The Amsterdam Cohort Studies on HIV infection
Annual Report 2005

Introduction

The Amsterdam Cohort Studies (ACS) on HIV and AIDS among homosexual men was initiated in 1984, followed shortly by the Amsterdam Cohort Studies among drug users in 1985. The ACS are a collaboration of the Health Service of Amsterdam, the Department of Human Retrovirology, the AIDS unit of the department of infectious diseases and the International Antiviral Therapy Evaluation Center (IATEC) of the Academic Medical Center at the University of Amsterdam, Sanquin Blood Supply foundation, and the Department of Immunology at the University Medical Center Utrecht.

Thus far, 2243 homosexual men (HM) and 1640 (injecting) drug users (DU) have been included in the ACS. Every 3-6 months they complete(d) a standardized questionnaire to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognition's, health care use, depression, psychological disorders and demographics. In addition, they undergo a medical examination (HIV positives and in the past HIV-negative drug users as well) and blood is drawn for biological and immunological tests and storage.

Of the 2243 HM, 566 were HIV-positive at study entry and 177 seroconverted during follow-up. For the 1640 DU, these figures are 322 and 95, respectively. By December 31 2005, 323 HM and 362 DU had died, other participants were requested to leave the study (e.g. all 'old' seronegative homosexual men), or left at their own request. On average, 90%-92% of participants that visited the ACS a given calendar year returned for a follw-up visit the next year. In total, the HM and DU have visited the Amsterdam Health Service about 45.000 and 23.000 times, respectively.

The cohorts in 2005

Homosexual men

In 2005, 517 HM were followed at the Health Service of Amsterdam. Eighty-seven of them were newly recruited in 2005. In 2005, recruitment was open for HM of all ages with at least one sexual partner in the preceding 6 months. 484 men are HIV negative and 33 men are HIV positive. These positive men, of whom 20 are HIV seroconverters, are followed according to the HOP protocol, which was initiated in October 2003 for HM who seroconverted or were HIV positive at study entry in the cohort among young HM after 1999.

In 2005, 218 HIV-infected HM that 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-two of them are HIV seroconverters. From HM in active follow-up at the Jan van Goyen clinic, plasma and cells are stored of those HIV-positives (1) who seroconverted during follow-up, (2) who had been defined as slow/non progressor or matched fast progressor in 1996 and (3) who were HIV-positive for > 10 years and had a CD4 count >400 cells/mm3 after 10 years of HIV-positive follow-up without effective therapy (n=94). In 2005, the 6-monthly questionnaire of the HM was expanded to include questions regarding sexual networks and drug use during sex.

Drug users

In 2005, 465 drug users were followed at the Health Service of Amsterdam: 66 were young drug users aged 30 years or less and recruited after 2000. In 2005 one new drug user was included, although the cohort was still open for drug users less than 30 years of age who used cocaine, heroin or amphetamines at least 3 times a week in the 2 months preceding enrolment. Sixty-six of the 465 drug users are HIV-infected, of whom 23 have seroconverted during follow-up in the ACS. To assess quality of life, the MOS Short-Form 36 (SF-36) questionnaire was completed by almost 400 drug users. In close collaboration with the Amsterdam Institute for Addiction Research (AIAR), the MATE-interview (Measuring Addiction for Triage and Evaluation) was administered to study psychosocial functioning and health care needs. The hospital anxiety and depression score (HADS) was used to assess the levels of depression among drug users.

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) 7 DU of the cohort have started HCV therapy.

HIV incidence

Seven homosexual men and two drug users seroconverted for HIV in 2005. Figure 1 and 2 show the yearly HIV incidence rates for homosexual men and drug users since the start of the ACS up to 2004.

