0303-8408/94/060387-08 $ 1.50 + 0.20/0

Soz Präventivmed 1994; 39: 387–394

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The Swiss HIV Cohort Study: Rationale, organization and selected baseline characteristics

Summary

Objectives: *This paper describes the rationale and design features of the Swiss HIV Cohort Study (SHCS) and the baseline characteristics of participants enrolled up to March 31st 1993. The objectives include epidemiological, clinical and laboratory research.*

Design: *The SHCS is a prospective cohort study of HIV infected adolescents and adults seen at the outpatient clinics of the Swiss University Hospitals in Basle, Berne, Geneva, Lausanne and Zurich and the Cantonal Hospital St. Gall. The multicentre collaboration was initiated in September 1988 by the Swiss Federal Office of Public Health. Data collected prior to this date by several participating centers using a similar protocol were included, the earliest records dating back to 1982. Follow-up visits are scheduled every 6 months.*

Enrollment: *As of March 31st 1993, 6253 participants (M: 4580, F: 1675) were included with a total of 16015 person-years of follow-up (mean 2.6 years). HIV transmission categories were 46% intravenous drug users (IDU), 32% men who had sex with men (MSM), 18% heterosexual contacts (HET) and 4% other. The proportion of MSM among male participants decreased from 62% in 1985 to 40% in 1987, to remain stable thereafter. The proportion of IDU among males was around 40% throughout, whereas in females, there was a pronounced decline from 90% IDU in 1985 to 50% in 1992. Conversely, there was a striking increase in registrations of women presumably infected by HET, from 8% in 1985 to 50% in 1992. Among men, the proportion classified as HET increased from 2% to 15%. It is estimated, that a large proportion of all Swiss AIDS patients (70%) and HIV infected individuals (32%–47%) are enrolled in the Swiss HIV Cohort Study. Losses to follow-up, however, are common.*

Conclusions: *The SHCS serves multiple purposes as a research project, as infrastructure for multidisciplinary research and as a tool to improve patient care. Several international and national trials, post-marketing surveillances and expanded access protocols were or still are based upon its infrastructure. The large number of female participants and of participants AIDS-free at entry, make the database especially valuable.*

Background

In Switzerland, the first three patients with the acquired immunodeficiency syndrome (AIDS) were recorded in 1982. In 1985, when the first HIV antibody tests became available, several University Hospitals began to prospectively follow HIV infected patients. In 1988, these efforts were coordinated by the Federal Office of Public Health (FOPH). The Swiss HIV Cohort Study (SHCS) was initiated as a collaborative project of all Swiss University Hospitals to promote research on HIV infection in Switzerland, and to provide a logistical network to support multidisciplinary and multicenter projects on preventive, epidemiological, clinical and laboratory aspects of HIV infection in Switzerland.

This paper focuses on the rationale, organization and design features of the SHCS and describes selected characteristics of the participants enrolled up to March 31, 1993.

Objectives

In detail, the following areas of interest were defined:

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* See Appendix for details on the participating institutions of the Swiss HIV Cohort Study

Epidemiologic and Clinical Research

- To observe the natural course and progression of HIV infection.
- To compare HIV infection in groups of patients with different modes of HIV acquisition and between sexes.
- To determine the impact of therapeutic interventions.
- To identify risk factors and predictive markers of HIV disease progression.
- To determine the appropriate criteria for institution of prophylaxis against opportunistic diseases.

Laboratory Research

- To collect prospectively consecutive serum and cell specimens, in order to analyse and to identify laboratory markers of HIV disease progression.
- To develop projects on biological aspects of HIV infection linked to clinical observations.
- To provide accurate and comparable laboratory data (e.g. surrogate markers).

Improvement of Patient Care

- To optimize and standardize patient care through the rapid spread of new scientific information at regular meetings (e.g. primary/secondary prophylaxis against opportunistic infections).
- To support projects studying improvement of patient care, especially care based in out-patient clinics.
- To provide access to new medication within expanded access protocols and post-marketing surveillance.

Service and Infrastructure for other Projects

- To establish a logistical network for interdisciplinary collaboration with investigators from different fields including epidemiology, prevention, clinical research, and basic research.
- To serve as a complementary tool to the federal epidemiological surveillance instruments.

Design features

Study Organization

Participating centers are the five University Hospitals in Basle, Berne, Geneva, Lausanne, and Zurich, and the Cantonal Hospital in St. Gall. The steering committee consists of a representative from the clinic and the laboratory of each hospital, and representatives from the Institute for Social and Preventive Medicine of the University of Zurich and the coordinating center (see appendix for details).

