Swiss HIV Cohort Study (SHCS)

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO).[1]
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A
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PROTOCOL SIGNATURE FORM

Study Title *Swiss HIV Cohort Study*

The project leader (main center) and the center representatives (at the local center) have approved the protocol **version 0.3 (28.05.2024)**, and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on human research with the exception of Clinical trials*

1 BACKGROUND AND PROJECT RATIONALE

1.1 Background

Over the past decades, the understanding of the HIV/AIDS epidemiology, pathogenesis, prevention, and treatment steadily improved. Despite all the efforts and improvements, important goals were not reached until today: Stopping HIV transmission was not achieved despite highly effective antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP) and extensive information campaigns. The development of an effective vaccine to prevent new HIV infections is not within reach and HIV-related stigma and discrimination are still prevalent. Furthermore, there is an urgent need to improve the knowledge on the long-term consequences of HIV infection and ART, and to better understand the consequences of co-infections in this population. Clinical trials only include persons fulfilling specific inclusion criteria and accordingly, their results are typically not representative for the entire population of people living with HIV (PLHIV). Furthermore, the follow-up time in these trials is mostly restricted to several months or few years, and there is no long-term information. Longitudinal cohort studies such as the Swiss HIV Cohort Study (SHCS, www.shcs.ch) provide both representative and long-term data on PLHIV, and thereby close essential gaps in HIV research.

SHCS research priorities

The aim of today's ART is to stop disease progression by long-term inhibition of HIV replication. For a successful therapy with sustained viral suppression, a regular, life-long ART intake is necessary. Over the last decades, ART became highly effective, less toxic and is mostly well tolerated. Continuous improvements in ART regimens led to a reduction in pill burden and simplified therapies. Effective dual therapies or long-acting agents are now available.[4–7] Treatment success is achieved among the vast majority of people living with HIV. Mother-to-child transmission of HIV has been greatly reduced. Recent studies showed that the life expectancy of PLHIV in Switzerland comes close to the life expectancy of the normal population.[8] As a result, the median age of the population of people living with HIV in s is steadily increasing. In the last decades, the clinical picture of an HIV infection has developed from a fatal to a chronic disease.[9,10]

The SHCS was established in 1988 and initially primarily addressed questions regarding natural history of HIV disease, early treatment options and opportunistic infections. However, key characteristics of the HIV epidemic and people living with HIV are changing with new challenges arising and new priorities in HIV research. Accordingly, the SHCS research agenda constantly adapted to the most urgent research needs in HIV. Examples of such priorities include:

a) Treatment of the aging population: The number of co-morbidities and the number of co-medications are increasing in people living with HIV in Switzerland.[11,12] The interactions of HIV and ART with other chronic conditions and non-communicable diseases such as neurocognitive and cardiovascular diseases become more important and need to be investigated. New antiretrovirals, such as long-acting agents and modern simplified therapies need to be studied. Side effects of long-term therapy and drug-drug interactions need further investigation.[13,14]
b) HIV transmission and HIV epidemiology: Treatment-as-prevention and pre-exposure prophylaxis (PrEP) are highly effective for preventing HIV transmissions. The impact of these new developments need to be studied in detail to further improve HIV prevention efforts.[15] Furthermore, modern analytical tools such as molecular epidemiology bring new insights in HIV transmission patterns, and help to better understand the ongoing HIV epidemic in Switzerland.

c) Co-infections: The incidence and prevalence of co-infections including viral hepatitis or sexually transmitted diseases (STDs) have changed considerably in recent years.[9,16–19] Understanding the health impact including prevention and treatment of coinfections and STD is a research priority in HIV medicine.

d) HIV and pregnancy: Monitoring treatment is particularly important during pregnancy as a successful HIV therapy prevents transmission to the newborns. Furthermore, it is highly relevant to study HIV-related health conditions during pregnancy.

e) Health economic assessments: The increasing number of people living with HIV and the life-long therapy lead to high costs and put pressure on the health care system. Health economic assessments and cost-effectiveness analyses are needed to better understand the main cost drivers in HIV.

f) Stigma and discrimination: HIV-related stigma is persistent and insidious. It is of high importance to spotlight stigma and discrimination to further improve access to testing and treatment and to improve the social and psychological situation of people living with HIV.

g) Patient and public involvement (PPI): PPI involvement is increasingly important in HIV research. Patient representatives are actively involved in planning, conduction and interpretation of SHCS research.

To tackle the pandemic and finally eliminate HIV, a vaccine or cure by novel therapeutics would be highly effective. Major research efforts have been dedicated to these topics but it is still a long way to go to achieve this ultimate goal.

h) HIV reservoir and cure: Further efforts are needed to better understand the pathogenesis of persistent HIV infection and to develop therapeutic strategies aimed at eradicating HIV in PLHIV.[20,21]

i) Host genetic factors: Human genomic studies contribute to a better understanding of HIV pathogenesis and are currently paving the way toward more individualized treatment strategies.[22–24] The clinical utility of these precision approaches in HIV care need to be evaluated.

j) Immune responses including broadly neutralizing antibodies (bNabs): Immune responses to HIV and coinfections are key for understanding pathogenesis of these infections.. bNabs are a prerequisite for an HIV-vaccine. The better understanding of the evolution of bNab and the identification of unique viral envelopes that are able to induce bNabs in different individuals are important steps towards the development of preventive and therapeutic HIV vaccines .[25–27]

During the HIV pandemic, cohorts have played an essential role in HIV research.[28–31] Long-term studies are essential for obtaining information on clinical events and pharmacovigilance in HIV treatment, as well as for obtaining information on long-term surrogate marker data, treatment success, transmission pattern and on the socio-economic situation of people living with HIV. Furthermore, long-term cohort studies have been essential in the detection of emerging epidemics including HCV and syphilis.[32] Randomized controlled trials (RCTs) are the gold standard for making treatment comparisons. However, RCTs are not always feasible, for either ethical, financial or practical reasons. Even when trials are underway, there is often an urgent need to obtain additional information from a population that is more representative of the general population of PLHIV. Observational data from cohort studies can be especially critical for groups of people who often are not enrolled in RCTs. Randomized trials are also not generally well suited for assessing rare harms, which often only become apparent when a treatment is rolled out in a much larger population and the pivotal trial phase has ended. In addition, observational studies provide valuable insights into the feasibility and implementation challenges associated with a given intervention.[33] Furthermore, cohort studies also offer a unique framework as a recruitment platform for large-scale RCTs including TwiCs (Trials within Cohorts), see section 1.3.

