

COHORT PROFILE

Cohort Profile: The Swiss HIV Cohort Study

The Swiss HIV Cohort Study^{*,†}

Accepted 24 September 2009

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 ≥ 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.schoeni-affolter@chuv.ch

† The Cohort Study members list are included in acknowledgment 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 ≥ 18 years and is estimated to cover $\sim 45\%$ 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.								

IQR: inter-quartile range.

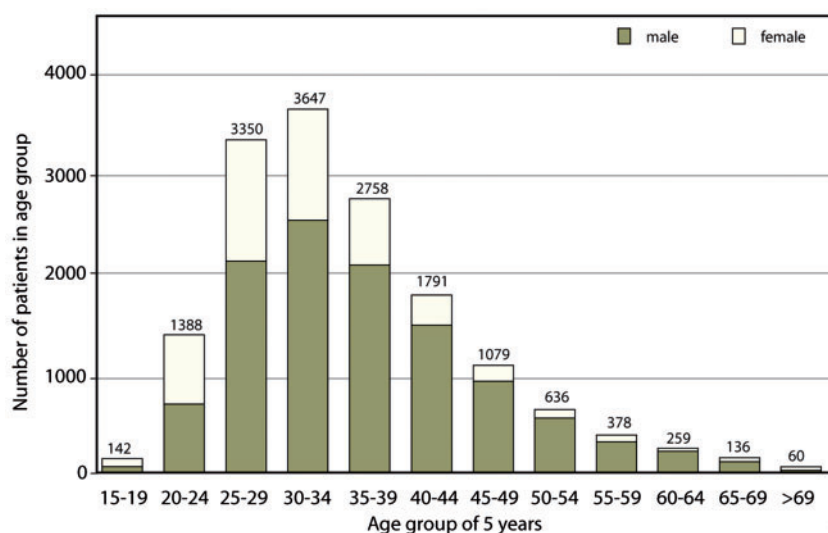


Figure 1 Age and gender structure of all participants in the SHCS ($n=15\,624$) at registration

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

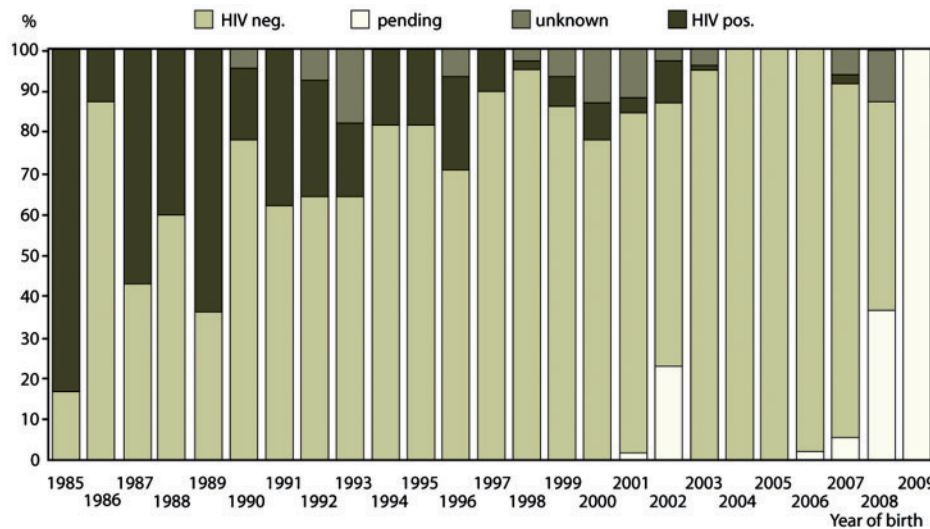


Figure 2 Percentage of vertical HIV transmission in all registered deliveries per year

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 2008⁴ 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 contributions⁹⁻¹⁶ 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 field¹⁸ 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