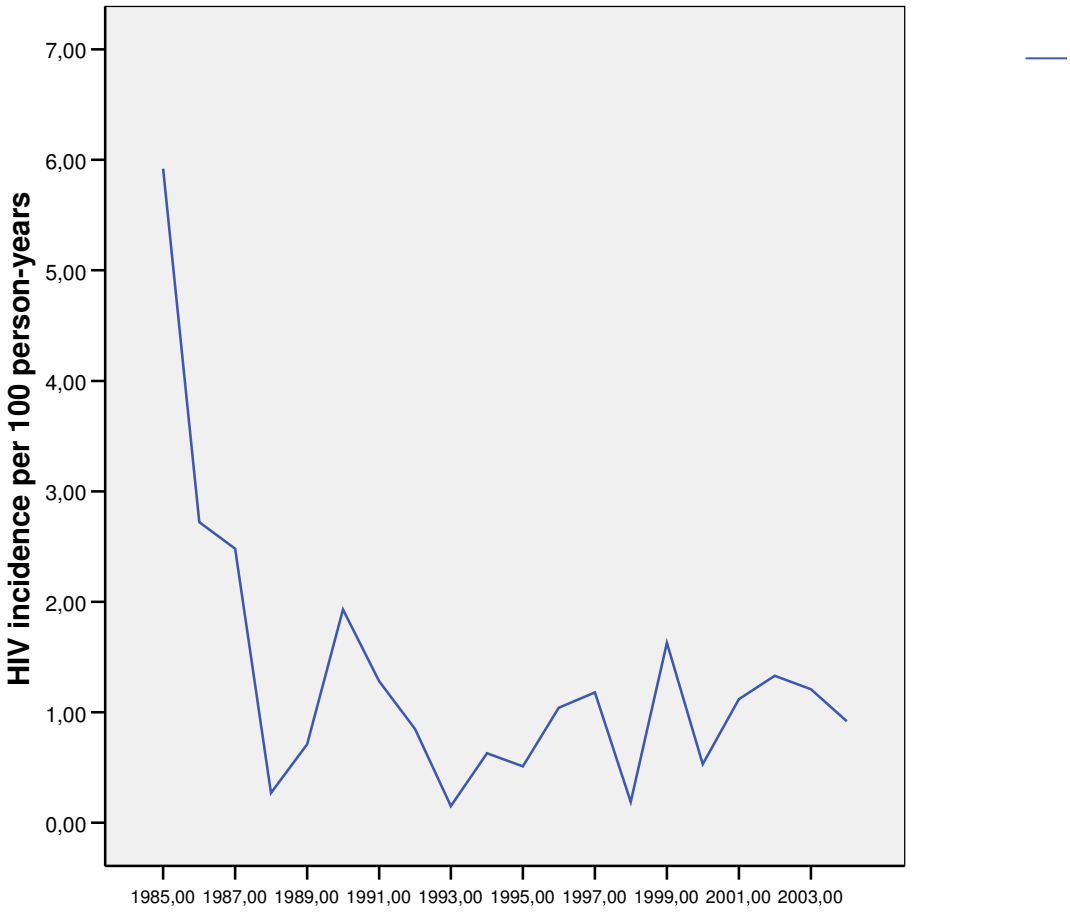

Figure .1 Yearly HIV incidence per calendar year in the Amsterdam Cohort Study among homosexual men

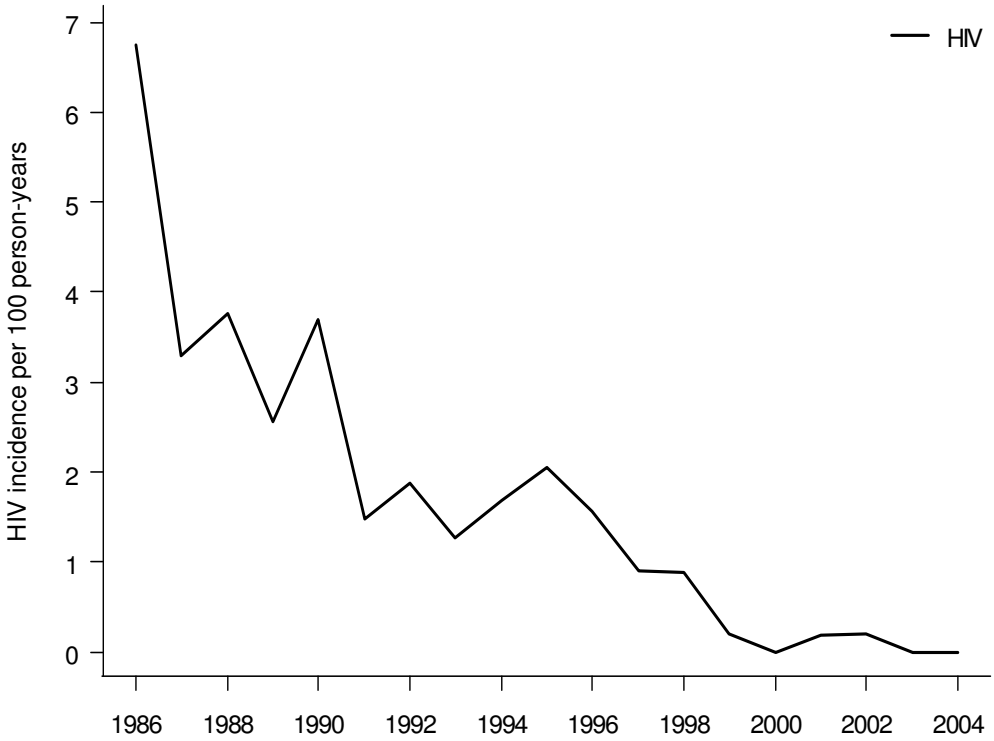

Figure 2. Yearly HIV incidence per calendar year in the Amsterdam Cohort Study among drug users

Transmission of therapy resistant HIV strains
A total of 100 primary HIV-1 infections (32 AMC hospital and 68 ACS) were identified from 1994-2002. Transmission of drug-resistant mutations deceased over calendar time with 20% of infection bearing drug-resistant mutations before 1998 versus only 6% after 1998 (Bezemer et al, AIDS 2004). In 2005 2/9 seroconverters within the ACS, became infected with a drug-resistant strain.

Risk behaviour
In de cohort of HIV negative HM, until 1995 trends in HIV and STI incidence were concurrent among young men, however since 1995 there was a significant increase in syphilis and gonorrhoea incidence (see figure 3), but no change in HIV incidence (van der Bij et al, 2005).
In the cohort of HIV negative DU, reports of both injecting and borrowing needles significantly declined over the period 1985-2004. Reports of sexual risk behaviour and STI at follow-up visits decreased before 1996, but not after 1996 (see figure 4). It was estimated that at least 27% of all drug users included in the ACS had died within 20 years after starting regular drug use: for half, death had been due to causes unrelated to HIV. The estimated prevalence of abstinence for at least 4 months from drugs and methadone was only 27% at 20 years since imitation (Termorshuizen et al, 2005)

