

The Amsterdam Cohort Studies on HIV infection: annual report

~~2016~~2017

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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 people who use drugs (PWUD) was initiated in 1985. In ~~2016~~2017, the cohorts reached ~~32-33~~ 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 ~~32-33~~ 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 decade, research on the epidemiology of other blood-borne and sexually transmitted infections (STI) and their interaction with HIV has become an important component of the ACS research programme.

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, in turn, has contributed directly to advances in prevention, diagnosis, and management of HIV infection.

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 Public Health Service of Amsterdam (*Gemeentelijke Gezondheidsdienst Amsterdam*; GGD Amsterdam) (Department of Infectious Diseases, Research and Prevention), the [Amsterdam University Medical Centers \(UMC\)](#), ~~Academic Medical Center (AMC) of the~~ University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, ~~and the Department of~~ Internal Medicine, Division of Infectious Diseases, [the Emma's Childrens hospital \(Emma Kinderziekenhuis\)](#), HIV treatment centre, ~~Emma Kinderziekenhuis~~), 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 AMC's Department of Experimental Immunology. 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 of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu*, RIVM-CIb).

Ethics statement

The ACS have been conducted in accordance with the ethical principles set out in the declaration of Helsinki. Participation in the ACS is voluntary and written informed consent is obtained from each participant. The most recent version was approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the PWUD cohort.

The ACS in 2016-2017

The cohort of men who have sex with men

As of 31 December 2016-2017, 2,736 MSM 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. Blood is collected for diagnostic tests and storage. Of the 2,736 MSM, 607 were HIV-positive at entry into the study, and 251 seroconverted during follow up. In total, the GGD Amsterdam was visited 57,467 times by MSM.

Met opmaak: Markeren

~~Until 1988, 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. From 1988 to 1998, the cohort was also open for MSM infected with HIV at enrolment. During the period 1995–2004, only men aged ≤30 years with at least one male sexual partner in the previous six months could enter the study. From 2005 to 2013, recruitment has been open to MSM of all ages with at least one sexual partner in the preceding six months. Since 2013, HIV-negative men of all age groups are eligible to participate if they live in or are closely connected with the city of Amsterdam and had had at least one male sexual partner in the preceding six months. 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.~~ In line with the advice issued by the international scientific advisory committee in 2013, the cohort ~~made~~ makes additional efforts to recruit young HIV-negative MSM (age ≤30 years). 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 Centre. In 2003, the ‘HIV Onderzoek onder Positieven’ (HOP) protocol (*HIV Research in Positive Individuals*) was

Opmerking [AAM1]: In eerste incl round iedereen welkom?

Opmerking [AAM2]: Hier staat dat we alleen HIV-neg includeerden, maar dat is niet waar. HIV+ zijn ook toegelaten De laatste in 2013 en daarna mocht het niet meer. Hoe zit dit nu? Boekje 2001-2009 zegt dat er MSM werden geïncludeerd en zegt daarbij niets over HIV status. Zie suggestie nieuwe tekst hierboven

initiated. Individuals with a recent HIV infection at study entry at the GGD Amsterdam and those who seroconverted for HIV during follow-up within the cohort continue to return for study visits 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 ~~2016~~2017, 630 HIV-negative, and 64 HIV-positive MSM were in active follow up within the ACS (6-monthly visits to the GGD Amsterdam for STI testing, including HIV). Of these 64 HIV-positive MSM, 62 filled in behavioural questionnaires. Apart from the HIV-positive MSM visiting the GGD Amsterdam, 267 HIV-positive MSM were followed outside the GGD Amsterdam at the Jan van Goyen Medical Centre or the HIV Focus Centre in Amsterdam. Behavioural questionnaires were filled in by 20 of these men. In 2017, 23 new HIV-negative MSM were recruited. The median age in this group was 23.9 years (IQR 23.2-26.6). The median age of the total group of MSM was 44.5 years (interquartile range [IQR] 37.3-52.1), 8.2% were non-Dutch, and 72.8% had attained a high level of education. The majority of the participants (84.6%) were residents of Amsterdam. In 2016, 23 new HIV-negative MSM were recruited. The median age in this group was 23.9 years (IQR 23.2-26.6).

