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COHORT PROFILE

Cohort Profile: The Swiss HIV Cohort Study

The Swiss HIV Cohort Study*,†

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How did the study come about?

The Swiss HIV Cohort study (SHCS) was established in 1988. It is an ongoing multicentre, prospective observational study for interdisciplinary human immunodeficiency virus (HIV) research in clinical, translational, basic, epidemiological and social sciences, and for addressing public health questions. It started with the enrolment of HIV-infected adults aged $\geqslant 16$ years in a multicentre study and originally was financed by the Swiss Federal Office of Public Health (FOPH). Some data going back to 1981 have been collected retrospectively. In 1995, the SHCS was reorganized with a clear separation between research and infrastructure budget. A Scientific Board, responsible for the evaluation of nested research projects within a defined budget envelop, was established. Moreover, each centre has been compensated/penalized according to its performance and, last but not least, quality control programmes have been implemented. In 2000 the representatives of clinics and laboratories were merged in the Clinics & Laboratories Committee. At the same time, funding was transferred from the FOPH to the Swiss National Science Foundation (SNSF).

The Swiss Mother & Child HIV Cohort Study (MoCHiV) founded in 1998 as a merger of the 'Swiss Neonatal HIV Study' and the 'Swiss HIV & Pregnancy Study' (initiated in 1986 and 1989, respectively) was fully integrated in the adult SHCS in 2003. Thus, longitudinal data in women included in both cohorts became available for research, rendering MoCHiV a very unique mother–child cohort.

The data collection is strictly anonymous and written informed consent is mandatory prior to inclusion. Since 2002 an additional informed consent for genetic analyses is asked for and since 2006 patients general informed consent includes consent for genetic analyses.

Today, the SHCS is a powerful tool for the investigation of HIV-infected patients in respect to:

(i) challenges of modern antiretroviral treatment [e.g. combined antiretroviral therapy (cART) effectiveness, drug resistance and toxicity] in adults and children;
(ii) monitoring the effects of cART on a national and international level (e.g. cardiovascular side effects of treatment);
(iii) social aspects of the disease in an increasingly aging population;
(iv) virus–host interactions, cell biological and genetic mechanisms of the disease;
(v) transmission of HIV-1 on population level; and
(vi) treatment during and outcome of pregnancy; vertical transmission.

Who is in the sample and what does it cover?

The number of newly registered patients in the cohort has increased in parallel to the epidemic character of the disease in the Swiss population. The peak of registrations ($n = 836$) in the SHCS (1997) was reached, however, with a delay of 5 years to the peak of infections newly declared to the Swiss health authorities. This peak marks as well the time when cART and highly active antiretroviral therapy (HAART) were introduced and therefore a newly available treatment option became available, which made it more attractive for infected patients to seek for care at one of the specialized centres. Thereafter, the number of registered patients decreased to 576 in the year 2000 and has remained stable since. Furthermore, a stable number of 60 mother–child pairs have been recruited per year.

Switzerland has a federalistic health-care system without national patient registries, therefore the SHCS and the MoCHiV have been a collaboration of seven specialized centres (all five Swiss university hospitals situated in Basel, Bern, Geneva, Lausanne and Zurich, and additionally two cantonal reference hospitals St Gallen and Ticino) acquiring patients for the cohort. Since 1995, interested private physicians

* Corresponding author. Franziska Schoeni-Affolter, Data- and Coordination Center, University Hospital Center and University of Lausanne, Av. Pierre-Decker 2, 1011 Lausanne-CHUV, Switzerland.
E-mail: franziska.schoni-affolter@chuv.ch
† The Cohort Study members list are included in acknowledgement section.

and regional hospitals taking care of HIV-infected patients can also participate in the SHCS by sending their reports and blood samples for storage to the next local centre. The cohort study is managed by the coordination- and datacentre in Lausanne.