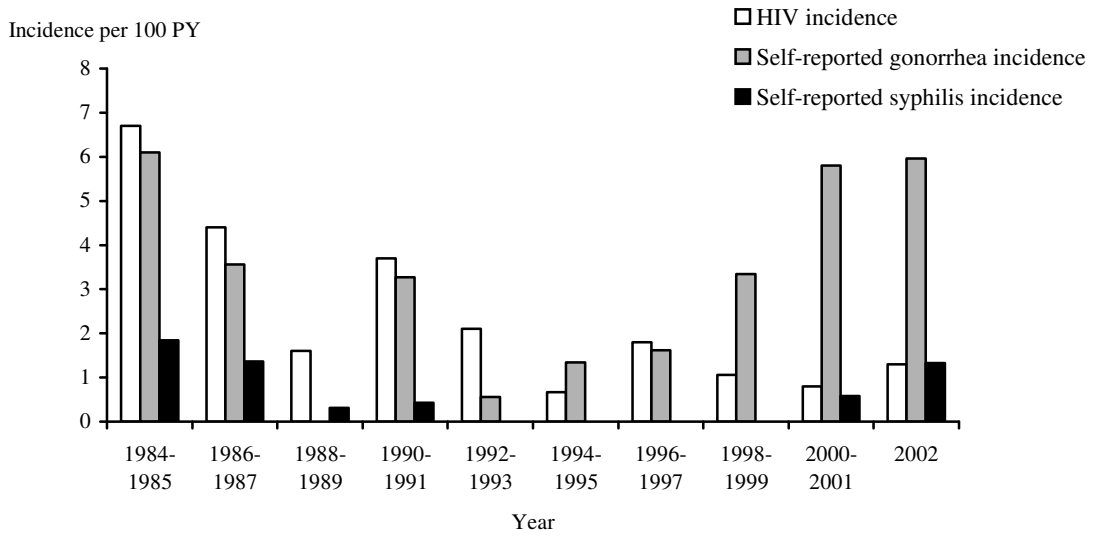

Figure 3. Incidence of gonorrhea, syphilis and HIV per 100 PY among 863 HIV-negative young (<=30 at entry until 35 years) gay men, in Amsterdam 1984-2002.

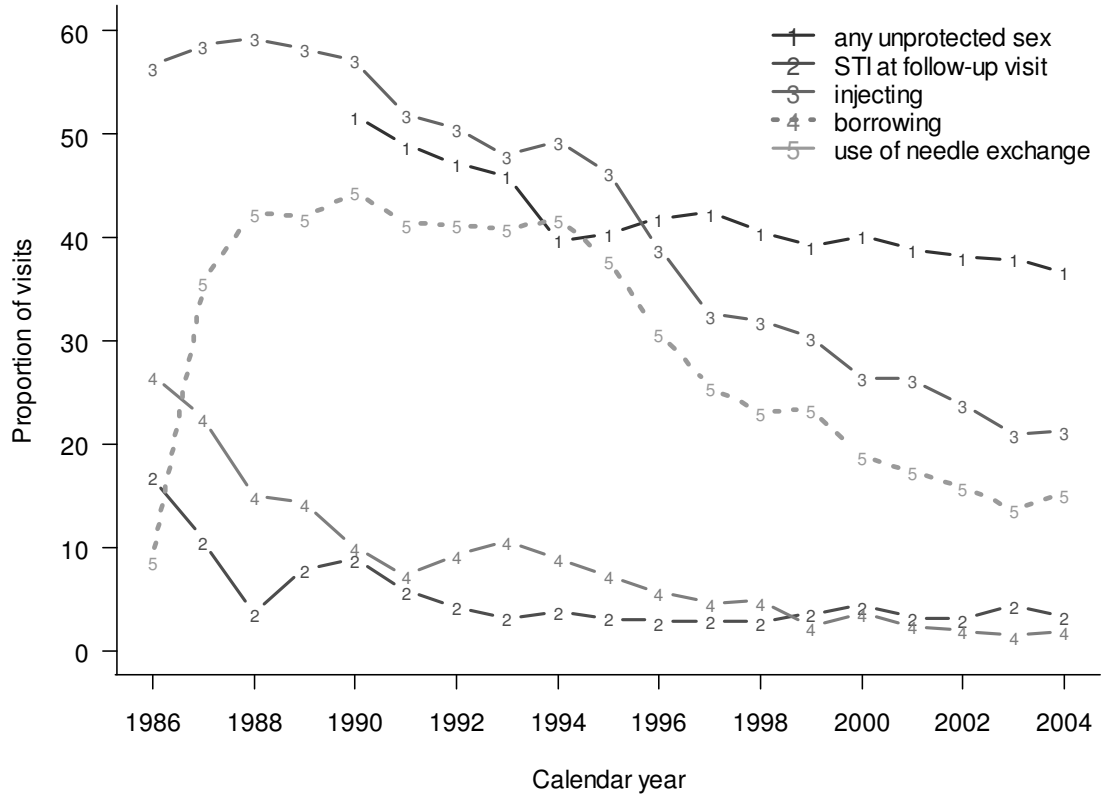

Figure 4. Proportion of visits per calendar year at which injecting and sexual risk behaviour was reported among 1315 DU who were HIV negative on ACS entry, 1986-2004.

HCV and GBV-C co-infections

Infection with GBV virus C (GBV-C) causes no clinical disease (GBV-C) but was determined in stored samples to study its relationship with HIV disease progression (see scientific highlights). The prevalence of GBV-C antibodies was 41%. among HM at HIV seroconversion/HIV positive at study entry, whereas 42% tested positive for GBV-C RNA (van der Bij et al, 2005).

Although injecting risk behaviour and hepatitis C virus (HCV) prevalence decreased sharply over time in young ever-injectors - HCV prevalence was 90% in 1985-1989 -, in 2000-2004 HCV prevalence remains high (44%) among young DU who have ever injected (van de Laar et al, 2005).
In 2005, the retrospective testing for HCV, HBV and HSV1 and 2 infections of all participants with at least two study visits has been continued and is expected to be completed in 2006.

HAART uptake
For the 218 HIV-positive homosexual men visiting the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2005, 177 (81%) received any form of antiretroviral therapy. Viral load was < 400 cells/ml (bDNA) for 157/177 (89%).
Of the 66 HIV-positive drug users who visited the Health Service of Amsterdam in 2005, 31 (47%) received any combination of antiretroviral therapy. Of these, 26 (84%) had undetectable viral load (Nuclisens < 400 copies/ml) at their latest visit.