Recruitment Procedures

HIV seropositive subjects over 16 years of age seen at the outpatient clinics of the participating hospitals are continuously enrolled. Recruitment according to the standardised protocol started in September 1988. However, all centers had been prospectively collecting information using a similar protocol since HIV screening tests became available in June 1985. In addition, Zurich and Geneva included a number of well-documented patients ($n = 42$) retrospectively, the earliest record dating back to 1982. These participants were included in the multicenter database. Interviews for the baseline data include demographic data, HIV transmission category, HIV-associated diseases, and medication. Categories of presumed transmission were: i) injecting drug users who shared needles (IDU), ii) men who had sexual intercourse with men (MSM) including both homosexual and bisexual men, iii) subjects infected via heterosexual contacts (HET), iv) subjects infected via blood products, transfusions, or unclear routes of transmission (OTHER): Male IDU who also had sexual contact with men are classified as IDU.

Follow-Up Examinations

Regular semiannual outpatient visits are arranged with additional documentation and specimen collection. The questionnaires and examinations cover new and recurring HIV-associated diseases, and an update on treatment and socio-economic aspects. If participants do not return for a follow-up visit, they receive at least two written invitations before they are considered as lost to follow-up.

Laboratory Data Collection

The following laboratory tests are performed at every visit: hemoglobin, platelets, leukocytes, lymphocytes, lymphocyte subpopulations (CD3, CD4 and CD8), HIV p24 antigen, HIV p24 antibody and β-2 microglobulin. Tuberculin skin reactivity, syphilis TPHA and VDRL-titer, cytomegalovirus IgG and Toxoplasma gondii IgG are measured at baseline and every two years. All participating laboratories are Swiss HIV reference sites, and perform regular quality controls to assure the comparability of results. Serum and cell samples are stored according to a standard protocol.

Ethical Issues

Informed consent is obtained at registration. All clinical studies conducted within the framework of the SHCS are subjected to separate review by the ethical review boards of the institutions involved. Data collection is strictly anonymous with a participant number being the unique identifier.

Enrolment up to March 31st 1993

As of March 31 1993, a total of 6253 participants, contributing 16015 person-years of observation, had been registered. Forty-one percent had been recruited at the Zurich center (Table 1). Overall, 27% were women, with the proportion ranging from 32% at Lausanne to 25% in Zurich ($p = 0.0006$ by chi-square test for heterogeneity).

Characteristics at Baseline

Categories of transmission were 46% IDU, 32% MSM, 18% HET and 4% OTHER. The proportion of MSM decreases with decreasing size of the population the center serves, whereas a trend in the opposite direction is evident for heterosexually infected participants ($p < 0.0001$ by chi-square test for trend).

The mean (standard deviation) age at registration was 28.9 (4.7) years for IDU, 37.2 (9.6) years for MSM, 32.7 (9.8) years for HET, 36.8 (15.6) years for recipients of HIV contaminated blood products or transfusions, and 34.4 (11.5) years for participants infected via other or unclear routes ($p < 0.0001$ by analysis of variance). As shown in Figure 1, the proportion of MSM among male participants decreased from 62% in 1985 to 40% in 1987 to remain stable thereafter. The proportion of IDU among males was around 40% throughout, whereas in females there was a pronounced decline, from 90% IDU in 1985 to 50% in 1992. Conversely, there was a striking increase in registrations of women presumably infected by HET, from 8% in 1985 to 50% in 1992. The proportion of female participants rose from 19% to 25%. All the changes observed over the years were statistically significant ($p < 0.05$ by chi-square tests for trend).

After 1986, the distribution of disease stages of new participants at entry remained stable with approximately 20% AIDS, 20% AIDS-related complex (ARC) and 60% asymptomatic individuals.

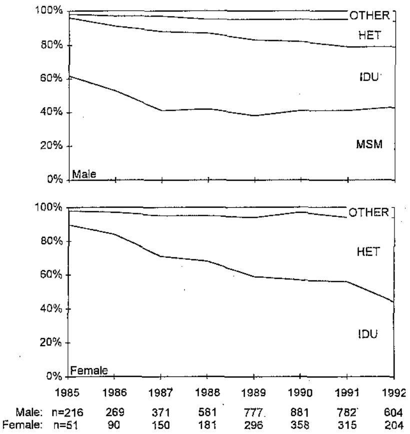

Figure 1. *Presumed HIV transmission categories at study entry in male and female participants, 1985–1992 (MSM: men who had sex with men; IDU: injecting drug users; HET: heterosexual contacts; OTHER: blood products, transfusions or unclear routes of transmission). The absolute number of individuals registered each year is shown at the bottom.*