Today the SHCS includes HIV-infected individuals aged $\geqslant$18 years and is estimated to cover ~45% of the cumulative number of HIV infections declared to the Swiss health authorities and 69% of people with acquired immune deficiency syndrome (AIDS) living in Switzerland. The demographic and selected baseline characteristics of the SHCS are presented in Table 1. By March 2009, a total of 15 624 patients were included cumulatively, of whom 71.2% were males [69.5% males of active participants ($n=7340$)] (Figure 1). Men having sex with men (MSM) was reported as the presumed route of infection in 34.7% of all cases (40.1% of active patients) and 5020 persons (32.1%) were infected heterosexually (38.8% of active patients). Of all patients, 29.5% were infected through intravenous drug use (16.8% of active patients). The median age at enrolment has increased slightly over time. By March 2009 the age at enrolment of men is 34.3 years and of women is 30.0 years. The MoCHiV cohort covers data of children (infected or uninfected) born to infected mothers ($n=1363$) and, additionally, infected children of unknown mothers. In total, 1540 children—of whom 257 are HIV infected—have been registered in MoCHiV. Currently, 136 healthy and 77 infected children have been under follow-up and 61 infected children have died so far (Table 2).

What data are collected on a regular basis?

In the SHCS, a standardized protocol is used for data collection. Socio-demographic and behavioural data are recorded at entry to the study (i.e. year of birth, gender, last negative HIV test, presumed mode of transmission, comorbidities, etc.). Categories of presumed transmission include MSM, heterosexually infected patients, injecting drug users, patients infected via blood products and patients with unknown route of infection. Various serological laboratory tests are routinely performed at registration. At each semi-annual follow-up visit laboratory and clinical data are obtained. The antiretroviral treatment is documented in detail. Additional interim CD3/4/8, viral load and general safety laboratory determinations are also recorded, if available. Related to pregnancy, additional gynaecological and neonatal data are collected. Moreover, in the SHCS a repository of plasma/serum (twice a year), and viable cells/cell pellets (once a year) has been built up since the beginning of the cohort. To date, 547 646 plasma, 239 999 cell, 245 719 serum and 18 720 cell pellet

Table 1 Demographic and selected baseline characteristics of all SHCS participants in the seven centres

SHCS	Total	Basel	Bern	Genf	Lausanne	St Gallen	Ticino	Zürich
Registered patients	15 624	1497	1998	2488	2406	895	521	5819
Female patients (%)	4491 (28.8)	468 (31.3)	640 (32)	729 (29.3)	806 (33.5)	280 (31.3)	180 (34.6)	1388 (23.8)
Ethnicity: number of patients (% of all patients)								
White	10 327 (66.1)	838 (56)	1058 (53)	1083 (43.5)	1167 (48.5)	523 (58.4)	366 (70.2)	5292 (90.9)
Black	1314 (8.4)	127 (8.5)	247 (12.4)	302 (12.1)	298 (12.4)	63 (7)	9 (1.7)	273 (4.7)
Hispano-American	244 (1.6)	26 (1.7)	21 (1.1)	49 (2)	41 (1.7)	8 (0.9)	12 (2.3)	87 (1.5)
Asian	355 (2.3)	50 (3.4)	60 (3)	32 (1.3)	34 (1.4)	17 (1.9)	7 (1.3)	155 (2.7)
Unknown	3351 (21.5)	455 (30.4)	607 (30.4)	1017 (40.9)	861 (35.8)	284 (31.7)	122 (23.4)	5 (0.1)
Other	27 (0.2)	1 (0.1)	5 (0.3)	5 (0.2)	4 (0.2)	5 (1)	0	7 (0.1)
Active number of patients								
Total (% of all patients)	7340 (47)	726 (48.5)	1002 (50.2)	1102 (44.6)	1076 (44.8)	446 (49.8)	289 (55.4)	2699 (46.4)
Female patients (% of active patients)	2238 (30.5)	239 (32.9)	350 (34.9)	355 (32.2)	396 (36.8)	152 (34.1)	106 (36.7)	640 (23.7)

(continued)