Scientfic Highlights
Some studies found that infection with GB virus C – a virus related to hepatitis C – delays HIV disease progression. Within the Amsterdam Cohort Studies we could not confirm this finding. We found evidence that the presence of GBV-C RNA is dependent on the presence of sufficient CD4 cells, which gives new insights in the pathogenesis of GBV-C (van der Bij et al, 2005). In another study in the Amsterdam Cohort Studies we showed that the effect of age and polymorphisms in CCR-5 and CCR-2 on HIV disease progression “works” through CD4-cells and HIV-1 RNA (Geskus et al, 2005). Ethiopians have low CD4 counts and this could mean that after HIV-1 infection they have a faster progression to disease and death. In our cohort study in Ethiopia, we studied the CD4-slope with Markov models among HIV-1 infected adults and compared this with the slope of HIV-1 infected homosexual men in Amsterdam: no evidence for a faster progression was found among Ethiopians which indicates that the immune activation within this group does not lead to a shorter survival time after HIV-1 infection, which was postulated by others (Mekonnen et al, 2005).

The availability of HAART has led to a dramatic decrease in disease progression and mortality, but the drugs can cause a range of adverse effects, which include peripheral neuropathy, myopathy (including cardio-myopathy), hepatic steatosis, lactic acidosis, and peripheral lipoatrophy. The drugs may induce toxicity through an effect on mitochondria. We now reported that infection with HIV-1 may, itself, reduce the mitochondrial DNA content of blood cells (Casula et al J Inf Dis, 2005]. This analysis was performed as a longitudinal study in a group of individuals with documented HIV-1 seroconversion.

Although the majority of HIV-1 drug resistance is observed in treated patients, these drug-resistant virus variants can also be transmitted to therapy-naïve individuals. We analyzed the prevalence of transmitted drug resistance among seroconverters as part of the CASCADE program. Forty-five of 438 patients (10.3%), seroconverting between 1987 and 2003, are infected with a drug-resistant HIV-1 variant (Masquelier et al JAIDS) 2005. Importantly, evidence was found for a rise of incidence over time.

New York City health officials announced on 11 February 2005 that a patient developed full-blown AIDS shortly after being diagnosed with a rare, drug-resistant strain of HIV-1. We discussed in a commentary that the hype about the spread of a super aggressive HIV-1 strain seemed unfounded (Berkhout, Retrovirology, 2005). It was argued that one can only link a particular pathogenicity phenotype to a circulating virus strain when a distinct disease pattern is seen in multiple infected persons. When an isolated case is observed, it is equally possible that the particular disease pattern is not due to the virus, but rather due to a special property of the infected human host. Person-to-person variation in the immune system or other cellular factors that interact with HIV-1 (receptors, innate immune factors, etc) can greatly influence disease progression.

Another human herpesvirus, HHV8, is the causative agent of Kaposi’s sarcoma. To score the potential predictive value of measuring the viral loads of CMV and HHV8, we screened ACS cohort samples at the time of AIDS diagnosis. We found that HHV8 DNA and CMV DNA measured in the blood of AIDS patients relates exclusively to the respective viral disease, without having an additional predictive value (van der Kuyll et al., J Med Virol 2005).

Other studies are ongoing or have recently been initiated, including the analysis of attenuated HIV-1 variants in ACS-patients with an extremely slow disease progression (Vici program Berkhout), the

analysis of sialoadhesin (CD169) as new marker for disease progression and as important molecule for monocyte function, the description of new HIV-1 variants (a new subtype has been identified recently!), the search for novel viruses in immunocompromised patients (Vidi program Lia van der Hoek), and a detailed analysis of the viral fitness of “old” (1984) versus “recent” (2004) samples from the Amsterdam epidemic.

Some individuals have remained HIV seronegative despite high risk sexual behaviour. In five out of six high risk seronegative homosexual men and in five out of five individuals 7.8 to 1.6 years prior to seroconversion, we detected HIV-1 proviral DNA at very low levels in sequential peripheral blood mononuclear cell samples. These data indicate a high prevalence of low-level HIV-1 DNA in exposed seronegative individuals. This proviral DNA could either reflect transmission of replication incompetent virus or dead-end infection of initially replication competent virus (Koning et al. J Virol 2005).
In a subsequent study we analysed host factors associated with protection from productive infection in the same group of high risk seronegative individuals. Sofar, different features have been associated with low susceptibility to HIV type 1 (HIV-1) infection in exposed seronegative individuals. These include genetic make-up such as homozygosity for the CCR5-D32 allele and the presence of HIV-specific CTLs. We studied immune activation and immune responsiveness in relation to HIV-1 susceptibility in 42 high-risk seronegative (HRSN) participants of the Amsterdam Cohort Studies and 54 men from the same cohort who were seronegative at the moment of analysis but later became HIV seropositive. HRSN had higher naive (CD45RO CD27) CD4 and CD8 T cell numbers and lower percentages of activated (HLADR CD38, CD70) CD4 and proliferating (Ki67) CD4 and CD8 T cells, irrespective of previous episodes of sexually transmittable infections. Furthermore, whole blood cultures from HRSN showed lower lymphoproliferative responses than healthy laboratory controls. These data suggest that low levels of immune activation and low T cell responsiveness may contribute to low HIV susceptibility (Koning et al. J Imm 2005).

