

# Overview of the Amsterdam Cohort Studies among homosexual men and drug users

## Introduction

The Amsterdam Cohort Study (ACS) on Human Immunodeficiency Virus (HIV) infection and AIDS among homosexual men was started in 1984, followed shortly by the Amsterdam cohort study among drug users in 1985. The ACS, a collaboration between the Health Service of Amsterdam, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation and the University Medical Center Utrecht, are part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment. Website: <http://www.amsterdamcohortstudies.org/>

This overview is primarily written for these collaborators and to give an understanding of the main characteristics of the Amsterdam Cohort Studies. The various subgroups and studies are briefly described, followed by tables with numbers of participants under follow-up and HIV incidence over calendar time.

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## **Amsterdam Cohort Study among homosexual men**

The study population consists of homosexual men living mainly in and around the city of Amsterdam, The Netherlands. Table 3 shows how many participate(d) in ACS among homosexual men and its substudies. The first wave of enrolment took place between October 1984 and April 1985 (Protocol 1). Included were asymptomatic homosexual men aged 18-65 with at least two sexual partners in the six months prior to intake. They were recruited through announcements in the gay press, advertisements and by word of mouth. Between April 1985 and February 1988 only seronegative men could enter the study (Protocol 2). Enrolment was re-opened to HIV-1 infected individuals from February 1988 until December 1998 (6000 numbers). Some of these participants entered the ACS because they were found to be HIV positive while participating in another Municipal Health Service study or to start with antiretroviral treatment (open and double blind AZT study). In February 1996, the follow-up of the 'old' HIV seronegative participants was terminated. In June 1995 a special recruitment campaign was started among young ( $\leq 30$ ) homosexual men. From April 2005 homosexual men of all ages are invited to participate. This study is still ongoing. A few participants entered the ACS but could not be classified in either of the abovementioned studies (9000 numbers) or were allowed to start their treatment within the ACS from February 1997 onwards (7000 numbers).

In February 1999, follow-up of all HIV-infected participants was transferred to the Jan van Goyen clinic in the scope of the HIV Monitoring Foundation (formerly National Athena monitoring project). However, from October 2003, HIV-positive homosexual men with a recent HIV-negative test result are followed at the Health Service of Amsterdam in the HOP ('HIV study among recent HIV-positives'). This is a collaborative study with the primo cohort of the AMC. From June 2006 also HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants are invited into the ACS.

### *Daily routine*

HIV-positives are seen every three months. Clinical, epidemiological and social scientific data are collected with standardised questionnaires (six monthly) and by physical examination. Blood is taken for virological and immunological tests and for storage. HIV-negatives are seen by a nurse every six months and similar data are collected but no immunological tests are done nor are cells stored.

Participants who developed an AIDS event during follow-up were referred to the AMC and since 1996 much effort has been put into aligning the AMC and the ACS registry regarding events (clinical follow-up). Until 2000, AIDS cases are also ascertained through cross-linking with the Amsterdam AIDS registry.

Once a year information on survival status is obtained through active follow-up and matching with local population registries and the HIV Monitoring Foundation. The cause of death is obtained from the Amsterdam AIDS surveillance registry (until 2000), hospital records and from next of kin.

### *Intervention/vaccination studies*

At the beginning of 1987 a preliminary study of AZT in asymptomatic HIV infected subjects was started within ACS. Followed one year later in April 1988 by a multi-centered double-blind-placebo-controlled study. Since then ACS has participated in several different (multi-centered) trials like Delta, Triple, Atlantic, Prometheus, Native and D4T/3TC study.

ACS has also participated as a study-site in three vaccination studies. Recruitment of the P24-HIV and rgp120 study among HIV positives started between March 1993 and March 1994. The Vaxgen (multi-centered) double-blind placebo-controlled study among high risk HIV uninfected homosexual men started in 1999 and ended in 2002.

