unprotected anal intercourse (UAI) in the preceding 6 months. Higher proportions of UAI were reported for steady partners (57%) compared to casual partners (28%). Trends in UAI among HIV-negative MSM participating in the ACS have slowly increased since 1996, but they have remained relatively stable in recent years (*Figure 7.4*).

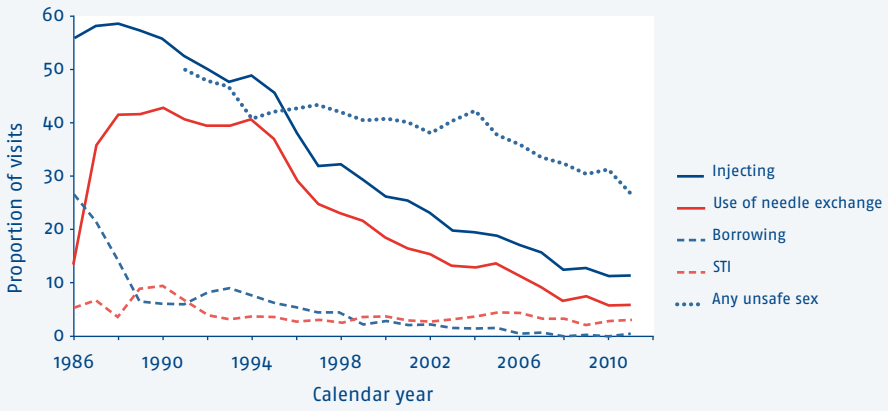
Figure 7.4: Trends in unprotected anal intercourse (UAI) in the past 6 months amongst HIV-negative men having sex with men (MSM) from the Amsterdam Cohort Studies (ACS), 1984–2011.



Risk behaviour of DU

In HIV-negative DU, reports of both injection and borrowing needles significantly declined over the period 1985-2011. Reports of high-risk sexual behaviour at follow-up visits decreased before 1996, remained relatively stable until 2005 and further decreased to approximately 35% in 2011. Reports of STI have remained relatively stable at approximately 6% in recent years (see *Figure 7.5*).

Figure 7.5: Proportion of visits per calendar year at which injecting and high-risk sexual behaviour was reported amongst 1315 drug users (DU) who were HIV-negative on entry to the Amsterdam Cohort Studies (ACS), 1986-2011.



Legend: STI=sexually transmitted infection

STI screening among MSM and DU in ACS

Since October 2008, all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea by polymerase chain reaction (PCR) techniques on samples of urine and pharyngeal and rectal swabs. Cases of syphilis are detected by TPHA (*Treponema pallidum* haemagglutination assay). In 2011, a total of 527 MSM from the ACS were screened for STI; 95 MSM were screened once, 394 twice and 5 more than twice. The prevalence of any STI at the first visit in 2011 was 8.7% (46/527), and the prevalence of any STI at the subsequent visit in 2011 was 7.8% (37/475). The prevalence of STI was significantly higher among HIV-infected MSM (18.3%) compared to HIV-uninfected MSM (7.0%).

Between November 2010 and June 2011, 197 (72%) of the 272 DU followed at the PHSA were also screened for chlamydia, gonorrhoea and syphilis as part of a pilot study to assess whether regular STI screening is indicated for this group. No infectious syphilis or gonorrhoea was found. The prevalence of chlamydia was 1.5% (3/197). On the basis of these results, it was decided that regular STI screening is not indicated for the DU in the ACS.

ACS research highlights 2011

To gain insight into the ongoing HIV transmission among MSM, we compared sexual risk behaviour pre- and post-HIV-seroconversion in 206 MSM participating in the Amsterdam Cohort Studies (1984-2008), both before and after the introduction of combination antiretroviral therapy (cART). MSM completed behavioural questionnaires and were tested for HIV antibodies every 6 months. Trends in anal intercourse and number of sex partners from 4 years before HIV seroconversion until 4 years after diagnosis were analysed with latent class random effects logistic regression models. We found that the risk of having UAI one year after HIV diagnosis decreased significantly when compared with 1 year before diagnosis in both the pre-cART era (difference=30% [95%CI:22%-36%]) and the cART era (difference=19% [95%CI:9%-30%]). In contrast to a continuing decrease of UAI in the pre-cART era, the probability of UAI in the cART era increased again to pre-seroconversion levels (61% (95%CI: 48%-74%)) 4 years after diagnosis. This study provides evidence that recently seroconverted MSM have reduced their sexual risk behaviour following HIV diagnosis both in the pre-cART era and in the cART period. However, in the cART period there has been less reduction in sexual risk behaviour, and it has returned to pre-cART levels within 4 years. These findings not only confirm the need for early HIV testing, but they also make it clear that much more effort should go into identifying, counselling and possibly treating recently seroconverted MSM who have been found to be one of the most important drivers of HIV transmission amongst MSM [289].