The importance of the SHCS with regard to HIV elimination

Worldwide, the HIV pandemic is a major public health issue with an estimated number of 38.4 million people living with HIV in 2021.[34] In the last two decades, progress was made in terms of disease control. The number of new HIV infections steadily decreased. The key element was the successful rollout of antiretroviral therapy (ART) in almost all countries worldwide.[34] The percentage of people living with HIV and receiving ART is steadily increasing. In 2021, UNAIDS estimated that 73% of people living with HIV were on treatment. The World Health Organization (WHO) set the ambitious goal of reaching "95-95-95" along the HIV care cascade that may translate into a 90% reduction in incidence to achieve elimination.[35,36] In short, 95% of all people living with HIV should be diagnosed, 95% of those should be treated and 95% of treated PLHIV should achieve viral suppression until 2030. Switzerland is coming very close to reaching the "95-95-95" targets. In 2020, the Federal Office for Public Health reported a cascade of "93-98-96" with an estimated number of 17'100 people living with HIV in Switzerland. Despite this considerable progress, Switzerland is off-track in reaching the WHO elimination goal of a 90% reduction in HIV incidence.[37] The SHCS network provides updated representative information on the HIV care cascade in Switzerland including data on molecular surveillance using phylogenetic methods, and is an invaluable tool to monitor and improve the efforts of achieving HIV elimination in Switzerland.

Providing services to patients, researchers and public health authorities is a key element of the SHCS. **The SHCS is recognized as a cohort of national importance by the State Secretariat for Education, Research and Innovation (SERI), Federal Office for Public Health (FOPH, and Swiss National Science Foundation (SNSF)** in the frame of the Data Infrastructure and Services (DIS) program (https://www.snf.ch/en/boHVMEhCqdhoHijS/news/news-190522-snsf-funding-2021-2024-new-opportunities-for-Swiss-research).

There is a continuous need for longitudinal cohort studies in the field of HIV to tackle upcoming challenges in the population of people living with HIV. The SHCS is a unique, long lasting project and internationally leading in this field and provides invaluable information to patients, scientists, clinicians and public health authorities.

1.2 The Swiss HIV Cohort Study (SHCS)

Overview

The SHCS is an ongoing project. It provides a unique research platform for clinical, translational, epidemiological, social and basic research.[30,38]

The SHCS is a multicenter, clinic-based, prospective longitudinal observational study including adults living with HIV in Switzerland (Figure 1). The SHCS was established in 1988 and has been recruiting study participants continuously for over 35 years. The study design provides continuous enrolment and regular study visits, where socio-demographic, clinical and laboratory information from routine clinical care is collected. Plasma and peripheral blood mononuclear cells (PBMCs) are collected in regular intervals and stored in biobanks. This broad network ensures high nationwide representativity. Participants are recruited by all university hospitals in Switzerland, by numerous regional hospitals (16 by July 2023) and private physicians (45 by July 2023). In these participating sites, all people diagnosed with an HIV infection are offered to participate in the SHCS. The participation is voluntary, and all participants have signed a written informed consent. By the end of 2022, a total of 21'621 individuals were included in the SHCS, of whom 9'517 participants were still under follow-up end of 2022. Since its foundation in 1988, the SHCS has published over 1300 articles in peer-reviewed journals.

Figure 1: The Swiss HIV Cohort Study (SHCS) has seven study centers illustrated in the figure. All centers have affiliated regional hospitals and/or private physicians (http://www.shcs.ch/181-participating-regional-hospitalsinstitutions & https://www.shcs.ch/physicians?reset).[39,40]

Organization

The SHCS has a well-coordinated organization with an established decision-making process (https://www.shcs.ch/164-organigram).[41] The executive board (EB) is formed by the president and the chairpersons of the following boards: 1) The scientific board (SB) evaluates all projects that are performed with data from the SHCS according to the SHCS rules. The SB entails members from all centres and research fields, where the SHCS is actively involved, and includes two patient representatives. The rules and templates for proposal funding, submission and research project conduct, as well as authorship and collaboration rules are outlined on the open SHCS website (http://shcs.ch/162-researchers);[42] 2) the clinics and laboratories committee (CLC) decides on all clinical and laboratory parameters collected within the SHCS. CLC members are from all centers and laboratories and also include a representative from the private physicians; 3) the Swiss Mother and Child HIV Cohort Study (MoCHiV) board includes pediatricians, laboratory scientists and gynaecologists from the different centres. EB, SB, CLC, MoCHiV board and YRG form the Full Assembly (FA). The FA is ultimately responsible for the composition of the various boards and approves the SHCS financial statements. The data center and coordination center are hosted at the University of Zurich. All other study infrastructure are located and managed by the collaborating centres. Centres and laboratories are paid per numbers of patients enrolled and followed. The organization and governance of the SHCS form an independent structure, which is not dependent on individual principal investigator.