In approximately 50% of HIV-1 subtype B-infected individuals, progression to AIDS is preceded by the emergence of CXCR4-using (X4) variants, whereas the rest progress to AIDS in the presence of CCR5-using (R5) variants only. In a previous study, we showed that during disease progression in the presence of R5 variants only, HIV-1 variants emerge with a decreased sensitivity to inhibition by RANTES, a natural ligand of CCR5 that inhibits cellular entry of R5 variants. This observation was of potential clinical relevance as HIV-1 small-molecule R5 entry inhibitors are a new class of drugs that, in analogy to RANTES, target the binding and subsequent entry of HIV into the target cell. Here we show that R5 HIV-1 sensitivity to RANTES correlates with sensitivity to the R5 small-molecule inhibitor AD101. HIV-1 small-molecule entry inhibitors are a new class of drugs that target the binding and subsequent entry of HIV into the target cell. Furthermore, we found that R5 variants obtained from individuals who later developed X4 variants were less sensitive to AD101 inhibition compared with R5 variants obtained from individuals who never developed X4 variants. These results may have implications for the evaluation of R5 inhibitors in future clinical trials (Koning et al. J Inf Dis 2005).

As a natural defence against retroviruses, human and non-human primate cells express inhibitory factors that interfere with virus replication at an early step after virus entry. One of these inhibitory factors has recently been identified to be the cytoplasmic body component Trim5α. Although the mechanism by which Trim5α interferes with HIV-1 infection is still unknown, the viral determinant involved in this restriction is located in the cyclophilin A (CyPA) binding region of the viral capsid protein. Interestingly, we previously observed that mutations in the cyclophilin A (CypA) binding region of the capsid protein makes HIV-1 resistant to Trim5α.

In our present study, we analyzed whether amino acid changes in the CyPA binding region of the capsid protein that are associated with resistance against Trim5α, occur during HIV-1 infection and whether Trim5α resistant variants play a role in disease progression. We observed that Trim5α escape mutants emerge predominantly in X4 progressor (17%) relatively late in infection. Emergence of Trim5α was associated with a prolonged asymptomatic stage and late development of X4 variants. This suggests that Trim5α might play a role in control of viral burden during the asymptomatic stage. However, an increase in disease progression (based on CD4 counts below 200/ul) was observed late in infection suggesting an accelerated disease progression after the emergence of Trim5α resistant variants.

We have shown that HIV specific CD4 T cells are low in number in asymptomatics that are not treated but these cells can be detected with several techniques. We have found that the current hypothesis that Il-2/ IFN gamma producing cells are causally related to low viral load and slow progression to

AIDS may not be true: 1. in patients that were treated during acute infection we showed that functional HIV specific CD4+ T cells were spared but when patients stopped treatment we did not subsequently see a relation with control of viremia (Jansen et al, AIDS 2005. This is in agreement with recent data from the laboratory of Bruce Walker who initially claimed an immunological and clinical benefit from treatment of acute HIV infection; 2. furthermore in a large prospective cohort study including all 102 seroconvertors from the Amsterdam Cohort we showed that CD4 helper reponses shortly (12 months) after seroconversion did not relate to sustain of CD8 responses and did not have prognostic value for time to progression to AIDS (Jansen et al, Blood 2006). Our data are in agreement with earlier work that proposed that not CD4 responses determine the viral load but viral load determines the quantity and quality of HIV specific CD4+ T cells (Jansen et al Trend Immunol 2006).

HLA-B57 has been shown to be associated with long-term asymptomatic HIV-1 infection. To investigate the biological mechanism by which the HLA-B57 allele could protect from HIV-1 disease, we studied both the number of CD8+ T cells as well as CD8+ T cell responsiveness directed to different HIV-1 Gag peptides presented by HLA-A2, -B8 or -B57. T cells specific for the HLA-B57 peptide KAFSPEVIPMF responded more readily and to a higher extend to antigenic stimulation in vitro than T cells specific for the HLA-A2 peptide SLYNTVATL or the HLA-B8 peptide EIYKRWII. This phenomenon was reproducible with T cells from individuals expressing HLA-B57 in combination with one or both of the other alleles and was persistent during long-term follow-up. Lower reactivity of A2- and B8-restricted T cells was not solely explained by mutations in the B8- or A2-restricted Gag-peptides. Moreover, no correlation between peptide mutation frequency and IFNγ production by the corresponding Gag-specific T cells was observed. In conclusion, functional differences were observed between T cells specific for HIV epitopes derived from the same protein presented by different HLA molecules. B57-restricted KAFSPEVIPMF-specific CD8+ T cells have relatively high responsiveness, which could contribute to the protective effect of HLA-B57 in HIV infection.

CD31 has been proposed as a marker that discriminates between (CD31+) recent thymic emigrants and (CD31-) naïve CD4+ T cells that have undergone peripheral T cell proliferation. Consistent with this idea, the percentage of CD31+ T cells in the naïve CD4+ T cell pool has been found to decline with age, and the TREC content of CD31+ naïve CD4+ T cells has been shown to be consistently higher than that of their CD31- counterparts. We found, however, that the TREC content of the CD31+ naïve CD4+ T cell pool declined with age, indicating that CD31+ naïve CD4+ T cells are at least in part generated by peripheral T cell proliferation.
Since chronic immune activation is thought to cause accelerated ageing of the immune system, one would expect to find a decreased fraction of CD31+ cells within the naïve CD4+ T cell pool in HIV infected individuals. This was indeed the case relatively early in HIV infection, but at more progressed stages of HIV infection the CD31 fraction appeared to be increased. Although CD31 was originally introduced as a marker for thymic output, we show that the observed CD31 dynamics during HIV infection are more readily explained by increased levels of immune activation. Together, these studies provide novel insights into the use of CD31 as a CD4+ T cell thymic proximity marker. (Vrisekoop et al 2005 submitted for publication).