- Met opmaak: Markeren

The cohort of drug users

As of 31 December 2016, 1,680 people who use drugs (PWUD) were included in the ACS and contributed 28,194 visits. ~~Before 2014, participants visited the GGD Amsterdam every four to six months. They completed 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, HIV-positive participants, and in the past also HIV-negative participants, underwent a medical examination. Blood was collected for diagnostic tests and storage.~~

In 2014, the cohort was closed for new participants. ~~and PWUD included in the ACS were divided into two groups in line with the advice of the international scientific advisory committee~~

~~in 2013. Group 1 consisted of PWUD who visited the GGD Amsterdam once a year to complete questionnaires with no testing and blood sampling. Group 2, the focus group, consisted of PWUD who were 1) HIV positive; 2) hepatitis C virus (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 previous years.~~ Regular follow-up of drug users continued until February 2016. Finally, all drug users who had ever participated in the ACS were invited for an end-of-study interview. ~~A total of 182 end-of-study interviews were held between~~ February and July 2016, after which the follow up of drug users was successfully ended.

Of the 1,680 PWUD, 323 were HIV-positive at entry, and 99 seroconverted during follow up. The last HIV seroconversion was seen in 2012. By 31 December 2016, 576 deaths had been confirmed among PWUD. The median age of the PWUD who visited the ACS in 2016 was 55 (IQR 49-59), 8.1% had attained a high level of education, and 63.4% were born in the Netherlands.

ACS Biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies embedded in the ACS, have resulted in a large collection of stored samples. The ACS biobank includes plasma/serum and PBMC 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 HIV-positive and HIV-exposed children at the Emma Kinderziekenhuis in the AMC until 2008. All stored samples are available for ACS research.

Subgroup studies and affiliated studies

Opmerking [AAM3]: @ allen, zijn er andere substudies om hier te vermelden?

AGE_hIV cohort study

Opmerking [AAM4]: Maarten, wil je onderstaande tekst updaten? In ieder geval de gele markeringen.

The AGE_hIV cohort study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health, 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 comorbidities and known risk factors for these comorbidities in HIV-infected patients aged ≥ 45 years, and to determine the extent to which comorbidities, their risk factors and their relation to quality of life differ between HIV-infected and uninfected groups. Participants undergo a comprehensive assessment for comorbidities and complete a questionnaire at intake and follow-up questionnaires every 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 similar risk groups 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 2016/2017, 437 HIV-1-infected participants and 457 HIV-uninfected individuals had completed the third follow-up visit. In October 2016/2017 the fourth round of study visits started, which is expected to continue until summer 2019.

Met opmaak: Markeren

Met opmaak: Markeren

Met opmaak: Markeren

H2M cohort study

From 2010 to 2013, the H2M (HIV and human papillomavirus [HPV] in MSM) cohort study was conducted in a subset of the HIV-negative (n=459) and HIV-positive (n=40) participants of the ACS who were in active follow up, and also among patients of the STI clinic of GGD Amsterdam and the Jan van Goyen Medical Centre. The aim of the study was to compare the prevalence, incidence, and clearance of high-risk (hr) HPV infections between HIV-negative and HIV-infected MSM.

Opmerking [AAM5]: Maarten, wil je onderstaande tekst updaten? In ieder geval de gele markeringen

In 2015, a study based on the H2M cohort was initiated to identify potential predictors for high-grade anal intra-epithelial neoplasia in the HIV-infected MSM population. This study, the H2M2, is an Aids Fonds-supported project and a collaboration between the GGD Amsterdam, AMC, DC Klinieken Oud-Zuid, the RIVM-CIb, DDL diagnostic laboratories and VUmc. The study includes a subset of the HIV-positive participants of the ACS (n=19). In 2016, initial analyses showed that among 193 HIV-infected MSM, neither persistence of anal HPV infection nor HPV viral load in the anal mucosa nor anti-HPV antibodies in serum were good predictors of anal high-grade dysplasia.