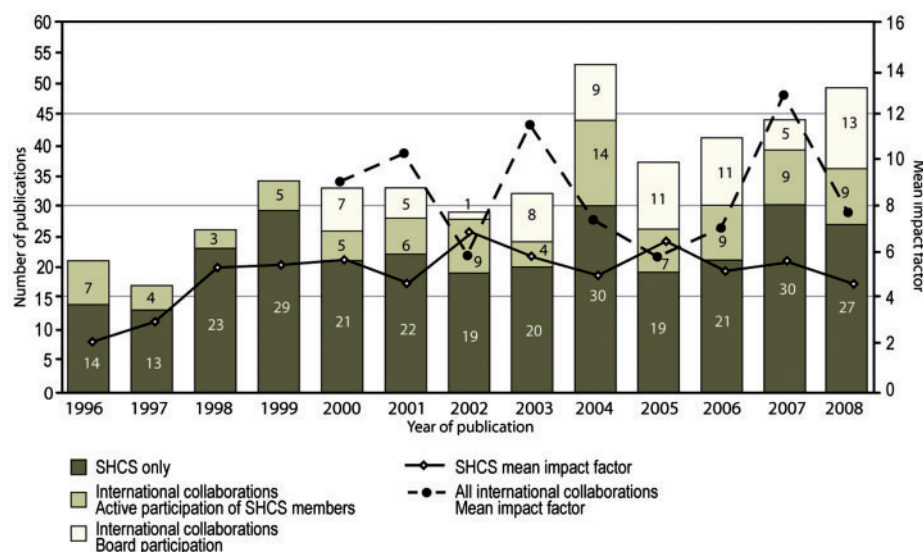


Figure 3 Number of publications and mean impact factor of the journals, in which the respective studies were published

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; and²⁴
- (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 papers⁸⁶ 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 envelope 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>.

Acknowledgements

First of all we would like to thank all patients, caregivers and children who continuously participate in the cohort and render research in the field of HIV

possible. Without their ongoing participation a cohort of high quality would not be possible. We thank as well the dedicated staff of the local centres and the respective laboratories for their continuous support and enthusiasm. Finally, we also thank the Swiss National Science Foundation for its generous ongoing financial support.

**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.

Conflict of interest: None declared.

References

- 1 Fellay J, Boubaker K, Ledergerber B *et al.* Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001;**358**:1322–27.
- 2 Egger M, Hirschel B, Francioli P *et al.* Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. *BMJ* 1997;**315**:1194–99.
- 3 Ledergerber B, Egger M, Opravil M *et al.* Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 1999;**353**:863–68.
- 4 Hirsch MS, Gunthard HF, Schapiro JM *et al.* Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis* 2008;**47**:266–85.
- 5 Yerly S, von Wyl V, Ledergerber B *et al.* Transmission of HIV-1 drug resistance in Switzerland: a 10-year molecular epidemiology survey. *AIDS* 2007;**21**:2223–29.
- 6 von Wyl V, Yerly S, Burgisser P *et al.* Long-term trends of HIV type 1 drug resistance prevalence among antiretroviral treatment-experienced patients in Switzerland. *Clin Infect Dis* 2009;**48**:979–87.
- 7 Sendi P, Gunthard HF, Simcock M, Ledergerber B, Schüpbach J, Battegay M. Cost-effectiveness of genotypic antiretroviral resistance testing in HIV-infected patients with treatment failure. *PLoS ONE* 2007;**2**:e173.
- 8 von Wyl V, Yerly S, Boni J *et al.* Emergence of HIV-1 drug resistance in previously untreated patients initiating combination antiretroviral treatment: a comparison of