HIV-infected individuals have a highly increased incidence of (EBV-positive) B cell non-Hodgkin's lymphomas (AIDS-NHL) due to uncontrolled EBV-driven B cell proliferation because of loss of functional EBV-specific CD8+ T cells. Since CD4+ T cells seem to play an important role in the functional maintenance of CD8+ T cells, we aimed to document the CD4+ T helper cell response against EBV in AIDS-NHL patients both quantitatively and qualitatively. To measure EBV-specific memory CD4+ T cells we developed a specific and reproducible assay, combining ex vivo expansion of specific T cells directed against a latent (EBNA1) and a Lytic (BZLF1) antigen with flow-cytometric analysis of IFNg production. Using this assay, we studied the role of EBV-specific CD4+ T cells in the maintenance of control over EBV-infected cells in vivo. CD4+ and CD8+ memory T cells directed against EBNA1 and BZLF1 were studied longitudinally in 9 progressors to NHL, 4 progressors to non-EBV-related AIDS and 4 slow progressors to AIDS. In all 3 groups, we observed a decline of EBV-specific memory CD4+ and CD8+ T-cell responses during HIV infection. However, whereas latent antigen EBNA1-specific CD4+ T cells were lost well before diagnosis in all subjects who developed an AIDS-related NHL, these cells were better preserved in progressors to non-EBV-related disease and slow progressors. Subsequently, EBV-specific CD4+ and CD8+ T-cell responses were studied in 10 subjects from early in HIV infection up to 5 years after HAART. All individuals responded to HAART by a decline in HIV viral load, a restoration of total CD4+ T cell numbers, and a decline in T-cell immune activation. In contrast, EBV load remained unaltered, even after 5 years of therapy, although a decline

in both CD4+ and CD8+ T cells specific for lytic EBV protein BZLF1 suggested a decreased EBV reactivation rate. In contrast, after 5 years of treatment, latent EBV antigen EBNA1-specific CD4+ and CD8+ T-cell responses were restored to levels comparable with healthy individuals. Overall, during chronic HIV infection, responses to the latent antigen EBNA1 are more important to avoid NHL, than responses to the early lytic switch protein BZLF1. As long as sufficient CD4+ T cells are present to help the CD8+ T cells, control over EBV-infected cells is maintained. However, the EBV-specific CD4+ T-cell response declines during HIV infection, and is ultimately lost in most HIV-infected subjects. Finally, the quasi disappearance of AIDS-NHL since the wide-spread use of HAART can be explained by a decreased immune activation, which diminishes the rate of B-cell activation and EBV reactivation, on one hand, and to an improved CD4+ and CD8+ T-cell response to latent antigen EBNA1, which appears to be important in the control of EBV-infected B cells. These results provide more insight in the importance of EBNA-1 specific T cells as a rationale for immunotherapy of EBV-positive lymphomas.

To identify factors which might be related to progression to CMV end-organ disease, cytokine production, proliferative capacity and phenotype of CMV-specific $CD4^+$ T-cells were analysed longitudinally in progressors to AIDS with CMV end-organ disease (AIDS-CMV) in comparison to long-term asymptomatics (LTA) and a separate group of progressors to AIDS with opportunistic infections (AIDS-OI). Numbers of CMV-specific IFNγ-producing $CD4^+$ T-cells were higher than IL-2-producing $CD4^+$ T-cells after stimulation with CMV lysate. In LTA and progressors to AIDS-OI, numbers of IFNγ-producing $CD4^+$ T-cells remained detectable during follow-up, but decreased in individuals progressing to AIDS-CMV. In parallel, CMV-specific IL-2 production and proliferative capacity decreased in progressors to AIDS-CMV. Most CMV-specific cytokine-producing $CD4^+$ T-cells were of the $CD27^-$ phenotype. Initially, the majority of the $IFNg^+CD4^+$ T-cells were of the $CD45RO^+CD27^-$ effector subset, but during progression to AIDS-CMV a shift in phenotype to the highly differentiated $CD45RO^-CD27^-$ subset was observed. Our data indicate that the decrease in CMV-specific cytokine production and proliferative capacity is associated with progression to AIDS-CMV. Accumulation of $CD4^+$ T-cells with a $CD45RO^-CD27^-$ phenotype suggests that persistent antigen exposure drives differentiation of CMV-specific $CD4^+$ T-cells towards a non-IL-2-producing, poorly proliferating, and highly differentiated "effector" subset, which eventually also fails to produce IFNγ in patients developing AIDS-CMV.
To study the effect of HAART on HIV- and CMV-specific T cell responses, we analyzed both cytokine production and proliferation of virus-specific CD4+ T cells after specific stimulation in 10 HIV-infected individuals before and 1 and 5 years after start of HAART. The number of HIV-specific IFNgamma producing CD4+ T cells decreased after HAART. The number of IL-2 positive cells, however, initially increased after start of HAART, but 5 years of HAART treatment subjects were not able to sufficiently maintain these higher numbers of IL-2 producing CD4+ T cell. For CMV, no effect of HAART was observed on either the the number of IFNgamma producing CD4+ T cells as the number of IL-2 producing T cells. The proliferative capacity of both HIV- as well as CMV-specific CD4+ T cells increased after long-term treatment with HAART. Since also the anti-CD3 proliferative response increased, this suggest a general mechanism of immune reconstitution established by HAART.

Steering committee: The politburo
In 2005 the Politburo was extended with 4 persons and met several times. Hanneke Schuitemaker replaced Roel Coutinho as the coordinator of the ACS.
Fourteen new proposals for use of data and/or samples (serum/PBMCs) were submitted to the politburo: 5 from Sanquin, 4 AZU, 2 GGD, 1 AMC, 1 IATEC, and 1 from abroad (UK). All have been approved, some of them after revision.