Met opmaak: Markeren

Since September 2014, collection of anal and genital swabs has been resumed in all consenting ACS participants. The key aim of this second new study (the H2M3 study), which builds on the H2M study, is to examine long-term incidence and clearance of anal and penile hrHPV infections. Between September 2014 and November 2015, 700 men provided samples for HPV testing during ACS cohort visits. Of these, 434 (62%) were already participating in the H2M study (recruited 2010-2011), and 266 (38%) were new participants who joined the ACS after inclusion in the H2M study had ended. Samples at two time points (6 months apart) have been tested in the laboratory for HPV DNA, and initial analyses have been conducted. This study found that one-third of MSM had not cleared an anal HPV-16 infection after four years; thus, persistence of anal HPV is common. Twenty-two percent of men who were not infected with HPV-16 at baseline acquired an anal HPV-16 infection over a four-year period. So, even in highly pre-exposed men, the incidence rate of hrHPV infections is high. In 2017, XX anal swabs from XX MSM have been collected. The H2M3 study is a collaboration between GGD Amsterdam, ACS, and Crucell.

Met opmaak: Markeren

Opmerking [AAM6]: Klopt het dat er nu wel swabs worden verzameld maar deze niet worden getest? Alleen opslag?

AMPrEP project in H-TEAM

The Amsterdam pre-exposure prophylaxis (AMPrEP) project is a prospective, longitudinal, open-label demonstration study. The aim of the study is to assess the uptake and ~~acceptability~~ acceptability of daily versus event-driven PrEP among MSM and transgender

Opmerking [AAM7]: Elske, wil je onderstaande tekst updaten? Ik heb met gele markering de punten aangegeven die in ieder geval geupdate moeten worden

persons (TG) at increased risk for HIV infection, as part of a comprehensive HIV reduction package offered at a large STI clinic.

In total, 374 MSM and 2 TG were enrolled between August 2015 and May 2016 at the STI outpatient clinic of the GGD Amsterdam. In ~~2016~~2017, 35 ACS participants also participated in the AMPrEP project at their own initiative. Participants were asked to return for follow-up visits one month after the PrEP start visit and then every three months. At every visit participants fill in questionnaires on risk behaviour, adherence and general wellbeing and are screened for STI and HIV. Participants will be provided with PrEP until June 2018.

Met opmaak: Markeren

Met opmaak: Markeren

The AMPrEP project is part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic (www.hteam.nl).

The HIV epidemic

HIV incidence

In ~~2016~~2017, 3 MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable in recent years and was 0.5 per 100 person years in ~~2016~~2017. ~~The HIV incidence in PWUD has been stable since 2008, with between zero to less than one case per 100 person years. As follow up was restricted to a selection of PWUD and inclusion stopped in 2014, followed by closure of the cohort in 2016, the yearly observed incidence of PWUD can only be presented until 2013. Figure 8.1 and 8.2 show~~ the yearly observed HIV incidence rates for MSM ~~and PWUD~~ from the start of the ACS through ~~2016~~2017 ~~and 2013~~, respectively.

Met opmaak: Markeren

Met opmaak: Markeren

Figure 8.1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1985-~~2016~~2017.

Figure 8.2: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among people who use drugs, 1986-2013.

Legend: PWID=people who inject drugs; PWUD=people who use drugs (including injecting).

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.

Opmerking [AAM8]: @ Neeltje, kun je onderstaande paragraaf updaten? We hebben het vorig jaar weggelaten, maar Maria wil het er toch graag ook, ook als er niemand is getest

Combination antiretroviral therapy (cART) uptake

Of all 320 HIV-positive MSM from the ACS visiting the HIV Focus Centre, the Jan van Goyen Medical Centre or one of the other HIV treatment centres in the Netherlands in 2016-2017, treatment data were available for 317 men. Of these, 314 (99%) received some form of antiretroviral therapy. Of the 308 MSM for whom viral load results were available in 2016-2017, 286 (93%) had a viral load of <50 copies/ml (M2000rt assays).