The SHCS has a strong focus on engaging young researchers. The Young Researchers Group (YRG) is a collective of early-career-stage researchers collaborating with the SHCS and includes clinicians, microbiologists, methodologists, mathematicians and statisticians. The YRG is represented in the SB.

An International Advisory Board including two leading experts in the field provide general advice.

SHCS databases

The SHCS maintains the following databases:

- Core SHCS database hosted at the University of Zürich: Includes information collected during the regular study visits (questionnaires, lab values, clinical events etc.)
- Resistance database hosted by Smartgene (https://www.smartgene.com/): Includes viral sequences, which were done for routine drug resistance tests (genotypic drug resistance testing)
- HIV near full-length sequence database hosted by the University of Zürich: Includes near full length HIV sequences generated by next generation sequencing technologies within various research projects.
- Human genome database hosted at EPFL Lausanne: Includes human genome genetic data.

Furthermore, the SHCS includes an extensive biobank with stored plasma samples and PBMCs collected during routine clinical visits (see description in section 7.3).

1.3 SHCS research

SHCS nested research projects

The SHCS conducts nested research projects based on the database and biobank described in this protocol within the frame of the patient informed consent. Any use of SHCS data and samples for research purpose must be submitted to the SHCS scientific board (SB). The SB includes experienced clinicians, researchers from different fields, data scientists and patient representatives. The SB and the responsible investigators (members of the SHCS) carefully assess the use of SHCS data and biological materials for every research project to ensure that all analyses are within the frame of the patient informed consent.

For research studies involving SHCS patients that foresee interventions or invasive procedures outside the clinical routine and not covered by the SHCS protocol, a separate study protocol and informed consent is submitted to the appropriate local ethics committee.

Embedding randomized trials using the Trials within Cohorts (TwiCs) design

Randomized clinical trials (RCTs) are the gold standard to evaluate interventions in health care.[43] However, RCTs can be challenging in terms of slow participant recruitment, limited external validity, burdensome consent procedures, or undesirable study-related behavior of participants ('disappointment effects') when RCTs are designed open label. [44–46] The Trials within Cohorts (TwiCs) design is a pragmatic[47,48] RCT design for cohort studies that aim to overcome these challenges.[49,50]

The SHCS is the first national Swiss cohort study to enable the conduct of trials using the TwiCs design. In addition to the consent for regular data and sample collection (cohort consent), cohort participants have the option to consent to be randomized in future trials assessing pragmatic low-risk interventions (randomization consent). In case a TwiC is implemented, eligible cohort participants with signed randomization consent will be enrolled. The control group in a TwiC will not need to provide consent to the specific TwiC as individuals in that group continue receiving regular routine care according to the SHCS cohort protocol. In contrast, participants in the intervention group are approached, informed, and offered the intervention. They may accept or decline the intervention (intervention consent).

This consent procedure mimics usual care, where people are informed about new treatment options but not about treatments they may not receive. The routinely collected cohort data and infrastructure are not only leveraged for recruitment purposes (eligibility check, enrolment flagging), but also for the outcome collection during the follow-up. Figure 2 outlines the design in detail.

As such, TwiCs can improve efficiency in trial recruitment and follow-up, minimalize study-related behavioral changes among participants (disappointment effects if randomized to control group), and increase clinical applicability of trial results (external validity).

Consent for randomization is voluntary and independent of cohort consent. Therefore, participants who decline the randomization consent remain in the cohort and continue to receive routine cohort services.

Each trial using the TwiCs design will require a separate ethics approval and the review of its intervention consent on the basis of this study protocol and randomization consent.

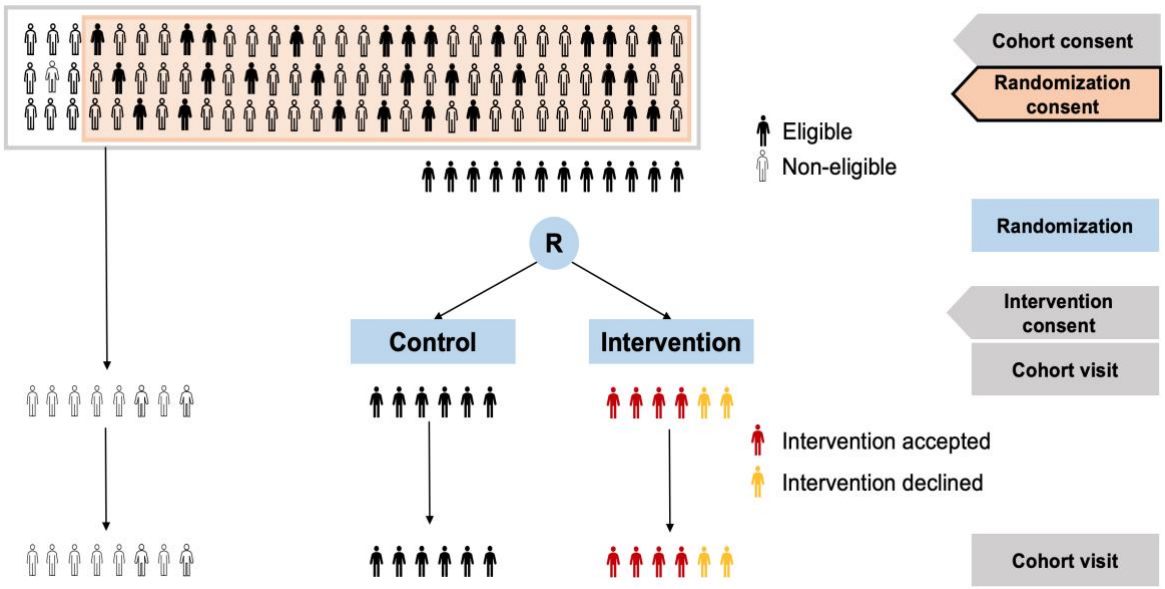


Figure 2: Trials within cohorts (TwiCs) design. Cohort participants may consent or refuse to be randomized in future TwiCs (randomization consent) they will be eligible for. For a given TwiC, individuals who consented to be randomized (subset in orange) will be assessed for trial eligibility (individuals in bold = eligible, individuals in white = non-eligible). After randomization, individuals assigned to the control arm (individuals in green) will not be informed, will continue usual clinical care and data collection according to the SHCS protocol, and will not provide additional consent. Individuals randomized to the intervention arm will be asked to provide additional consent to approve (individuals in yellow) or decline (individuals in red) the intervention (intervention consent).