Publications in 2005 that include ACS data

van Asten L, Zangerle R, Hernandez Aguado I, Boufassa F, Broers B, Brettle RP, Roy Robertson J, McMenamin J, Coutinho RA, Prins M. Do HIV Disease Progression and HAART Response Vary among Injecting Drug Users in Europe? Eur J Epidemiol. 2005;20:795-804.

van der Bij AK, Kloosterboer N, Prins M, Boeser-Nunnink B, Geskus RB, Lange JM, Coutinho RA, Schuitemaker H. GB Virus C Coinfection and HIV-1 Disease Progression: The Amsterdam Cohort Study. J Infect Dis 2005;191:678-85.

van der Bij AK, Stolte IG, Coutinho RA, Dukers NH. Increase of sexually transmitted infections, but not HIV, among young homosexual men in Amsterdam: are STIs still reliable markers for HIV transmission? Sex Transm Infect 2005;81:34-7.

Bekker, V., C. Bronke, H. J. Scherpbier, J. F. Weel, S. Jurriaans, P. M. Wertheim-van Dillen, L. F. van, J. M. Lange, K. Tesselaar, Baarle. D. van, and T. W. Kuijpers. Cytomegalovirus rather than HIV triggers the outgrowth of effector CD8+CD45RA+. AIDS 19, 2005: 1025-1034.

Borghans JA, Hazenberg MD, Miedema F. Limited role for the thymus in SIV pathogenesis. Eur J Immunol. 2005 Jan;35(1):42-5. Review.

Bronke, C., G. H. Westerlaken, F. Miedema, K. Tesselaar, and Baarle. D. van. Progression to CMV end-organ disease in HIV-1-infected individuals despite abundance of highly differentiated CMV-specific CD8(+) T-cells. Immunol. Lett. 97, 2005: 215-224.

Bronke, C., N. M. Palmer, C. A. Jansen, G. H. Westerlaken, A. M. Polstra, P. Reiss, M. Bakker, F. Miedema, K. Tesselaar, and Baarle. D. van. Dynamics of cytomegalovirus (CMV)-specific T cells in HIV-1-infected individuals progressing to AIDS with CMV end-organ disease. J. Infect. Dis. 191, 2005: 873-880.

Bronke, C., N. M. Palmer, G. H. Westerlaken, M. Toebes, G. M. van Schijndel, Purwaha V., K. E. van Meijgaarden, T. N. Schumacher, D. van Baarle, K. Tesselaar, and A. Geluk. Direct ex vivo detection of HLA-DR3-restricted cytomegalovirus- and Mycobacterium tuberculosis-specific CD4+ T cells. Hum. Immunol. 66(9), 2005: 950-9

Casula M, Bosboom-Dobbelaer I, Smolders K, Otto S, Bakker M, de Baar MP, Reiss P, de Ronde A. Infection with HIV-1 induces a decrease in mtDNA. J Infect Dis. 2005 May 1;191(9):1468-71.

Geels MJ, Cornelissen M, Schuitemaker H, Anderson K, Kwa D, Maas J, Dekker JT, Baan E, Zorgdrager F, van den Burg R, van Beelen M, Lukashov VV, Fu TM, Paxton WA, van der Hoek L, Dubey SA, Shiver JW, Goudsmit J. Identification of sequential viral escape mutants associated with altered T-cell responses in a human immunodeficiency virus type 1-infected individual. J Virol. 2003 Dec;77(23):12430-40.

Geskus RB, Meyer L, Hubert JB, Schuitemaker H, Berkhout B, Rouzioux C, Theodorou ID, Delfraissy JF, Prins M, Coutinho RA. Causal Pathways of the Effects of Age and the CCR5-Delta32, CCR2-64I, and SDF-1 3'A Alleles on AIDS Development. J Acquir Immune Defic Syndr 2005;39:321-6

Jansen CA, De Cuyper IM, Hooibrink B, van der Bij AK**,** van Baarle D, Miedema F. Prognostic value of HIV-1 Gag-specific $CD4^+$ T-cell responses for progression to AIDS analyzed in a prospective cohort study. Blood, Oct 2005;207:1427-33

Jansen, C. A., S. Kostense, K. Vandenberghe, N. M. Nanlohy, I. M. De Cuyper, E. Piriou, E. H. Manting, Miedema F., and D. van Baarle. High responsiveness of HLA-B57-restricted Gag-specific CD8+ T cells in vitro may contribute to the protective effect of HLA-B57 in HIV-infection. European Journal of Immunology 35, 2005: 150-158.

Jansen, C. A., I. M. De Cuyper, R. Steingrover, S. Jurriaans, S. U. C. Sankatsing, J. M. Prins, J. M. A. Lange, D. van Baarle, and Miedema F. Analysis of the effect of highly active anti-retroviral therapy during acute HIV-1 infection on HIV-specific CD4+ T-cell functions. AIDS 19, 2005: 1145-1154.

Kivela PS, Krol A, Salminen MO, Geskus RB, Suni JI, Anttilla VJ, Liitsola K, Zetterberg V, Miedema F, Berkhout B, Coutinho RA, Ristola MA. High plasma HIV load in the CRF01-AE outbreak among injecting drug users in Finland. Scand J Infect Dis 2005;37:276-83

Koning FA, Otto SA, Hazenberg MD, Dekker L, Prins M, Miedema F, Schuitemaker H. Low-level CD4+ T cell activation is associated with low susceptibility to HIV-1 infection.J Immunol. 2005 Nov 1;175(9):6117-22.