## **Amsterdam Cohort Study among drug users**

Participants are recruited at methadone outposts, the weekly STD-clinic for drug-using prostitutes and by word of mouth. HIV-negative and asymptomatic HIV-positive injecting and non-injecting drug users (IDU and non-IDU) are invited to participate. Table 6 shows how many participate(d) in ACS among drug users and its substudies. The first wave of enrolment took place between December 1985 and September 1990 where after inclusion stopped until August 1991. Enrolment was then re-opened and in 1998 a special recruitment campaign was started among young drug users ( $\leq 30$  years). Although it was a cross sectional study design, a quarter is being followed in the drug user cohort. Again, in June 2000, much effort was put into recruiting young drug users. This follow-up study is still ongoing. From February 2001 'old' drug users can no longer enter the study. From December 2006 onwards, some drug users are allowed to start their hepatitis C treatment within the DUTCH-C treatment study which started in 2005.

### *Daily routine*

Participants are seen every four months and since 1 January 2003 every 6 months regardless of HIV status, but many return more irregularly. Clinical, epidemiological and drug use related information is collected at each occasion by interviewing participants using a standardised questionnaire. Since April 1989 this questionnaire was thoroughly revised and all participants were physically examined by a physician at each visit. In January 1999 this examination was terminated for the HIV negatives. Blood is taken for virological tests and storage and from April 1989 immunological tests are part of the daily routine in HIV-negative as well as HIV-positive participants. Since 1995 these are limited performed in a small subset of the HIV negatives.

Data on hospitalisation are collected at each visit from the participants, independently through the Drug Department of the Municipal Health Service and since 1997 for all seroconverters and HAART using drug users effort has been put into aligning hospital and ACS event registration (clinical follow-up). Cases of AIDS are also ascertained through cross-linking with the Amsterdam AIDS registry (until 2000). After AIDS has been diagnosed drug users can still participate.

Yearly, deaths and causes of death are identified by determining participants' vital status at the register of population in their city of residence and through locating and examining hospital records and coroners' reports.

### *Substudies*

Several substudies have been done among the drug users. Participants were tested for Hepatitis A, B and C, HTLV-1 and 2 and haematology. Also in depth interviews were held to investigate why participants stopped injecting drugs and a cohort of abstinent drug users was followed from January 2003 until the end of 2004 to study relapses. From 2005 all cohort participants were offered HCV testing and treatment combined with methadone programs. In collaboration with the Amsterdam Institute for Addiction Research, from August until November 2005, the MATE interview (measuring addiction for triage and evaluation) was used to study its usability in the ACS among drug users. Furthermore there is a close collaboration with the STD clinic of the Health Service and the Central Methadone Registry.

## Immunological and virological assays

Table 1. Overview of applied immunological assays performed in the ACS.

Period	Proliferation assays										T cell subsets								MT-2(*)	
	PHA		ALS		ACD3		CD228		CD328		CD2		CD3		CD4		CD8			
	Hm	Du	Hm	Du	Hm	Du	Hm	Du	Hm	Du	Hm	Du	Hm	Du	Hm	Du	Hm	Du		
1984		X		X		X		X		X		X		X		X		X		X
1985																				
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(\*) Although the MT-2 assay is not really an immunological assay, it is presented here because it is developed and routinely determined in the Clinical Viro-Immunological laboratory (AMC Experimental Immunology since January 2008). Once a year, done on fresh material.

X: the cohort among drug users started in 1985, Hm: Homosexual men, Du: Drug users, PHA: phytohemagglutinin, before 1994, human pooled serum (HPS) was added to the culture medium, after 1994, no HPS was added: PHA responses with and without HPS were not comparable, ALS: horse anti-lymphocyte stimulation test, ACD3: T cell function measured after stimulation with monoclonal antibodies (mAb) against the CD3 receptor, CD228: T cell function stimulation with CD2 and CD28 mAb, CD328: T cell function stimulation with CD3 and CD28 mAb. T cell immuno-phenotyping CD2,CD3,CD4 and CD8: before 1988, the single indirect staining, a single indirect immuno-fluorescence staining on Ficoll isolated peripheral blood mononuclear cells (PBMC) was used and replaced by a double direct staining thereafter. Since 1994, lymphocyte immunophenotyping was accomplished in whole blood. For homosexual men seen at the Jan van Goyen clinic from 2003, CD4/CD8 phenotyping is performed at the OLVG. For hiv-positives seen at the Amsterdam Health Service, from January 2007 T-cel subsets were generated using the single platform method.