Table 1 Continued

SHCS	Total	Basel	Bern	Genf	Lausanne	St Gallen	Ticino	Zürich
Loss to follow-up								
Total (% of all patients)	8284 (53.1)	771 (51.4)	996 (50.2)	1386 (56)	1330 (55.1)	449 (49.7)	232 (44.1)	3120 (53.8)
Died (% of loss to follow-up)	4337 (52.4)	345 (44.7)	538 (54)	753 (54.3)	653 (49.1)	276 (61.4)	114 (49.1)	1664 (54)
Most likely route of infection: number of patients (% of all patients), 1 missing								
Homosexual contacts	5424 (34.7)	483 (32.3)	539 (27)	910 (36.5)	697 (29)	185 (20.7)	109 (20.9)	2501 (43)
Heterosexual contacts	5020 (32.1)	562 (37.5)	731 (36.6)	853 (34.3)	965 (40.1)	335 (37.4)	190 (36.4)	1384 (23.8)
Intravenous drug use	4594 (29.5)	385 (25.7)	617 (30.9)	620 (24.9)	648 (26.9)	335 (37.4)	202 (28.7)	1787 (30.7)
Contaminated blood	174 (1.1)	5 (0.3)	25 (1.2)	44 (1.8)	32 (1.3)	7 (0.8)	5 (1)	56 (1)
Perinatally contaminated	30 (0.2)	3	2	7	8	1	1	8
Unknown/other	381 (2.4)	59 (3.9)	84 (4.2)	54 (2.2)	55 (2.3)	32 (3.6)	14 (2.7)	83 (1.4)
Age at HIV diagnosis (years)								
Mean (median)	32.9 (30.6)	33.3 (31.2)	32.6 (30.4)	32.9 (30.6)	32.7 (30.5)	32.3 (29.8)	31.8 (29.5)	33.3 (31.2)
IQR	25.5–38.2	25.8–39.4	25.5–37.5	25.6–38.1	25.6–37.7	24.7–37.6	24.6–35.9	25.8–38.7
Treatment: number of patients (% of all patients)								
Naïv	3863 (24.7)	368 (24.6)	513 (25.7)	598 (24)	628 (26.1)	220 (24.6)	117 (22.5)	1419 (24.4)
ART	2702 (17.3)	234 (15.7)	280 (14)	530 (21.3)	473 (19.6)	128 (14.3)	42 (8.1)	1015 (17.4)
HAART	9059 (57.7)	895 (59.8)	1205 (60.3)	1360 (54.6)	1305 (54)	547 (61.1)	362 (69.5)	3385 (58.2)
Age when HAART started: years								
Mean (median)	38.3 (36.7)	39.4 (37.4)	38 (36.4)	38.2 (36.9)	38 (36.5)	38.3 (37.1)	38.0 (36.4)	38.4 (36.7)
IQR	31.7–43.4	32–44.6	31.4–43	31.7–43.5	31.3–43.5	31.1–43.8	32.1–41.7	31.9–43.3
Time between HIV diagnosis and HAART: years								
Mean (median)	4.7 (3.1)	5.1 (3.4)	4.5 (2.5)	5.0 (3.7)	4.5 (2.7)	4.5 (2.4)	5.6 (4.2)	4.7 (3.1)
IQR	(0.2–8.4)	(0.2–9.4)	(0.3–7.6)	(0.3–8.7)	(0.1–8.3)	(0.2–7.4)	(0.4–10.3)	(0.3–8.3)
CD4 cell count at start of ART: cell count/µl								
Mean (median)	231 (200)	244 (212)	219 (190)	252 (217)	249 (219)	244 (200)	261 (228)	215 (185)
IQR	80–319	98–334	83–299	104–336	101–326	80–341	105–345	80–300
HIV related diseases (% of all patients)								
Patients with B-event	3561 (22.8)	421 (28)	489 (24.5)	477 (19.2)	548 (22.7)	222 (24.8)	153 (29.4)	1251 (21.5)
Patients with C-event	5946 (38.1)	550 (36.7)	721 (36.1)	1030 (41.4)	888 (36.9)	378 (42.2)	188 (36.1)	2191 (37.7)

IQR: inter-quartile range.