Given the potential of the TwiCs design approach in terms of producing efficient, pragmatic, and high-quality randomized evidence, the SHCS has incorporated the randomization consent for randomization in future TwiCs into its ICF (see appendix 2).

1.4 Categorization of the project

According to the HRA this study belongs to the category A. Data and sample collection for this cohort study follows routine clinical care and for any additional non-routine care intervention or invasive procedures a separate ethical protocol is submitted.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

The SHCS is a platform designed to provide a high-quality dataset and a comprehensive biobank as a basis for various research projects in the context of HIV, and associated conditions always with the goal of optimizing the treatment and care of people living with HIV and improving the understanding of the epidemic and pathogenesis of HIV and associated conditions.

The SHCS also provides epidemiological surveillance data to the Swiss Federal Office for Public Health (FOPH) to efficiently monitor the HIV epidemic and supports – through its research and network activities – high-quality care for people living with HIV in Switzerland.

2.2 Primary and secondary endpoints

The SHCS investigates research questions based on the database and biobank described in this protocol within the boundaries of the patient-informed consent. This includes endpoints with regard to health conditions which could be influenced through HIV infection, and endpoints of conditions that could influence the course of HIV infection.

In particular, the SHCS focuses currently on the following research questions:

- **Antiretroviral therapy (ART):** Short- and long-term safety, efficacy, tolerability and mechanisms of action of antiretroviral therapies. Patient preferences, acceptance and treatment adherence of antiretroviral treatment regimens. Pharmacokinetics and drug-drug interactions.
- **HIV resistance, acute HIV and cure research:** Transmission and emergence of HIV drug resistance. Diagnostics, treatment and biological mechanisms of acute HIV infections. Understanding the latent HIV reservoir.
- **Neutralizing antibodies in HIV-1 infection:** Characteristics and development of neutralizing antibodies in PLHIV.
- **Prevention of HIV and coinfections:** Studies on the impact of behavioural changes and evolving treatments on the epidemiology of HIV and coinfections.
- **Molecular epidemiology and HIV transmission**: Molecular epidemiology approaches to characterise the HIV epidemic.
- **Host and virus genetics in HIV infection**: Human and virus genomic studies, including pharmacogenomics studies aimed at a better understanding of HIV pathogenesis and treatment.
- **Viral hepatitis and sexually transmitted diseases**: Epidemiology, transmission, natural history and treatment of viral hepatitis co-infections and sexually transmitted diseases.
- **Opportunistic diseases and co-infections**: Epidemiology, pathogenesis, disease progression, clinical presentation, prevention and immunity of opportunistic diseases, as well as their treatment and prophylaxis.
- **Health conditions associated with HIV and associated diseases:** Identification, epidemiology, treatment and pathogenesis of health-conditions which could be influenced by HIV infection (non-communicable diseases including cancer, neurocognitive disorders, metabolic complications and cardiovascular disease, mental health, aging, vaccine responses, causes of death).
- **Immunopathogenesis**: Understanding the impact of HIV and ART on the immune system, including chronic inflammation, cell depletion, immune reconstitution, cell exhaustion.
- **Women's health and pregnancy:** Impact of hormonal treatments, contraception and menopause in women with HIV. Clinical care and treatment of pregnant women with HIV.
- **Transgender medicine:** Treatment of HIV and related health and social issues in transgender medicine.
- **Co-medication:** Side effects, pharmacokinetics, drug-drug interactions and treatment outcomes.
- **Patient-reported outcome measures (PROM) and patient and public involvement (PPI) research in PLHIV:** Addressing health issues using PROMs (including adherence, physical, cognitive and psychological problems), and investigating the role of patients and public involvement (PPI) in HIV research.

- **Social and health economic assessments and cost-effectiveness analyses:** Health economic analyses and the study of socio-economic factors in HIV disease.
- **Digital health and data management:** Optimizing IT infrastructure and data management for longitudinal studies including data privacy aspects.

2.3 Project design

The SHCS is a national multicenter study recruiting PLHIV in Switzerland. The SHCS has a prospective longitudinal observational study design. Patients are recruited by all university hospitals in Switzerland, by numerous regional hospitals and private physicians (see 3.1). The SHCS is highly representative by including >70% of treated PLHIV in Switzerland.

The prospective study design foresees data collection blood sampling for the SHCS biobank within routine clinical visits (see section 3.3).

Additionally, the consent procedure of the SHCS contains a randomization consent to enable the conduct of trials using the TwiCs design (see section 1.3).