Koning FA, van der Vorst TJ, Schuitemaker H. Low levels of human immunodeficiency virus type 1 DNA in high-risk seronegative men. J Virol. 2005 May;79(10):6551-3.

Koning FA, Koevoets C, van der Vorst TJ, Schuitemaker H. Sensitivity of primary R5 HTV-1 to inhibition by RANTES correlates with sensitivity to small-molecule R5 inhibitors. Antivir Ther. 2005;10(2):231-7.

van der Kuyl AC, Polstra AM, van den Burg R, Jan Weverling G, Goudsmit J, Cornelissen M. Cytomegalovirus and human herpesvirus 8 DNA detection in peripheral blood monocytic cells of AIDS patients: correlations with the presence of Kaposi's sarcoma and CMV disease. J Med Virol. 2005;76(4):541-6.

van de Laar TJW, Langendam MW, Bruisten SM, Welp EAE, Verhaest I, van Ameijden EJC, Coutinho RA, Prins M. Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. J Med Virol 2005;77:509-18

Mekonnen Y, Geskus RB, Hendriks JCM, Messele T, Borghans J, Miedema F, Wolday D, Coutinho RA, Dukers NHTM. Low CD4 T Cell Counts before HIV-1 Seroconversion Do Not Affect Disease Progression in Ethiopian Factory Workers. J Infect Dis 2005;192:739-48.

Madec Y, Boufassa F, Porter K, and Meyer L on behalf of the CASCADE Collaboration Spontaneous control of viral load and CD4 cell count progression among HIV-1 seroconverters AIDS 2005;19:2001-7.

Masquelier B, Bhaskaran K, Pillay D, Gifford R, Balestre E, Jorgensen LB, Pedersen C, van der Hoek L, Prins M, Balotta C, Longo B, Kucherer C, Poggensee G, Ortiz M, de Mendoza C, Gill J, Fleury H, Porter K; on behalf of the CASCADE Collaboration. Prevalence of Transmitted HIV-1 Drug Resistance and the Role of Resistance Algorithms: Data from Seroconverters in the CASCADE Collaboration from 1987 to 2003. J Acquir Immune Defic Syndr 2005;40:505-11.

Piriou, E. R., Dort. K. van, N. M. Nanlohy, M. H. van Oers, F. Miedema, and Baarle. D. van. Novel method for detection of virus-specific CD4(+) T cells indicates a decreased EBV-specific CD4(+) T cell response in untreated HIV-infected subjects. Eur. J. Immunol. 35, 2005: 796-805.

Piriou, E., C. A. Jansen, K. van Dort, C. De, I, N. M. Nanlohy, J. M. Lange, M. H. van Oers, F. Miedema, and Baarle. D. van. Reconstitution of EBV latent but not lytic antigen-specific CD4+ and CD8+ T cells after HIV treatment with highly active antiretroviral therapy. J. Immunol. 175, 2005: 2010-2017.

Piriou, E., Dort. K. van, N. M. Nanlohy, M. H. van Oers, F. Miedema, and Baarle. D. van. Loss of EBNA1-specific memory CD4+ and CD8+ T cells in HIV-infected patients progressing to AIDS-related non-Hodgkin Lymphoma. Blood 2005: 106(9): 3166-3174

Termorshuizen F, Krol A, Prins M, van Ameijden EJC. Long-term Outcome of Chronic Drug Use: The Amsterdam Cohort Study among Drug Users. Am J Epidemiol. 2005;161:271-9.

Termorshuizen F, Krol A, Prins M, Geskus R, van den Brink W, van Ameijden EJ. Prediction of relapse to frequent heroin use and the role of methadone prescription: An analysis of the Amsterdam Cohort Study among drug users. Drug and Alcohol Dependence 2005;79:231-40.

Thiebaut R, Jacqmin-Gadda H, Babiker A, Commenges D; CASCADE Collaboration. Joint modelling of bivariate longitudinal data with informative dropout and left-censoring, with application to the evolution of CD4+ cell count and HIV RNA viral load in response to treatment of HIV infection. Stat Med. 2005;24:65-82

Wolday D, Tegbaru B, Kassu A, Messele T, Coutinho R, van Baarle D, Miedema F. Expression of chemokine receptors CCR5 and CXCR4 on CD4+ T cells and plasma chemokine levels during treatment of active tuberculosis in HIV-1-coinfected patients. J Acquir Immune Defic Syndr 2005;39:265-71

Xiridou M, Kretzschmar M, Geskus R. Competition of pathogen strains leading to infection with variable infectivity and the effect of treatment. Mathematical Biosciences 2005;197:153-72

Thesis in 2005 that include ACS data

March 24, 2005. C. Bronke. Promotor: Prof dr F. Miedema, Co-promotor: Dr D. van Baarle and Dr. K. Tesselaar Cytomegalovirus-specific T-cell dynamics in HIV infection.

March 31, 2005. E. Piriou, Promotores: Prof dr F. Miedema and R. van Oers, Co-promotor: Dr D. van Baarle Viro-Immunology of EBV-HIV co-infection

May 13, 2005, C Jansen, Promotor: Prof dr F. Miedema, Co-promotor: Dr D. van Baarle Analysis of HIV-specific T-cell immunity in AIDS pathogenesis

September 22, 2005. L.C.H.I. van Asten. Promotor: Prof dr RA Coutinho. Co-promotor: Dr. M. Prins Epidemiological studies among injecting drug users infected with HIV: Highly active antiretroviral therapy, Tuberculosis, Hepatitis C, Immunology

December 16, 2005. G. Stolte. Promotor: Prof dr R.A Coutinho. Co-promotores: Dr. N.H.T.M. Dukers en Dr. J.B.F. de Wit. The impact of highly active antiretroviral therapy on sexual behaviour among homosexuals.