We investigated whether adaptations to cellular immunity have accumulated during the HIV-1 epidemic. To this end, we compared the number of CTL epitopes in HIV-1 strains isolated from individuals who seroconverted at the beginning of the HIV-1 epidemic (1985) and from individuals who seroconverted in recent calendar time (2005). The number of CTL epitopes in HIV-1 variants restricted by the most common HLA alleles in the population did not change significantly during the epidemic. In contrast, we found a significant loss of CTL epitopes restricted by HLA-B alleles associated with a low relative hazard of progression of HIV-1 disease during the epidemic. Such a loss was not observed for CTL epitopes restricted by HLA-A alleles. Thus, despite the large degree of HLA polymorphism, HIV-1 has accumulated adaptations to CTL responses within 20 years of the epidemic. The fact that such adaptations are driven by the HLA-B molecules that provide the best protection against progression of HIV-1 disease has important implications for our understanding of HIV evolution [290].

It was previously shown that HIV-1 has adapted to both the host cellular and humoral immune responses over the course of the epidemic. HIV-1 variants of recently infected individuals were more resistant to antibody neutralization than those from individuals infected in the beginning of the epidemic. With the recent discovery of more potent and cross-reactive broadly neutralizing antibodies, it was thought that these antibodies would overcome this phenomenon. However, the same trend was also observed with the broadly neutralizing antibodies VRC01, PG9 and PG16 [291]. This increased neutralizing resistance

could be attributed to longer V1-V2 regions and an increased number of potential N-linked glycosylation sites (PNGS), as viruses isolated from recently infected individuals could be made sensitive for neutralization if these regions were exchanged between viruses isolated from the beginning of the epidemic [292].

The pressure of the humoral immune system on the virus evolution within one individual was underscored by the analysis on longitudinally sampled HIV-1 env sequences from a patient with cross-reactive neutralizing activity in serum [293]. In this study, it was shown that virus variants with different sensitivities to neutralizing antibody pressure and with different replication fitness may coexist for a certain amount of time but that a changing environment in the host with progression of disease may favour the persistence of HIV-1 variants with the most fit and neutralization-resistant phenotype.

To test whether cellular subsets of the innate arm of the immune response are affected early after HIV-1 transmission in terms of numbers and infection with HIV-1, we used a cohort of HIV-1-infected individuals from the ACS. We analyzed various cellular populations during acute infection. We observed that plasmacytoid DCs (pDCS) represented a non-negligible HIV-1 DNA reservoir and that CD16(+) monocytes contained higher HIV-1 DNA loads than their CD16(-) counterpart during acute infection. Our results demonstrate that cell populations of the innate arm of the immune response are a major reservoir for HIV-1 from very early after transmission. The infection of such cell types will likely contribute to subsequent disease progression and immunodeficiency seen with HIV-1 [294].

Steering committee: The politburo

In 2011, the "politburo" met three times. Twenty-nine proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: 12 from AMC-Experimental Immunology, 13 from the AMC-Medical Microbiology, 2 from the UMCU, 1 from the GGD and 1 from the AMC-Internal Medicine. All twenty-nine requests were approved; however, one request was withdrawn after approval.

Publications in 2011 that include ACS data

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8. Rachinger A, Groeneveld PH, van Assen S, Lemey P, Schuitemaker H. **Time-measured phylogenies of gag, pol and env sequence data reveal the direction and time interval of HIV-1 transmission.** *AIDS. 2011 May 15;25(8):1035-9.*

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Theses in 2011 that include ACS data

Diana Edo-Matas, 21 January 2011, "Within-host HIV-1 evolution in relation to viral coreceptor use and host environment". Promotor is Prof. H. Schuitemaker; co-promotor is Dr A. B. van 't Wout.

Marit van Gils, 1 April 2011, "Cross-reactive neutralizing humoral immunity in HIV-1 disease: dynamics of host-pathogen interactions". Promotor is Prof. H. Schuitemaker.

Danielle van Manen, 24 June 2011, "The influence of host genetic factors on HIV-1 infection". Promotor is Prof. H. Schuitemaker; co-promotor is Dr A. B. van 't Wout.

Sebastian Bol, 7 July 2011, "Host genetic effects on HIV-1 replication in macrophages". Promotor is Prof. H. Schuitemaker; co-promotor is Dr A. B. van 't Wout.