3 PROJECT POPULATION AND STUDY PROCEDURES

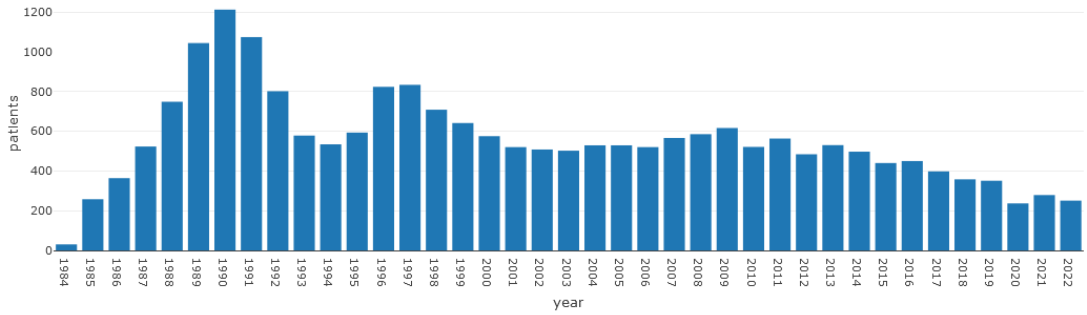
3.1 Project population, inclusion and exclusion criteria

Study population

The SHCS is recruiting adults living with HIV in Switzerland. At the end of 2022 the SHCS had 9’517 participants under active follow-up. A yearly number of 200-400 participants were recruited in 2017 to 2022 (Figure 3). The SHCS is an open prospective cohort study. No sample size calculation is performed.

For specific projects, comparative analyses with HIV-negative persons are performed using data from other cohorts. These subjects provide a separate informed consent outside the SHCS.

A: Number of newly recruited SHCS participants per calendar year



B: Annual number of visits by type of health care provider in the SHCS

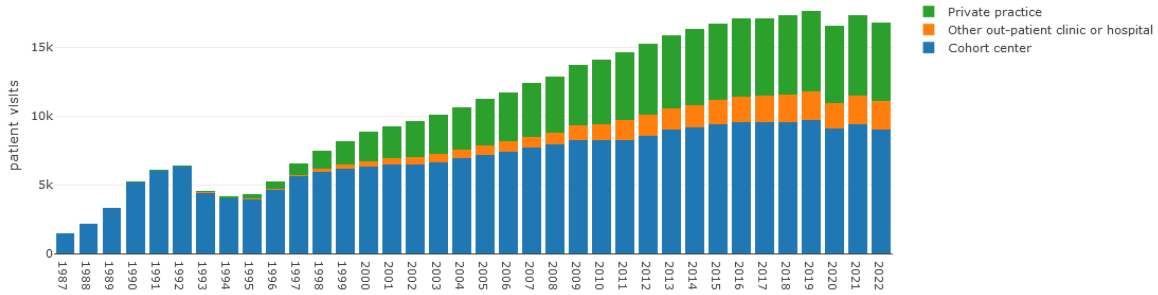


Figure 3: Overview of recruitment and visits. **A)** Number of newly recruited study participants in the Swiss HIV Cohort Study (SHCS), 1984-2022; **B)** Annual number of participants visits by type of health care provider in the SHCS.

Inclusion criteria

- Confirmed HIV-1 or HIV-2 infection
- Age ≥18 years at the time of signing the informed consent
- The participant provides written informed consent for the study.

Exclusion criteria

The SHCS aims to represent the general population of PLHIV, thus a minimal set of exclusion criteria are applied.

Exclusion criteria:

- Inability to provide an informed consent
- Treatment by a physician not participating in the SHCS
- Individuals aged <18 years

3.1 Recruitment, screening and informed consent procedure

The SHCS has a consecutive ongoing recruitment. Individuals diagnosed with HIV in routine clinical care are asked to participate in the study. No study specific screening procedure is performed. A confirmed HIV infection is sufficient for inclusion. The participation in the study is voluntary. The SHCS does not actively advertise the study but has a flyer for interested funders and study participants. The flyer is available online and in paper form at the different study sites (see Appendix 1). The flyer is available in English, German, French and Italian. No compensation or payments are given to the SHCS participants.

Prior to inclusion, each participant has to give written informed consent after he/she was comprehensively informed - verbally and in writing - on the nature, relevance and impact of the project. The content of this information is documented on the informed consent form (Appendix 2). Each participant is informed that the participation in the project is voluntary and that he/she may withdraw from the project at any time and that withdrawal of consent will not affect his/her subsequent medical treatment. The participants will be given the time needed to make their decision whether they would like to participate or not. Foreign-language participants will be informed about the study in presence of a qualified translator. Study documents are handed out in German, French, Italian, Spanish, Portuguese or English.

The consent to participate in the research project is signed and dated by both, the participant and the treating physician. A copy of the signed and dated subject information and informed consent form is handed out to the participant.

No project-related procedures are conducted before a legally accepted written informed consent has been given.

3.3 Study procedures

Study duration

The SHCS study started prospective recruitment in 1988: It is an ongoing study with continuous enrolment. Study participants are followed until death, change of routine care by a non-cohort physician, loss to follow-up, or withdrawal of the informed consent by the participant. Because the SHCS is an observational, longitudinal study and the HIV epidemic in Switzerland is continuously evolving, it is not meaningful to pre-define the end of the study. We plan to critically revise the current protocol every 10 years and evaluate whether the study should be continued. The following aspects will be taken into account: i) scientific relevance of the study, ii) funding situation, iii) available infrastructure (e.g. biobank resources) and iv) available resources of study personnel.

Study procedure

The SHCS collects data, which are collected within routine clinical visits (Table 1).

The SHCS has a study specific questionnaire for the baseline assessment (timepoint 0) and regular follow-up visits (every 6 months). The SHCS CRFs, the SHCS codebook and instructions are openly available online (http://www.shcs.ch/307-shcs-code-book, https://www.shcs.ch/258-shcs-forms, https://www.shcs.ch/292-instructions).

Baseline assessment (timepoint 0)

At baseline, socio-demographic information and information about the medical history is collected by interviewing the participant and by reviewing medical charts. Basic routine clinical data and laboratory parameters are collected and samples taken for the biobank.