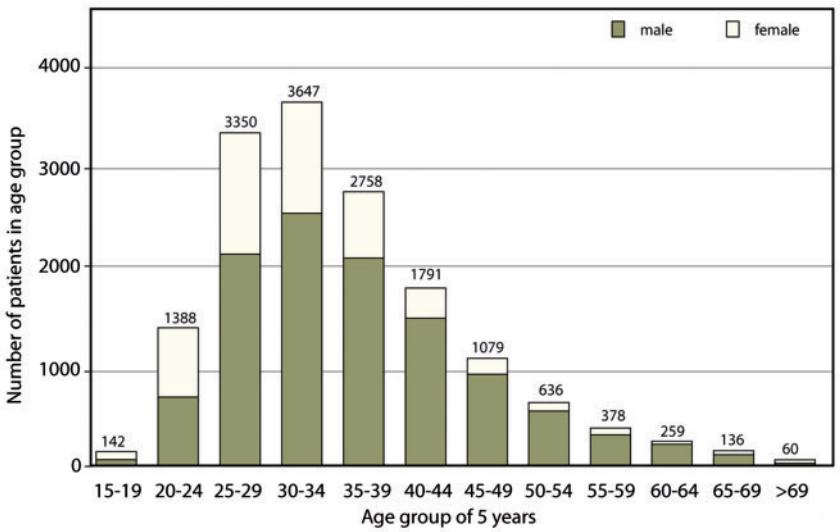

Figure 1 Age and gender structure of all participants in the SHCS ($n = 15\,624$) at registration

Table 2 Demographic and selected baseline characteristics of all MoCHiV participants in the seven centres

MoCHiV	Total	Basel	Bern	Genf	Lausanne	St Gallen	Ticino	Zürich
Registered children	1540	239	191	218	270	79	80	428
Female children (%)	768 (49.9)	126 (52.7)	86 (45)	114 (52.3)	143 (53)	37 (46.8)	41 (51.3)	205 (47.9)
Infected patients (%)	257 (17.2)	34 (14.7)	32 (17.1)	50 (24.2)	42 (15.8)	15 (19.5)	13 (17.1)	65 (15.5)
Missing infection status	44	8	4	11	4	2	4	9
Loss to follow-up								
Total loss to follow-up	641 (41.5)	80 (33.4)	76 (39.7)	86 (39.5)	100 (37)	33 (44.3)	35 (43.8)	222 (51.6)
Patients died (%)	78 (12.0)	6 (7.5)	9 (11.8)	11 (12.8)	14 (14)	2 (6)	7 (20)	27 (12.2)
Infected (two missing)	61	6	5	7	10	2	7	22
Uninfected	8	3	2	3	0	0	0	0
Unknown status	9	0	1	2	1	0	0	5
Patients transferred to and merged in SHCS	32	4	3	6	7	1	0	11

samples have been collected and are available for research purposes.

In MoCHiV a standardized protocol is used as well. The collection of data includes both pregnancy and delivery data of the infected mothers and clinical follow-up data of the children born to these infected mothers (Figure 2) and of infected children, where the mother is unknown. The inclusion of non-infected children exposed to maternal antiretroviral treatment during pregnancy enables the study of prospectively potential long-term adverse events of this multi-drug exposure.

The standardized protocol for data collection in both cohorts is adapted regularly to meet the needs of ever-changing research questions (i.e. adverse events of antiretroviral drugs, adherence to drug therapy and cardiovascular risk factors, presumably HIV-associated non-AIDS events such as liver or renal failure, cardiovascular diseases and others).

The written informed consent for genetic analyses, introduced in 2002, allows the analysis of genetic predictors of disease progression, adverse events to drugs and pharmacogenetics. So far, genetic analyses of 2481 patients have been performed with a mean of 60 single nucleotide polymorphisms (SNPs) (range 1–258 SNPs). Genome-wide high coverage genotyping has been performed in 1075 patients.