Met opmaak: Markeren

Risk behaviour of MSM in ACS

Information from the questionnaires completed by 610 HIV-negative MSM during cohort visits in 2016-2017 showed higher proportions of condomless anal intercourse (CAI) with steady partners (39.6%) compared to casual partners (30.4%). Trends in CAI among HIV-negative MSM participating in the ACS, especially CAI with casual partners, continue to show a gradual increase from 1996 onwards. (Figure 8.3).

Met opmaak: Markeren

Met opmaak: Markeren

Met opmaak: Markeren

Figure 8.3: Trends shown by the Amsterdam Cohort Studies (ACS) in condomless anal intercourse (CAI) with casual and steady partners in the past six months among HIV-negative men who have sex with men (MSM) with a casual and/or steady partner, 1992-~~2016~~2017.

Legend: CAI=condomless anal intercourse; SP=steady partner; CP=casual partner.

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 ~~2016~~2017, a total of 665 MSM from the ACS were screened for STI. The overall prevalence of any STI (i.e., chlamydia, gonorrhoea, syphilis, and HCV) was 15.9% (99/621) among HIV-negative MSM and 29.5% (13/44) among HIV-positive MSM.

Met opmaak: Markeren

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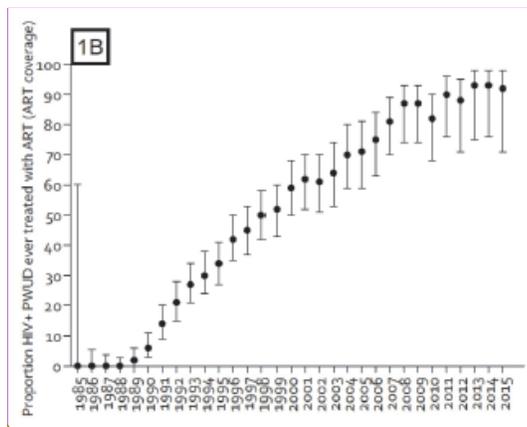
Met opmaak: Markeren

HIV and HCV treatment uptake among PWUD in ACS

ART coverage increased over time, from 5.7% in 1990 and 42.2% in 1996 to 91.7% in 2015 (see *Figure 8.4*). The proportion of PWUD initiating ART ranged from 4.8% in 1990 to 33.3% in 2011. At eight years after HIV seroconversion, the cumulative probability of ART uptake was 42.5% in the pre-cART era and 61.5% in the cART era. HCV treatment initiation peaked in 2006 (9.7%). HCV treatment coverage was 43.9% in 2015 (see *Figure 9.5*), but lower among HIV co-infected (23.5%) than HCV mono-infected PWUD (52.5%). In 2015, 3.0% initiated HCV treatment with direct-acting antivirals. [Van Santen D, et al. Intern J Drug Pol. 2017;47:95-101]

Opmerking [CE9]: Catriona: add reference

Figure 8.4: The proportion of HIV-positive people who use drugs (PWUD) participating in the Amsterdam Cohort Studies (ACS) ever treated with ART, 1989-2015. [Van Santen D, et al. Intern J Drug Pol. 2017;47:95-101]

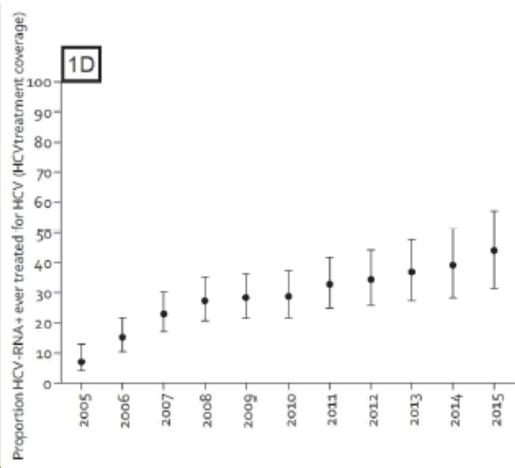


Opmerking [CE10]: Zest:
1) linksboven 1B verwijderen

Met opmaak: Lettertype: (Standaard)
Calibri, 12 pt, Vet, Cursief

Legend: PWUD=people who use drugs; ART=antiretroviral therapy.