Follow-up visits (every 6 months):

The follow-up visits take place every 6 months. Compared to the baseline assessment, a subset of information is collected in the questionnaire. If applicable, data and samples from routine clinical visits which occurred between the scheduled study visits are collected. The routine sampling interval for plasma depends on the HIV viral load (https://www.shcs.ch/194-frequency-of-storing-blood-samples), PBMCs are collected at yearly intervals.

Event forms:

In case of specific clinical events (e.g. cerebral infarction, myocardial infarction, bone fracture, liver transplantation, malignancies), an additional form including detailed information about the specific clinical event is collected (https://www.shcs.ch/191-checking-charts). These data are collected in the framework of the RESPOND collaboration.[28]

Loss to follow-up/death:

If a participant does not attend a clinic participating in the SHCS for up to 14 months or a physician became aware of the death of a participant, a stop form is filled in with the reason for loss-to follow-up.

Biobank information:

The SHCS biobanks have a decentral organization (see 7.3 Confidentiality and coding). A minimal set of information at each sampling time point is collected at the SHCS data center. The SHCS biobank received the *Biobank Solution for Quality Assessment and Normalization* VITA label by the Swiss biobank platform (SBP) (https://www.biobanksqan.ch/#/biobanks/4346).

Incidental findings

If a patient is diagnosed with a severe incidental finding, the treating physician will contact the patient by phone or in written and arrange a consultation to inform about this finding and its potential consequences.

Potential bias

As for all observational studies, the most common biases are selection bias and information bias.[51] The SHCS makes great efforts to minimize these biases.

Selection bias:

Selection bias occurs when the included study participants are systematically different in characteristics from eligible participants who are not included in the study[52,53]. Study personnel are instructed to ask all eligible patients to participate in the SHCS. Unfortunately and despite all efforts, recruitment success can still vary, for example, depending on language or cultural background.

The SHCS does not have the financial and human resources to include all physicians who treat PLHIV in Switzerland, but a representative number of PLHIV including both rural and urban areas from all language regions are included.

In general, the study population is highly representative. A high percentage of PLHIV in Switzerland are included in the SHCS, >70% of all individuals on antiretroviral therapy in Switzerland.[38] The SHCS closely works with patient representatives to identify measures on how to improve recruitment of people living with HIV in Switzerland that are underrepresented in the cohort.

Information bias:

Reporting bias and recall bias are an issue in the SHCS questionnaires, which we try to minimize.

Behavioral questions concerning the past do usually not go back more than 6 months (questions about the adherence to medication only 4 weeks). For all behavioral questions (e.g. number of sexual partners, condom use), the participants have the option to deny an answer.

Further biases, such as allocation bias, confounding by indication and others are addressed, if possible, in the statistical analyses. The SHCS research team includes statisticians and epidemiologists with extensive expertise on dealing with biases and confounders.

Table 1: Schedule of assessments

Time		**>-1 day**	**0**	**Every 6 months**	**Death/ Drop Out**
Visit		***Information***	***Start***	***Follow-up***	***Stop***
Oral and written information		+			
Written consent		+	+		
Check inclusion-/ exclusion criteria		+			
Demographic data[1]			+		
Medical history[1]			+		
Patient questionnaire (interview) [1]			+	+	
Clinical events (routine clinical data)			+	+	
Assessment of cognitive complaints[1]				(+)	
Medication[1,2]			+	+	
Laboratory[3]			+	+	
Plasma sampling[4]			+	+	
Cell sampling[5]			+	(+)	
Cause of death/drop out[6]					+
Event forms[7]			*if applicable*	*if applicable*	*if applicable*

(+) At every second follow-up visit (yearly), **1** The SHCS CRFs are available online on the SHCS website (https://shcs.ch/258-shcs-forms), **2** Information about antiretroviral treatment and co-medication is filled in the eCRF, **3** Routinely assessed laboratory analysis is collected (all belonging to the standard of care of a person living with HIV), **4** In general, one plasma sample per year composed of five aliquots (≥0.5 mL) is taken (every second follow-up visit). Exception: During the first two years after registration or after detection of a viral load >400 copies/mL a plasma sample is taken every 6 months. Details can be found here: https://shcs.ch/194-frequency-of-storing-blood-samples, **5** A cell samples (PBMC): A cell sample is taken every year, **6** If a participant does not show up for 14 months a drop out form is filled in, **7** In case of a specific clinical event, an additional form describing the event is filled in (https://shcs.ch/191-checking-charts)

3.4 Withdrawal and discontinuation

The SHCS participants can withdraw the informed consent at any time. The participation in the SHCS is voluntary. As it is a longitudinal observational study, the study protocol does not consider any other reason than the participants wish to discontinue. If a participant does not respond to invitations by the study personnel (phone call, invitation letter, contact through referring physician), the patient is considered as loss-to-follow-up after 14 months since the last visit. If available, reasons for the loss-to-follow-up are collected. A participant can apply to re-join the cohort after a longer period of absence.

In case of withdrawal, no data and no samples are collected anymore. Existing data and samples will continue to be processed in a pseudonymized form.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

The variables collected within the SHCS cohort are summarized in a yearly report using descriptive statistics such as counts, proportions with 95% confidence intervals, means with 95% confidence interval, and medians with interquartile range. Nested projects have a separate statistical analysis plan. The SHCS follows in all analyses and publications the STROBE guidelines.[54] Established statistical software is used (R, Stata, SAS or SPSS).

4.2. Handling of missing data

Missing data is reported according to the STROBE guidelines.[55] Multiple imputations techniques might be used to impute missing data.[56]

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project is conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations.