Since 2002, a large effort has been made to create the SHCS genotypic drug resistance database. All genotypic drug resistance tests generated in Switzerland are entered into a central database (Integrated Database Network System [SmartGene, Zug, Switzerland]) on the nucleotide level and—in 2005—were anonymously linked to the clinical database. In addition, more than 5000 genotypes were generated retrospectively including 100 in vertically infected children. Currently, over 12 000 linked

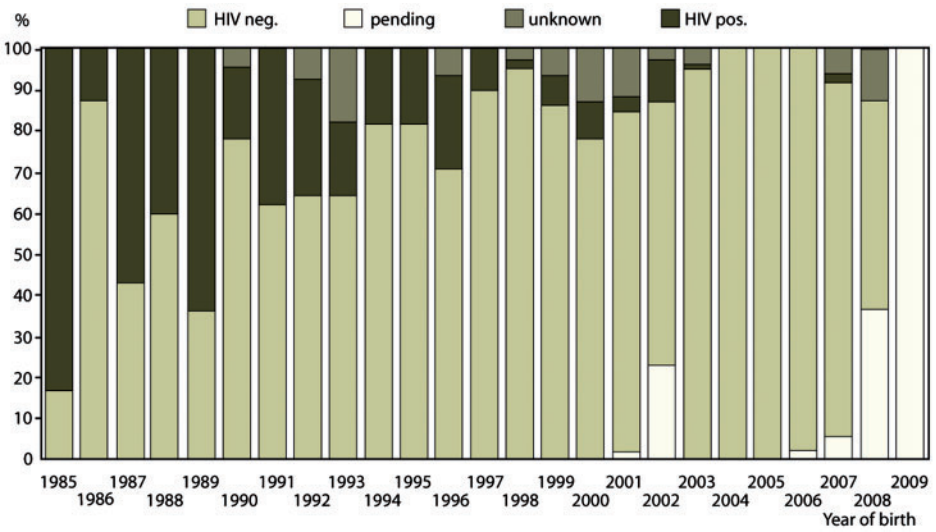

Figure 2 Percentage of vertical HIV transmission in all registered deliveries per year

sequences of genotypic resistance tests are available for analysis.

Data quality is regularly checked by the data centre and a quality incentive system is in place. Due to modern IT techniques it has become possible to automatically transfer the electronic reports from the main laboratories to the data centre, which has had an important impact on data quality.

How often have they been followed up, how long have they been followed up and what is the attrition rate?

The HIV patients are followed in the cohort on an outpatient basis semi-annually. The cohort has 91 701 years of follow-up from 15 624 patients. Loss to follow-up and death are reported by the local centres (total of 8275 patients). Thus far, 4337 (52.4%) patients died, 645 (7.8%) patients moved to a foreign country, 652 (7.9%) patients wanted to discontinue, 2177 (26.3%) changed address or did not respond to written invitations, 153 (1.8%) patients left the cohort for other reasons and, finally, 311 (3.8%) patients switched care to non-cohort physicians.

What has been found? Key findings and publications

The SHCS has a wide scope of research activities. The most important key findings in the SHCS since the beginning are as follows.

(i) Important contributions to the understanding of the HIV epidemic in Switzerland, to the clinical and psychosocial situation of people infected with HIV in this country, and to a country-wide high standard of the clinical management of HIV infection, guaranteed by the active network of the SHCS.

(ii) Repetitive timely and accurate documentations of the beneficial/adverse effects of cART.[1–3]

(iii) The drug resistance database has allowed the SHCS to make significant contributions to the recent new recommendations on drug resistance testing of the IAS-USA 2008[4] with regard to representative high-quality long-term studies on transmission of HIV-1 drug resistance,[5] on long-term trends in prevalence of HIV-1 drug resistance at the population level,[6] on emergence of drug resistance according to different regimen types after first line failure[7,8] and on cost effectiveness of resistance testing.[7]

(iv) Substantial contributions[9–16] to the most recent guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents, to recommendations from the U.S. Center of Disease Control and Prevention, the National Institutes of Health and the HIV Medicine Association of the Infectious Diseases Society of America.[17]