Losses to Follow-Up

Up to March 31 1993, 1653 (26%) participants have died. Despite repeated invitations, 42% of the participants presumed to be alive have not been seen at a study center during the last year. As shown in Table 2, those lost to follow-up are significantly ($p < 0.0001$) younger, more likely to be female ($p = 0.0005$), and more likely to belong to the category of IDU ($p < 0.0001$). The difference between IDU and other participants in the proportion not seen over the past year was

Center	Population 1992	Total Participants	% Women	% IDU	% MSM	% HET	% OTHER	Person-Years Total	Person-Years per Person
Zurich	345000	2547	25	45	36	15	4	6794	2.7
Basle	176000	512	26	46	34	16	4	1414	2.8
Geneva	170000	1123	28	43	31	20	6	3067	2.7
Berne	130000	711	25	45	30	20	5	1499	2.1
Lausanne	118000	1014	32	48	27	21	4	2349	2.3
St. Gall	72000	346	27	58	16	22	4	892	2.6
Total		6253	27	46[a]	32[b]	18	4	16015	2.6

[a] includes 3% male participants who also had sex with men
[b] includes 8% bisexual men

Table 1. *Recruitment, proportion of women, distribution of HIV transmission categories and duration of follow-up for the different participating centers.*

			no visit since March 31st 1992		documented visit since March 31st 1992		p[a]
Number of participants		(%)	1940	(42)	2660	(58)	–
Mean age	[years]	(SD)	30.3	(7.5)	32.6	(8.6)	0.0001
Gender	M	(%)	1310	(68)	1923	(72)	0.0005
	F		630	(32)	737	(28)	
Presumed category of transmission	IDU	(%)	1083	(56)	1142	(43)	< 0.0001
	MSM		406	(21)	872	(33)	
	HET		363	(19)	545	(20)	
	OTHER		88	(5)	101	(4)	
Stage at entry	Asymptomatic	(%)	1447	(74)	1908	(72)	0.09
	ARC		344	(18)	531	(20)	
	AIDS		149	(8)	221	(8)	
Median CD4 count at entry	[10^6/l]	(range)	450	(5–1950)	390	(2–1956)	0.0001

[a] probability by chi-square or unpaired t-tests (on log transformed data in case of CD4 counts)

Table 2. *Characteristics of 4600 participants registered by the Swiss HIV Cohort study and not reported dead by time period since last visit.*

		National Surveillance		Swiss HIV Cohort Study		p*
		n	(%)	n	(%)	
Number of AIDS patients		3028	(100)	2124	(70)	–
Gender	M	2408	(100)	1723	(72)	0.001
	F	620	(100)	401	(65)	
Presumed category of transmission	IDU	1180	(100)	754	(64)	< 0.0001
	MSM	1255	(100)	957	(76)	
	HET	436	(100)	271	(62)	
	OTHER	157	(100)	142	(90)	

* probability by chi-square tests

Table 3. *Characteristics of AIDS patients enrolled in the Swiss HIV Cohort Study compared with AIDS patients reported to the Federal Office of Public Health (National Surveillance) as of March 31st 1993*

particularly pronounced in males. Although the disease stage at baseline was not significantly different (p = 0.09), those lost to follow-up had significantly (p = 0.0001) higher CD4 counts at entry, suggesting less advanced disease in this group.

Antiretroviral Treatment and Participation in Controlled Studies

Up to the time of analysis, 2698 (43%) of participants had started antiretroviral treatment with Zidovudine (AZT) and 606 (10%) with Didanosine (ddI), generally within the framework of a controlled study or post-marketing surveillance protocol: 1928 participants in the Zidovudine post-marketing surveillance (5/87–9/91), 204 participants in the international MRC/

Inserm Alpha trial (7/90–9/92), 275 participants in the Swiss expanded access ddI protocol (11/91–11/92) and more than 80 participants in the ongoing international MRC/ANRS Delta trial which started in May 1992. Of the participants receiving antiretroviral therapy, 40% were IDU and 22% women.