Dark-grey box = performed at every visit; light-grey box = not performed on a routine basis.

Table 2. Overview of the used virological assays in the ACS.

<b>Virological assays</b>	<b>Company</b>	<b>Period Hm / Du</b>
<b>HIV screenings assays:</b>		
HTLV-III screening test	home made	1984-1985
HTLV III EIA	Abbott	1985-1989
Vironostika anti-HTLV-III ELISA	Organon International	1985-1987
Wellcozyme anti-HTLV III	Wellcome	± 1986
recombinant HIV-1/HIV-2 EIA	Abbott	1989-1993
recombinant HIV-1/HIV-2 3 <sup>e</sup> generation	Abbott	1993-1995
HIV-1/HIV-2 3 <sup>e</sup> generation plus EIA	Abbott	1995-1998
HIV IMX (MEIA systeem)	Abbott	1998-2001
VIDAS HIV DUO	Biomerieux	2001-2003
AxSym HIV Ag/Ab Combo	Abbott	Since July 1 <sup>st</sup> 2003
<b>Other used HIV-antibody assays:</b>		
HIV-1 anti-CORE EIA	Abbott	1986-1992
ENVACOR HIV-1 EIA	Abbott	
Detection of CORE		1989-1992
Detection of ENV		1987-1990
HIVAb p24 (rDNA)	Abbott	1992-1997
<b>HIV-antigen assays:</b>		
HTLV-III Antigen EIA	Abbott	1986-1992
HIVAg-1 EIA polyclonal	Abbott	1990-1998
<b>Confirmation assays:</b>		
HTLV-III Western Blot	Home made	1984 –1985
LiaTek HIV-1/HIV-2	Organon Teknika	± 1986
HIV Blot 2.2 (HIV-1 en HIV-2)	Diagnostic	Since 1986
HIV-2 Blot version 1.2	Diagnostic	Since 1995
<b>HIV RNA assays:</b>		
NASBA HIV-1 QT	Organon Teknika	1996-1997 / Feb 1997
NucliSens HIV-1 QT	Organon Teknika	1997- nov 2006
bDNA		HM since Aug 1999, HOP Oct 2003- Nov 2006
M2000rt (abbott)	Abbott	since Dec 2006

Hm: Homosexual men, Du: Drug users, HOP: HIV among seropositives study, EIA: Enzyme Immuno Assay, ELISA: Enzyme Linked immunoSorbent Assay, Liatek: Line Immuno Assay Technique, MEIA: Microparticle Enzyme Immuno Assay, Nasba: Nucleic Acid Sequence-based Amplification. bDNA: branched DNA. Remark: To compare test results, some assays have been used simultaneously.

## Main characteristics of the Amsterdam Cohort Study among homosexual men

**Table 3. History of total number of homosexual men ever included in a study until 31-12-2008. Each participant can participate in as many as 6 studies over calendartime**

	Total	Death	HIV antibody status		
			Negative	Positive	Seroconverter
At least 1 visit at the Health Service	2383	335	1588	585	210
Protocol 1	748	215	415	238	95
Protocol 2	265	24	225	1	39
Young homosexual men	872	1	775	29	68
6000 numbers	196	58		196	
7000 numbers	26	7		26	
9000 numbers	28	4	1	27	
Jan van Goyen *1	176	24		132	44
Open AZT	26	23		19	7
Doubleblind AZT	56	41		51	5
Early antiretroviral treatment	186	66		141	45
Combination Study	12	11		9	3
Delta Study	10	8		6	4
Triple Study	6	1		4	2
AZT/3TC/D4T	46	2		36	10
Native	12	3		10	2
Atlantic	9	3		8	1
RGP120 Vaccin	16	4		3	13
P24 Vaccin	21	6		20	1
Vaxgen *2	14		11		3
HOP *3	95	1		36	59
Intake from 1-4-2005	214		199	3	12
Inclusion of partners	28		12	11	5