(v) A strong commitment to the development of a genetic study. This required a careful assessment of legal and ethical issues, the universal request of informed consent from cohort participants, and the development of appropriate laboratory support for storage of nucleic acids and for genotyping. This structure allowed the conclusion of the first genome-wide association study in the field[18] as well as a continued development of pharmacogenetics.[19–23] The Swiss HIV Cohort is a partner of http://www.hiv-pharmacogenomics.org, a public domain

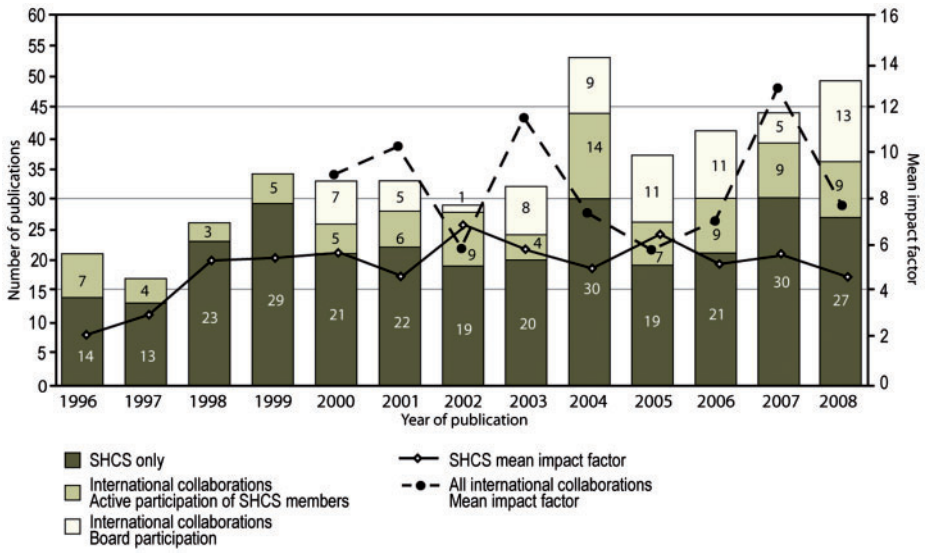

Figure 3 Number of publications and mean impact factor of the journals, in which the respective studies were published

database that provides a complete and updated report on all published genetic association in the field of HIV.

In MoCHiV the most important findings include:

(i) the protective effect of elective cesarean section for vertical transmission; and[24]
(ii) the observation of an increased prematurity rate after combined antiretroviral treatment (cART) during pregnancy.[25,26]

The SHCS rendered possible the publication of a vast number of scientific articles (Figure 3) since the beginning (127 original publications before the year 2000 and 205 since 2000). Since 2007, the core interest and main focus includes clinical and epidemiological questions of HIV infection. Several researchers have investigated questions concerning the treatment with the nowadays most potent cART therapy. Publications cover resistance to treatment, cost effectiveness and adherence problems,[5–8,27–31] side effects of treatment,[32–37] treatment efficacy[38–46] and natural history in children.[47] An increasing number of genetic analyses combined with efficacy, adverse reactions and efficiency of treatment are published.[48] Other fields of investigation comprise questions about co-infections[14,49] and comorbidity in the nowadays aging population of patients[50–52] and the side effect of continuous treatment.[34,53] Thereby, cardiovascular and metabolic problems are predominant,[51–56] other investigations include opportunistic infections and the nature and influence of HAART-associated immune reconstitution on opportunistic diseases.[14,57–61] HIV-related immunodeficiency as a risk factor for neoplasias is another field of investigation[60,62–67] and genetic determinants (viral and host) have become increasingly important in respect of treatment.[20,68–77]

Due to the combined MoChiV database, questions concerning the treatment in pregnancy and the influence of treatment in the newborn can be studied.[78–80] Social aspects of the HIV patients in Switzerland, which have become increasingly important due to the successful treatment options, are covered.[81–85] The broad range of investigations of the SHCS in the past 2 years is rounded off with methodological papers[86] and international collaboration studies.[18,50,87–103]

What are the main strengths and weaknesses?