Representativity

A review of all Swiss HIV/AIDS reporting sources provided a cumulative estimate of 13000–19000 HIV-infected individuals in Switzerland at the end of 1992[1]. The figure of 6111 participants enrolled in the SHCS up to this date suggests that 32%–47% of all HIV-infected persons were included. Since most participating centers are tertiary referral clinics, it is to be expected that the proportion of AIDS patients included will be higher. Indeed, with a cumulative number of 2124 AIDS patients, the cohort represents 70% of the 3028 AIDS cases reported to the Swiss Federal Office of Public Health up to March 31st 1993. As shown in Table 3, male AIDS patients were more likely to be registered with the SHCS than female patients ($p = 0.001$), and MSM who developed AIDS were more likely to join the study than IDU or HET with AIDS ($p < 0.0001$).

Discussion

Seventy percent of all AIDS cases reported to the Federal Office of Public Health are enrolled in the SHCS. National registration of AIDS cases in Switzerland, which includes a careful review of death certificates, has been shown to be near-complete[2]. More uncertainty is attached to the estimates of the total number of HIV-infected persons[1] but it is reasonable to assume that a considerable proportion, between 30% and 45%, are enrolled. Such high participation can only be achieved with a flexible study design. This, however, has resulted in a high rate of loss of follow-up. The study is likely to yield cross-sectional information which is representative for some patient groups – e.g for MSM who have developed AIDS – but less so for others – e.g. asymptomatic IDU. Because of differential loss to-follow-up the prospectively collected data will, in general, be less representative than the cross-sectional findings. A recent publication examines the survival experience of the different patient groups enrolled in the SHCS and provides an example of how the influence of such bias can be explored through extensive sensitivity analyses[3].

Comparisons with surveillance data nevertheless support the notion that the development of the epidemic in Switzerland is reflected in the SHCS enrolment. Both surveillance data and the SHCS suggest steadily increasing infection rates via the heterosexual route, while the rate of new infections among MSM and among IDU appear to have stabilized[1].

The possible mechanisms inolved in losses to follow-up must be examined. Those lost to follow-up for at least one year are younger, tend to have less advanced disease and higher CD4 counts. The main reason for not attending scheduled follow-up visits is probably a lack of motivation in asymptomatic individuals. The Swiss health care system is characterized by a high insurance coverage which guarantees access to health care from the provider of choice to over 99% of the population[4]. Asymptomatic patients may well prefer to consult their private physician in cases of minor problems.

Within the framework of national and international trials, the Swiss HIV Cohort Study has made antiretroviral therapies as well as prophylactic regimens available for testing before these therapies were registered with the licensing authority. Since 1987, over 40% of the participants have received antiretroviral therapy. In fact, Zidovudine (until 1991) and Didanosine (until 1992) were available exclusively from one of the participating outpatient clinics in the framework of post-marketing surveillance or expanded access protocols. This provided an important reason for patients to register with the SHCS or to return to the study after a period of non-attendance. The wider availability of Zidovudine may have contributed to the decline in patient recruitment in 1992. This underscores the need for intensified collaboration with other care providers, mainly private physicians, in the future.

The SHCS has contributed to the evaluation of therapeutic agents – for example through involvement in the MRC/Inserm Alpha Trial, and the ongoing MRC/ANRS Delta Trial, and has been used to assess the value of pentamidine inhalations in the prophylaxis and prevention of *Pneumocystis carinii* pneumonia[5,6]. After the initial discovery of *Mycobacterium genavense* as a pathogen in HIV infection, the SHCS allowed the identification of 15 additional cases throughout Switzerland, thus showing that infection with this agent is not a medical curiosity[7]. Epidemiological research so far has focused on differences in mortality between genders and transmission groups[3]. More recently, comparative analyses of mortality in the SHCS and a large U.S. cohort study with similar design have been performed[8].

In conclusion, we have illustrated and critically reviewed the multiple purposes of the SHCS as a clinical, epidemiological and public health resource. Increased efforts to improve registration and follow-up rates are required to maintain this important resource in the future.