\*1 Initially, 227 were eligible for follow-up at the Jan van Goyen, however decided to go to another hospital or had other reasons for refusing further follow-up

\*2 These men are also participant of the young homosexual men study

\*3 HIV study among recent HIV-positives

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**Table 4. Total number of homosexual men in follow-up in ongoing studies: participants who had a visit at the Health Service at or after 1-1-2008 or within SHM/Jan van Goyen Clinic at or after 1-1-2008**

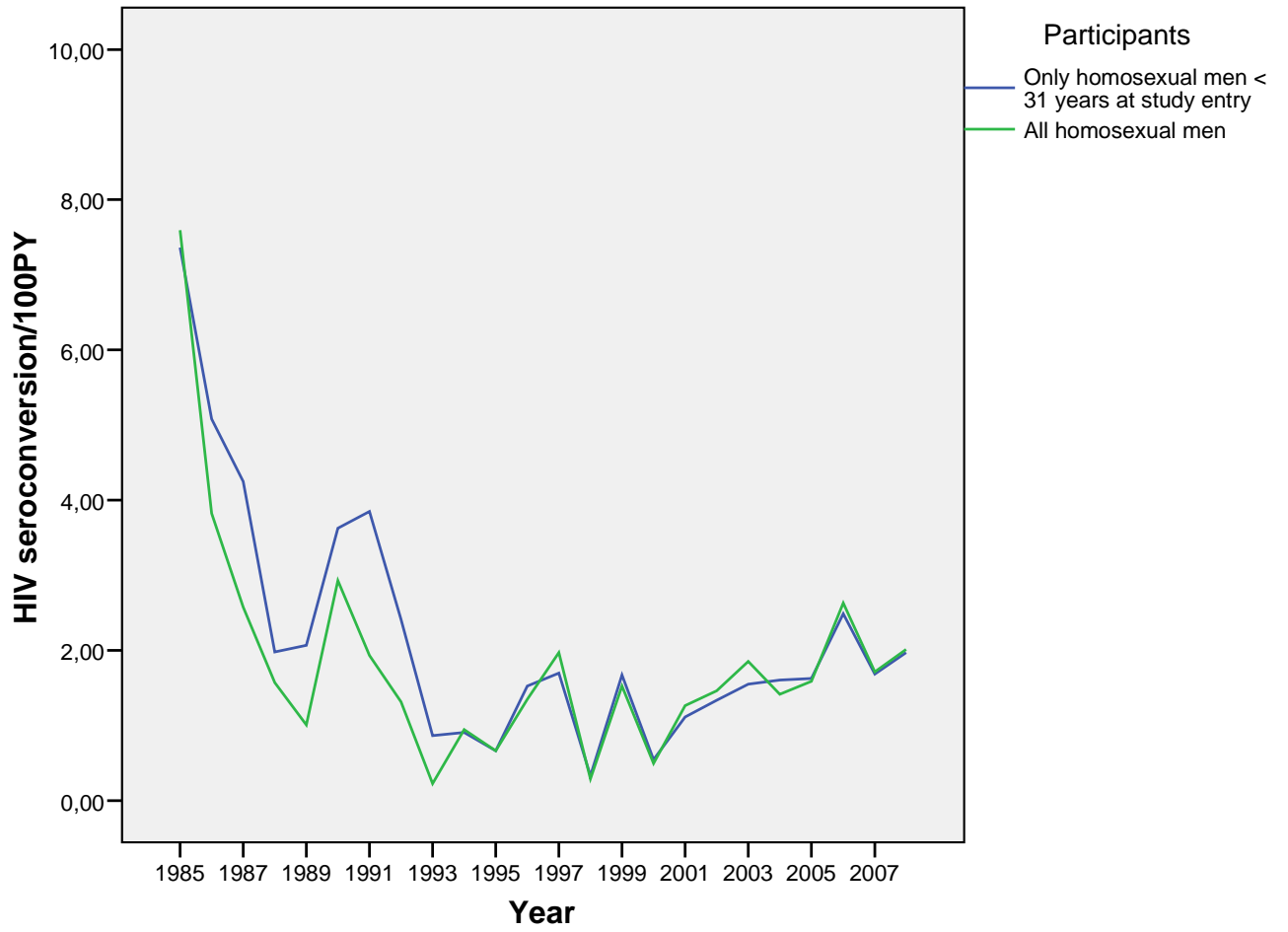
	Total	follow up visit	newly recruited	HIV antibody status		
				Negative	Positive	Seroconverter
site of last visit	208	208			140	68
JvG or somewhere else Health Service	532	504	28	481	13	38