5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.
The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

Overall, the likelihood of serious events (SE) related to this project is very low as there are no study-specific interventions. Biobanking does not involve additional venipunctures and only requires small amounts of additional blood (10-40ml).
If a related serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

The causal relationship of the SE with the project-specific measure is determined by the project leader or a person authorized for this purpose according to the following definitions:

Unrelated	The event started in no temporal relationship to the project-specific measures applied and the event can be definitely explained by underlying diseases or other situations. If an event is unrelated, it will not qualify as SE.
Related	The event started in plausible time relationship to the project-specific measures applied and the event cannot be definitely explained by underlying diseases or other situations.

All SEs are to be documented in the subjects´ file and on the SE report form (https://swissethics.ch/en/templates/meldungen).

5.4 Procedure for investigations involving radiation sources

No investigations involving radiation sources are used.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

5.7 Insurance

Insurance is covered by “Versicherung für klinische Versuche und nichtklinische Versuche“ by Zürich Versicherungs-Gesellschaft AG (Policy no.: 14.970.888).
Any damage developed during the course of the project is covered by this insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the project personal. Medical emergency treatment must be reported immediately to the project leader. The project leader must also be informed instantly, in the event of health problems or other damages during or after the course of the project.
The project leader will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to project participation. All involved parties will keep the participants’’ data strictly confidential.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The SHCS is embedded in a routine clinical care setting. The additional burden and time effort for the study participants are minimized by study design. Participants have the choice whether to be informed of incidental findings of hereditary factors of clinical importance.

The SHCS has a high scientific and social value, which was recognized by the State Secretariat for Education, Research and Innovation (SERI). The SERI and the Federal office of public health (FOPH) identified the SHCS as a cohort of high national importance (SNF_Multi-year-program). The SHCS was classified research-relevant data infrastructure (DIS). Since its introduction, the SHCS has published over 1'300 articles in peer-reviewed medical journals and supported a large number of master's and doctoral theses. Besides science, SHCS considers the training of new professionals as a core activity. The SHCS also ensures the monitoring of the HIV epidemic in Switzerland. It provides detailed data reports to the Federal Office of Public Health (FOPH).

The benefits of the study clearly outweigh the risks.

6.2 Risk-Benefit Assessment

The SHCS data is based on data collected during routine clinical visits. In the study specific questionnaires, the participant has always the option to refuse the answer to a question or to refuse sample collection.
The unwanted identification of study participants or the risk of unauthorized data access is minimized by very restricted data access and clearly defined roles in the project. All employees of the SHCS are subject to medical confidentiality. A participant's name does never leave the study center. The communication within the study is strictly based on pseudonymized study identifiers. To further protect the participant's identity, the SHCS does not share the date of birth (only the year of birth), canton of residence or the nationality in the regular data set.
The study contributes knowledge for the better understanding of HIV pathogenesis, side effects, tolerability of treatment, optimized treatment strategies and aging with HIV. The close collaboration and knowledge exchange within the SHCS network ensures state of the art treatment of PLHIV in Switzerland.

The benefits of the study clearly outweigh the risks.

6.3 Rationale for the non-inclusion of vulnerable participants

Vulnerable participants are not included in the SHCS (namely children, adolescents and adults lacking capacity to understand the study procedures).[2]

6.4 Public and Patient Involvement

The SHCS engages with cohort participants and the broader public using various mechanisms:

1) Involvement of two patient representatives in the scientific board
2) Review of all nested research projects by patient representatives
3) Active participation in SHCS research project implementation
4) Active result dissemination beyond scientific journals, e.g. to the general public and lay audiences

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

Regular data entry process

To ensure a very high data quality, the SHCS data entry procedure has three validation steps (Figure 4):

1. At the local study site, the data is collected by trained SHCS study nurses or physicians. The data is either entered directly in the electronic case report form (eCRF) or filled in on a paper form.
2. The data record is then validated, and if necessary supplemented, by a local research associate in the responsible SHCS center (University Hospital Basel, Inselspital Bern, University Hospital Geneva, University Hospital Lausanne, EOC - Ospedale Regionale di Lugano, Kantonsspital St. Gallen, University Hospital Zürich). After validation, the data is sent to the SHCS data center or electronically released for the data mangers at the national SHCS data center at the University of Zürich.
3. At the national data center, the data is validated and released for research purposes.

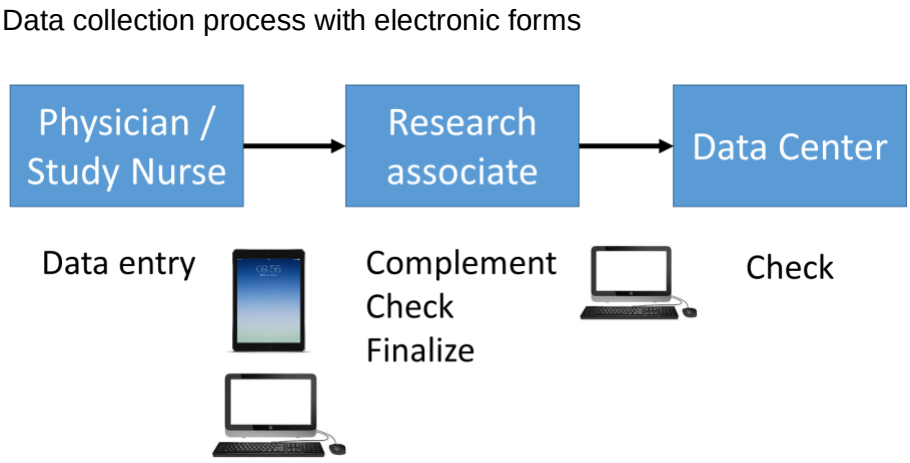


Figure 4: Data entry process of the Swiss HIV Cohort Study and quality checks. Study sites have the option to submit CRFs electronically or on paper forms. After initial data entry at the study site, a local research associate checks and supplements the entries done by physicians or study nurses. After validation, the data is sent to the national SHCS data center, where the entry is checked and released for research.