Due to the chronic character of the disease with dependence of patients to a close follow-up and compulsory treatment regimen the participants are rarely lost to follow-up (33.6/1000 patient years). Therefore, a long observation period can be guaranteed, which is most important for a cohort study. Further advantages are the standardized protocol, which guarantees a high quality of care. Concerning the organization, the strengths of the SHCS are mainly the participative and flexible manner, minimal administrative burden, the professional data management with quality control, the evolution and flexibility of the study protocol as well as a large coverage of patients concerned. A special strength of the SHCS is the participation and/or leadership role in international collaborations (EuroSIDA, PLATO, D:A:D., HIV & Cancer, ART-CC, CASCADE, COHERE, EuroCHAVI, CHAIN, PENTA and other international collaborations including the developing world ART-LINC). As a result, 154 publications from international active collaboration and participation in international steering boards involving the SHCS and MoCHiV have been

published since 1995. Rapid evaluation of projects through the Scientific Board, rules for authorship and a scientific independence concerning the funding of nested research projects within the given budget envelop are further advantages of the SHCS. Other benefits include complete data on HIV-infected patients over a long period of time, which allows the study of several effects of exposure and the calculation of rates and risks. In addition, the availability of stored plasma/serum and viable cells/cell pellets over the whole follow-up period of the patients allows laboratory analyses with the newest technologies on the whole study period addressing unique research questions such as historical virus and host characteristics.[28,60,104] With the possibility of genetic analyses and the integrated HIV resistance database the SHCS is well prepared for future innovative projects in the field. In addition, patients can also directly profit from stored samples, e.g. by retrospective resistance testing that can be done on demand if necessary for optimal treatment decisions.

Hence, due to the strict confidentiality laws in Switzerland to guarantee the protection of privacy, no hard data exist that could allow exact calculations, of how representative the SHCS is compared with all HIV-positive tested persons in Switzerland. Nevertheless, a recent comparison of drug sales data for Switzerland (Source: IMS Health GmbH, Sonnenbergstrasse 11, 6052 Hergiswil, Switzerland) with treatment data in the Swiss HIV Cohort Study for 2006–2008 showed that the 75.1% (weighted mean of all three years) of antiretroviral drug prescriptions in Switzerland can be attributed to patients enrolled in the SHCS. Ongoing challenges for the cohort are the rapidly changing treatment options and clinical presentations of new side effects, which have to be taken into account and adjusted for with new variables collected. Longstanding, dedicated and skilled staff are required, which increases the cost of the cohort.

How can I collaborate? Where can I find out more?

Physicians and regional hospital centres interested in a collaboration can contact one of the seven outpatient clinics (local centres), which will provide more information. Patients interested in participating are welcome and asked to contact a collaborating physician, regional hospital or directly one of the seven outpatient clinics. The SHCS has a website covering the most important information: http://www.shcs.ch.

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**Writing committee*: Franziska Schoeni-Affolter, Bruno Ledergerber, Martin Rickenbach, Christoph Rudin, Huldrych F. Günthard, Amalio Telenti, Hansjakob Furrer, Sabine Yerly, Patrick Francioli.

Collaborators: Aebi C, Battegay M, Bernasconi E, Boffi El Amari E, Böni J, Brazzola P, Bucher HC, Bürgisser P, Calmy A, Cavassini M, Cheseaux JJ, Drack G, Dubs R, Egger M, Elzi L, Fischer M, Flepp M, Fontana A, Francioli P (President of the SHCS), H. Furrer, Fux CA, Gerber S, Gorgievski M, Grawe C, Günthard HF, Gyr T, Hirsch HH, Hirschel B, Hösli I, Kaiser L, Kahlert C, Karrer U, Kind C, Klimkait T, Ledergerber B, Martinetti G, Martinez de Tejada B, Müller N, Nadal D, Paccaud F, Pantaleo G, Raio L, Rauch A, Regenass S, Rickenbach M, Rudin C (Chairman of the MoChiV Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Telenti A, Trkola A, Vernazza P, Weber R, Wyler CA, Yerly S.

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