Figure 8.5: The proportion HCV RNA-positive people who use drugs (PWUD) participating in the Amsterdam Cohort Studies (ACS) ever treated for HCV, 2005-2015. [Van Santen D, et al. Intern J Drug Pol. 2017;47:95-101]



Opmerking [CE11]: Zest:
 1) linksboven: 1D verwijderen
 2) y-as: verbindingstreepje tussen HCV en RNA verwijderen

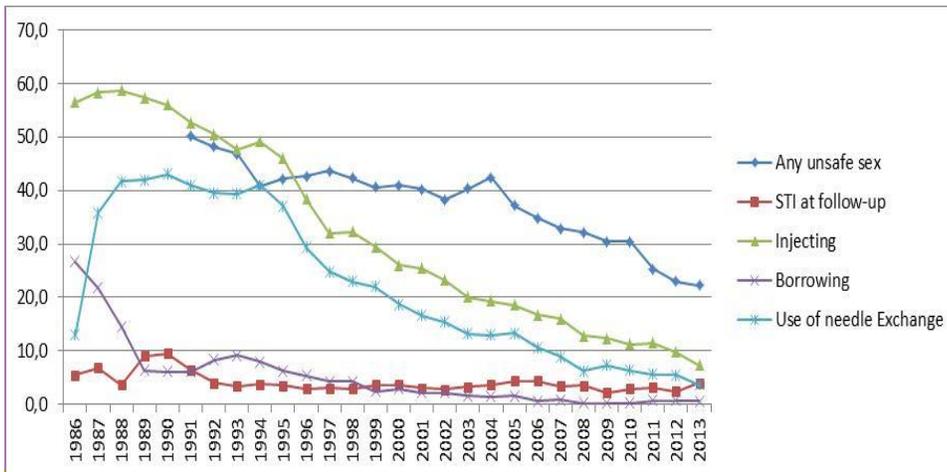
Met opmaak: Lettertype: (Standaard)
 Calibri, 12 pt, Vet, Cursief

Legend: HCV=hepatitis C virus.

Risk behaviour of PWUD in ACS

As follow-up was restricted to a selection of PWUD and inclusion stopped in 2014, and the cohort was closed in 2016, trends in risk behaviour of PWUD can only be presented until 2013. In HIV-negative PWUD, 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 8.6).

Figure 8.6: Proportion of visits per calendar year at which injecting and high risk sexual behaviour was reported amongst people who use drugs (PWUD) who were HIV negative on entry to the Amsterdam Cohort Studies (ACS), 1986-2013.



Opmerking [CE12]: Zest:
 1) X-as: *Calendar year*
 2) Y-as: *Proportion of visits*
 3) Y-as: ',0' verwijderen. Dus 0, 10, 20, 30 etc....
 4) Legende: streepje tussen follow en up vervangen met spatie
 5)Legende: geen hoofdletter bij Exchange

Met opmaak: Lettertype: (Standaard) Calibri, 12 pt, Cursief

Legend: STI=sexually transmitted infection.

ACS 20162017 research highlights

Opmerking [AAM13]: @ Neeltje en Lia, willen jullie de 2017 research highlights toevoegen?

Steering committee

In 20162017, the steering committee met three times. Twelve proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: six from the AMC Medical Microbiology department, four from the AMC Experimental Immunology, and 2 from GGD Amsterdam. Eight of the proposals were collaborations with groups outside the ACS. Nine requests were approved, and three were declined even after revision.

Publications in 20162017 that include ACS data

Opmerking [AAM14]: @ allen, graag aanvullen

Met opmaak: Engels (V.S.)

Met opmaak: Engels (V.S.)

Theses in **2016-2017** that include ACS data

Opmerking [AAM15]: @ allen,
graag aanvullen

S.W. de Taeye – 9 March 2017: **Stabilization of HIV-1 envelope glycoprotein trimers to induce neutralizing antibodies.** University of Amsterdam. Supervisors: Prof. B. Berkhout & Prof. R.W. Sanders