The SHCS data entry tool supports the correct entry of data with drop-down lists, pre-defined ranges, plausibility checks and with guiding users through an optimized user interface.

Quality Visits

Once a year, the national SHCS data center conducts quality visits. National data managers visit each SHCS center and check the entries of 40 participants at each SHCS center by reviewing the source documents (20 at the center, 20 at an affiliated hospital/physician). The SHCS provides incentives to increase the data quality by imposing a financial penalty on erroneous entries.

Feedback culture
Researchers can always report erroneous or suspicious values to the national SHCS data center. The data center then checks the values and asks for clarification at the local study sites.

7.2 Data recording and source data

The majority of records are collected with an electronic Case Report Form (eCRF). In addition, the SHCS offers the option to record data with a paper Case Report Form (CRF).

The SHCS eCRF is a Django-based web-application hosted at the University of Zürich (https://www.djangoproject.com). The application is based on an Oracle database (https://www.oracle.com/ch-de/). The application was developed by the SHCS and includes an audit trail, which means that it is traced who changed which data and when. A daily backup is done.

The paper CRFs are sent to the national SHCS data center by mail or email (pdf). At the data center a data manager enters the records in the SHCS eCRF.

The SHCS collects both, project-specific data and routinely collected data. The project-specific data include questionnaires filled in by study nurses and physicians during routine clinical visits. Routinely collected data (e.g. laboratory values, diagnosis of cancer, weight, blood pressure, cardio-vascular event) are transferred to the participant's CRF or sent directly to the data center (xml files). No copies of original source documents are collected by the SHCS. The CRF does not contain any information that identifies the patient (e.g. name or zip codes).

7.3 Confidentiality and coding

Project data
Project data is handled with utmost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the SHCS. On the CRFs/eCRFs and other project specific documents, participants are only identified by a unique participant 5-digit number.

The participant identification list is stored locally at the participants treating institution (study site). The SHCS does not provide a unified solution for the participant identification list. The handling of the list is in responsibility of each center. Only the local SHCS physicians and the local data managers have access to the identification list. The data is protected from unauthorized or accidental disclosure from alteration, deletion, copying and theft by password protection.

Biological material
The SHCS biobank has received the VITA label by the Swiss Biobanking Platform (see appendix 3). The SHCS biobank regulations define the purpose, the operational processes, and the organization of the SHCS biobank. It describes the requirements for collecting, storing, and distributing biological material and their associated data (i.e., biological resources) (see appendix 4).

The samples cannot be identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel.

The SHCS biobank is multicentric. The SHCS study centers are responsible for the local biobanks.

Data and material transfer agreement (DTA/MTA)
The SHCS has a DTA/MTA agreement for collaboration with third parties (appendix 5). It establishes the obligations and responsibilities of both parties concerning the transfer of material of a biobank before shipment. The DTA is mandatory when participant data are transferred to third parties. The obligations, which have not been expressly attributed to the receiving party by the DTA/MTA, remain under the responsibility and the management of the biobank. In all cases, the biobank remains responsible towards participants within the limits of its accountability.

7.4 Retention and destruction of project data and biological material

At the end of the project, the data will be stored for 10 years at the project leader's institution and the biological material for 10 years in the biobanks.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

Funding
The SHCS is primarily supported by the Swiss National Science Foundation (grant #201369. Additional funds originate from the SHCS research foundation and the Federal Office of Public Health (FOPH).

Support from pharmaceutical companies is governed through the SHCS association (https://www.shcs.ch/280-association-contre-le-vih-et-autres-infections-transmissibles).

Network agreement
The legal entity of the SHCS is a simple partnership ("Einfache Gesllschaft"). The respective contract is signed by all participating SHCS centers in a SHCS Registry Network Agreement (see Appendix 5).

Data sharing
The SHCS has a long-standing tradition of sharing data with national and international researchers and institutions. This data are by nature extremely sensitive and we have therefore implemented clear rules for data sharing in accordance with legal regulations and the patient consent. Patients are informed in the consent that their data can be used by researchers or institutions who have signed an agreement, which regulates the use of data and biological samples. The material and data sharing agreement is openly available on the SHCS website (see appendix 5 or https://www.shcs.ch/308-material-and-data-transfer-agreement). Within the boundaries of the informed consent and legal regulations, the SHCS has handled data sharing with numerous national and international research groups and cohorts. The conditions for sharing patient data are as follows: 1) Patient has signed the written informed consent, 2) The research project or collaboration has been approved by the scientific board of the SHCS, 3) The collaborators agree in written with the rules of sharing data. Individual patient data is always processed before publication to avoid any kind of backtracking (e.g. data jittering, data shuffling).

Publication policy
The SHCS has publication guidelines, which are based on the guidelines of the International Committee of Medical Journal Editors (ICMJE) ("Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication"), last update in December 2017, and published online https://www.icmje.org/. Authorship guidelines are openly available on the SHCS website http://www.shcs.ch/188-general-authorship-guidelines.

The STROBE guidelines are applied for epidemiological studies (https://www.strobe-statement.org/).

Declaration of interests

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Marcel Stoeckle is an advisory board participant at MSD, Gilead, ViiV, Pfizer and Morderna and received travel grants to participate at conferences from Gilead. All fees were paid to his institution.

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Matthias Cavassini's institution received research grants from Gilead, MSD and Viiv. Matthias Cavassini's institution received expert opinion financial compensation from Gilead, MSD and Viiv.

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