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**Table 5. Yearly HIV incidence, number of HIV positives and number of person years per calendar year**

	Participants									
	Only homosexual men < 31 years at study entry			Only homosexual men > 30 years at study entry			All homosexual men			
	No. HIV positives	Person years	Incidence	No. HIV positives	Person years	Incidence	No. HIV positives	Person years	Incidence	
Year	1985	11,00	149,41	7,36	26,00	337,91	7,69	37,00	487,32	7,59
	1986	9,00	177,12	5,08	13,00	397,90	3,27	22,00	575,02	3,83
	1987	7,00	164,73	4,25	7,00	378,57	1,85	14,00	543,29	2,58
	1988	3,00	151,56	1,98	5,00	357,54	1,40	8,00	509,10	1,57
	1989	3,00	145,03	2,07	2,00	350,97	,57	5,00	496,00	1,01
	1990	5,00	137,75	3,63	9,00	339,73	2,65	14,00	477,48	2,93
	1991	5,00	129,85	3,85	4,00	335,28	1,19	9,00	465,13	1,93
	1992	3,00	124,30	2,41	3,00	330,98	,91	6,00	455,28	1,32
	1993	1,00	115,42	,87	,00	322,26	,00	1,00	437,68	,23
	1994	1,00	109,93	,91	3,00	312,50	,96	4,00	422,43	,95
	1995	1,00	150,32	,67	2,00	299,58	,67	3,00	449,89	,67
	1996	5,00	327,16	1,53	3,00	265,24	1,13	8,00	592,40	1,35
	1997	5,00	294,17	1,70	2,00	60,70	3,29	7,00	354,88	1,97
	1998	1,00	300,21	,33	,00	45,03	,00	1,00	345,24	,29
	1999	6,00	358,45	1,67	,00	34,58	,00	6,00	393,03	1,53
	2000	2,00	367,00	,54	,00	36,05	,00	2,00	403,05	,50
	2001	4,00	359,38	1,11	1,00	35,37	2,83	5,00	394,75	1,27
	2002	5,00	374,38	1,34	1,00	35,23	2,84	6,00	409,61	1,46
	2003	6,00	386,32	1,55	2,00	44,94	4,45	8,00	431,25	1,86
	2004	6,00	373,16	1,61	,00	50,94	,00	6,00	424,10	1,41
	2005	6,00	368,97	1,63	1,00	71,44	1,40	7,00	440,41	1,59
	2006	9,00	361,68	2,49	3,00	94,53	3,17	12,00	456,21	2,63
	2007	6,00	355,62	1,69	2,00	111,08	1,80	8,00	466,70	1,71
	2008	5,00	253,45	1,97	2,00	94,43	2,12	7,00	347,88	2,01

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## Main characteristics of the Amsterdam Cohort Study among drug users

Table 6. History of total number of drug users ever included in a study up to 31-12-2008. Each participant can participate in more than one study over calendar time.