Zusammenfassung

Grundlagen, Organisation und Kenndaten der Schweizerischen HIV Kohortenstudie

Ziele: *Dieser Artikel beschreibt die Grundlagen und Strukturen der Schweizerischen HIV-Kohortenstudie, sowie die Kenndaten der bis zum 31. März 1993 rekrutierten Teilnehmer. Ziele der Studie sind epidemiologische, klinische und Grundlagenforschung.*
Methodik: *Eine Kohortenstudie mit Patienten der HIV Sprechstunden an den Universitätsspitälern von Basel, Bern, Genf, Lausanne und Zürich, sowie dem Kantonsspital St. Gallen. Die multizentrische Zusammenarbeit wurde im September 1988 durch das Bundesamt für Gesundheitswesen initiiert. Die frühesten Daten stammen aus dem Jahr 1982. Nachkontrollen sind alle 6 Monate vorgesehen.*
Resultate: *Per 31. März 1993 unfasste die Studie 6253 Teilnehmer (27% Frauen) mit total 16015 Personenjahren Beobachtungszeit. Die häufigsten HIV Ansteckungswege waren 46% intravenöser Drogenkonsum, 32% homosexuelle Sexualkontakte und 18% heterosexuelle Sexualkontakte. Bei den Männern verkleinerte sich der Anteil homosexueller Personen von 1985: 62% auf 1987: 40% und blieb seit dann konstant, währenddem der Prozentsatz der heterosexuell Infizierten von 1985: 2% auf 1992: 15% anstieg. Der Anteil drogenabhängiger Männer lag über die ganze Beobachtungszeit bei ungefähr 40%. Bei den Frauen hingegen reduzierte sich der Anteil der Drogenabhängigen von 1985: 90% auf 1992: 50%. Demgegenüber steht eine drastische Zunahme bei den durch heterosexuellen Geschlechtsverkehr infizierten Frauen von 1985: 8% auf 1992: 50%. Es wird geschätzt, dass ein grosser Teil der Schweizer AIDS Patienten (70%) und HIV infizierten Personen (32%–47%) in die Kohortenstudie aufgenommen wurden.*
Diskussion: *Die Kohortenstudie nimmt verschiedene Aufgaben wahr als eigenständiges epidemiologisches Forschungsinstrument, als Basis und Infrastruktur für multidisziplinäre Forschungsprojekte und als Hilfsmittel zur Vereinheitlichung und Verbesserung der Patientenbetreuung. Verschiedene nationale und internationale Therapiestudien sind bereits realisiert worden. Die Schweizerische HIV Kohortenstudie zeichnet sich gegenüber ähnlichen Projekten im Ausland durch einen grossen Anteil von Frauen und von asymptomatischen Personen aus.*

Résumé

Etude suisse de cohorte VIH: Buts, organisation et caractéristiques initiales

Objectif: *étude des données épidémiologiques et cliniques d'un collectif de patients infectés par le VIH en Suisse.*
Méthode: *étude de cohorte de patients adultes infectés par le VIH recrutés dans les hôpitaux universitaires de Bâle, Berne, Genève, Lausanne et Zurich ainsi qu'à l'hôpital cantonal de St. Gall. Cette étude multicentrique débuta en septembre 1988 et fut initiée par l'office fédéral de la santé publique. Certains centres ayant récolté des données dès 1982 les ont inclues rétrospectivement.*
Résultats: *Au 31.3.1993, 6253 personnes (4580 hommes, 1673 femmes) étaient inclues avec un suivi total de 16015 personnes-années (moyenne 2.6 année). La transmission présumée du VIH était dans 46% des cas due à l'utilisation de drogues intraveineuses (IDU), 32% à des relations homosexuelles (MSM), 18% à des relations hétérosexuelles (HET), et pour 4% des cas, elle provenait d'autres facteurs. Les transmissions présumées homosexuelles passèrent de 67% en 1987 à 40% en 1987, et sont dès lors restées stables. La proportion d'hommes infectés par IDU est stable et représente environ 40%, chez les femmes par contre la proportion d'infections par IDU passa de 90% en 1985 à 50% en 1992. Par contre le nombre de transmission par relation HET chez les femmes passa de 8% en 1985 à 50% en 1992. Chez les hommes les infections HET passeraient de 2 à 15% durant la même période. En Suisse environ 70% des patients sidéens et 32 à 47% des séropositifs sont inclus dans cette étude de cohorte. Les «lost for follow-up» sont un problème important.*
Conclusions: *l'étude de cohorte VIH en Suisse est non seulement un projet de recherche en soi. Elle sert aussi de base structurelle sur laquelle d'autres projets peuvent se gréffer. Ceci permit de participer à plusieurs études nationales et internationales dans le domaine thérapeutique. La large proportion de femmes dans cette cohorte est un aspect particulièrement intéressant et unique.*

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Acknowledgements

We thank the participants, physicians, nurses, data-managers and supporting personnel. We are especially grateful to George Davey Smith from the Department of Public Health, University of Glasgow, Glasgow, U.K. for the epidemiological advice and careful review of the manuscript. Financial Support: Federal Office of Public Health, Grant No 90-7027. M.E. is supported by the Swiss National Science foundation.

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