	Total	Death	HIV antibody status at entry		
			Negative	Positive	Serocon verter
At least 1 visit at the Municipal Health Service	1647	411	1229	322	96
Drug user cohort	1488		1075	318	95
Clinical follow-up	96 <sup>1</sup>		--	30	66
'98 Young cross sectional study	293 <sup>2</sup>		261	21	--
JODAM <sup>3</sup>	210		199	6	3
Abstinent cohort (from 1-1-2003)	177		122	9	8
MATE interviews <sup>4</sup> (from 1-8-2005)	170		150	12	8
Cohort entry because of hepatitis C treatment	18		17	1	

<sup>1</sup>Originally 110 participants participated, however of 14 participants no additional clinical information could be collected due to missing medical records, <sup>2</sup>Originally, 452 participated however, part of them appeared not to have met the inclusion criteria. Of 293, 11 provided too little saliva to determine HIV status and 88 are followed within the drug user cohort, <sup>3</sup>Follow-up study among young drug users from Amsterdam. <sup>4</sup>MATE: measuring addiction for triage and evaluation

Table 7. Total number of drug users in follow-up in ongoing studies: had a visit at the Health Service of Amsterdam at or after 1-1-2008

	Total in follow-up	HIV antibody status		
		Negative	Positive at entry	Seroconverter
Drug user cohort	335	284	34	17
JODAM	55	52	1	2

JODAM: Follow-up study among young drug users from Amsterdam.

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**Table 8. Number of AIDS and death cases among HIV positive and seroconverted drug users per calendar year.**

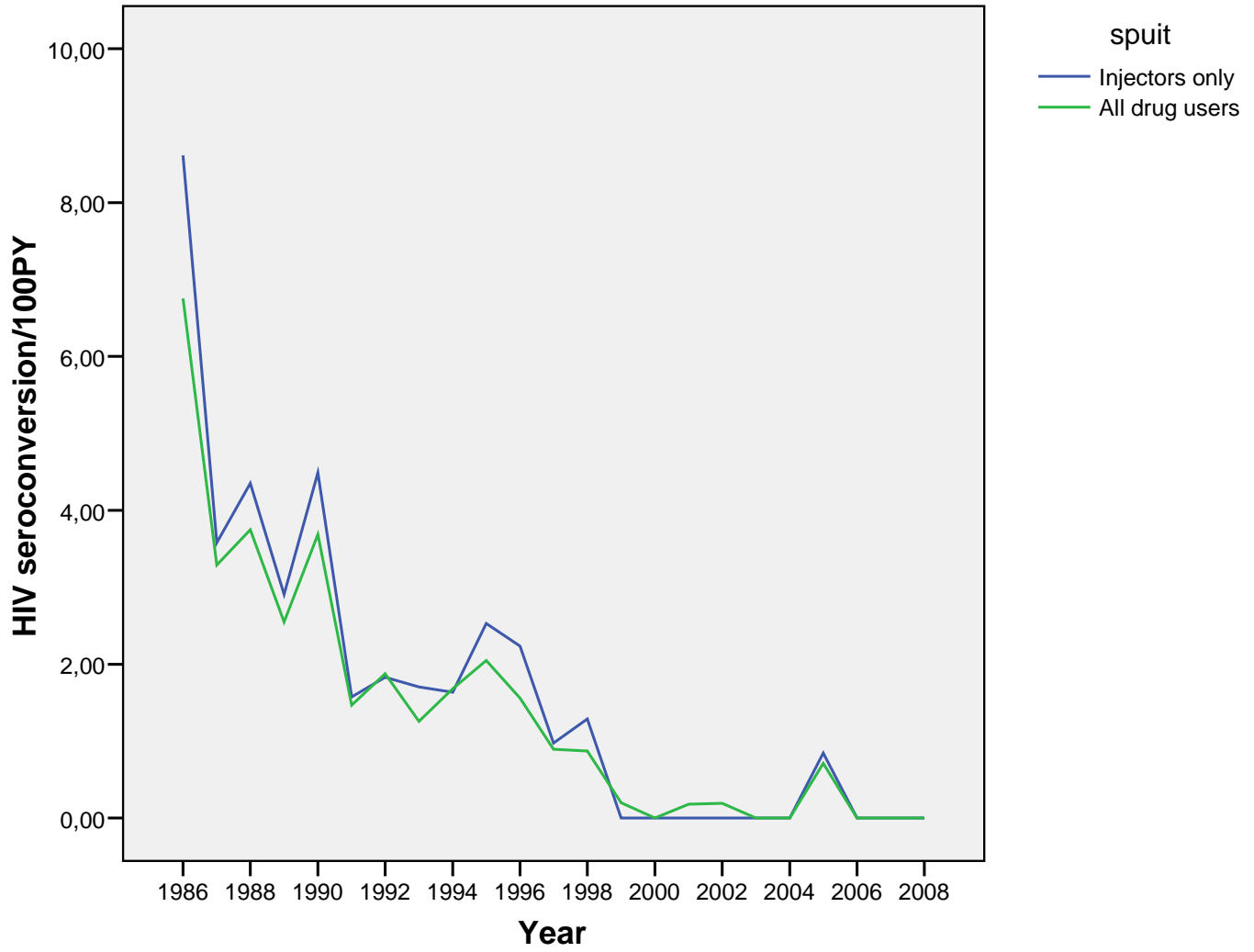
	AIDS	Total deaths	Death	
			1,00 with AIDS	3,00 without AIDS
1930 unknown year	3			
1986		2		2
1987	1	3		3
1988	7	9	2	7
1989	7	6		6
1990	7	14	3	11
1991	5	11	7	4
1992	10	11	7	4
1993	14	24	14	10
1994	21	17	9	8
1995	21	20	17	3
1996	15	14	9	5
1997	7	12	7	5
1998	2	16	7	9
1999	1	12	5	7
2000	7	14	6	8
2001	4	15	9	6
2002	2	7	3	4
2003		11		11
2004	1	3	1	2
2005		5	2	3
2006	1	6	3	3
2007		6	2	4
2008		1		1
Total	136	239	113	126

Created dd 03 Feb 09, GGD Amsterdam

**Table 9. Yearly HIV incidence, number of HIV positives and number of person years per calendar year according to injecting status at entry**

		1 Injectors only			3 All drug users		
		No. HIV positives	Person years	Incidence	No. HIV positives	Person years	Incidence
Year	1986	5,00	58,05	8,61	5,00	74,05	6,75
	1987	5,00	139,69	3,58	6,00	182,49	3,29
	1988	9,00	206,91	4,35	10,00	266,74	3,75
	1989	7,00	240,78	2,91	8,00	314,00	2,55
	1990	12,00	267,37	4,49	13,00	352,52	3,69
	1991	4,00	253,91	1,58	5,00	341,02	1,47
	1992	5,00	272,84	1,83	7,00	373,15	1,88
	1993	5,00	293,25	1,71	5,00	397,42	1,26
	1994	5,00	305,61	1,64	7,00	416,31	1,68
	1995	8,00	316,37	2,53	9,00	439,83	2,05
	1996	7,00	313,26	2,23	7,00	449,17	1,56
	1997	3,00	307,84	,97	4,00	446,56	,90
	1998	4,00	310,84	1,29	4,00	458,79	,87
	1999	,00	319,82	,00	1,00	500,76	,20
	2000	,00	307,11	,00	,00	491,74	,00
	2001	,00	321,07	,00	1,00	549,84	,18
	2002	,00	297,92	,00	1,00	519,89	,19
	2003	,00	275,25	,00	,00	486,40	,00
	2004	,00	259,06	,00	,00	459,81	,00
	2005	2,00	237,04	,84	3,00	420,74	,71
	2006	,00	220,07	,00	,00	389,18	,00
	2007	,00	198,67	,00	,00	351,27	,00
	2008	,00	128,56	,00	,00	228,23	,00

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