- different regimen types. *Arch Intern Med* 2007;**167**: 1782–90.
- ⁹ Greub G, Ledergerber B, Battegay M *et al*. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000;**356**:1800–5.
 - ¹⁰ Furrer H, Telenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against *Mycobacterium avium* in patients on successful antiretroviral combination therapy. The Swiss HIV Cohort Study. *AIDS* 2000;**14**:1409–12.
 - ¹¹ Furrer H, Egger M, Opravil M *et al*. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *N Engl J Med* 1999;**340**:1301–6.
 - ¹² Clifford GM, Polesel J, Rickenbach M *et al*. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005;**97**:425–32.
 - ¹³ Ledergerber B, Mocroft A, Reiss P *et al*. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med* 2001;**344**:168–74.
 - ¹⁴ Elzi L, Schlegel M, Weber R *et al*. Reducing tuberculosis incidence by tuberculin skin testing, preventive treatment, and antiretroviral therapy in an area of low tuberculosis transmission. *Clin Infect Dis* 2007;**44**: 94–102.
 - ¹⁵ Kirk O, Reiss P, Uberti-Foppa C *et al*. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med* 2002;**137**: 239–50.
 - ¹⁶ Zellweger C, Opravil M, Bernasconi E *et al*. Long-term safety of discontinuation of secondary prophylaxis against *Pneumocystis pneumonia*: prospective multicentre study. *AIDS* 2004;**18**:2047–53.
 - ¹⁷ Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009;**58**(RR-4):1–207; quiz CE1–4.
 - ¹⁸ Fellay J, Shianna KV, Ge D *et al*. A whole-genome association study of major determinants for host control of HIV-1. *Science* 2007;**317**:944–47.
 - ¹⁹ Arab-Alameddine M, Di Iulio J, Buclin T *et al*. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther* 2009;**85**:485–94.
 - ²⁰ Arnedo M, Taffe P, Sahli R *et al*. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. *Pharmacogenet Genomics* 2007;**17**:755–64.
 - ²¹ Felley C, Morris MA, Wonkam A *et al*. The role of CFTR and SPINK-1 mutations in pancreatic disorders in HIV-positive patients: a case-control study. *AIDS* 2004;**18**: 1521–27.
 - ²² Rotger M, Taffe P, Bleiber G *et al*. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. *J Infect Dis* 2005;**192**:1381–86.
 - ²³ Rotger M, Tegude H, Colombo S *et al*. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther* 2007;**81**:557–66.
 - ²⁴ Kind C, Rudin C, Siegrist CA *et al*. Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. Swiss Neonatal HIV Study Group. *AIDS* 1998;**12**:205–10.
 - ²⁵ Lorenzi P, Spicher VM, Laubereau B *et al*. Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. Swiss HIV Cohort Study, the Swiss Collaborative HIV and Pregnancy Study, and the Swiss Neonatal HIV Study. *AIDS* 1998;**12**:F241–47.
 - ²⁶ Thorne C, Rudin C, Newell M-L *et al*. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000;**14**:2913–20.
 - ²⁷ Glass TR, De Geest S, Hirschel B *et al*. Self-reported non-adherence to antiretroviral therapy repeatedly assessed by two questions predicts treatment failure in virologically suppressed patients. *Antivir Ther* 2008;**13**: 77–85.
 - ²⁸ von Wyl V, Yerly S, Boni J *et al*. Factors associated with the emergence of K65R in patients with HIV-1 infection treated with combination antiretroviral therapy containing tenofovir. *Clin Infect Dis* 2008;**46**:1299–309.
 - ²⁹ Scherrer AU, Hasse B, von Wyl V *et al*. Estimate of etravirine activity in drug naïve and drug experienced patients according to genotypic drug resistance information: The Swiss HIV Cohort Study (SHCS). *HIV Med* 2009 [Epub 1 September 2009].
 - ³⁰ Yerly S, Junier T, Gayet-Ageron A *et al*. The phylogeny of newly diagnosed HIV-1 infection reveals transmission clusters contributing to primary drug resistance. *AIDS* 2009;**23**:1415–23.
 - ³¹ Gupta R, Hill A, Sawyer A *et al*. The intensity of virological monitoring is associated with resistance to first line HAART in HIV-1 infected adults under the WHO public health approach to antiretroviral therapy: a systematic analysis of cohort and trial data. *Lancet Infect Dis* 2009;**9**:409–17.
 - ³² Bellini C, Keiser O, Chave JP *et al*. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med* 2009;**10**:12–18.
 - ³³ Fux CA, Rauch A, Simcock M *et al*. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. *Antivir Ther* 2008;**13**: 1077–82.
 - ³⁴ Fux CA, Simcock M, Wolbers M *et al*. Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir Ther* 2007;**12**:1165–73.
 - ³⁵ Keiser O, Fellay J, Opravil M *et al*. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. *Antivir Ther* 2007;**12**:1157–64.
 - ³⁶ Rudin C, Burri M, Shen Y, Rode R, Nadal D. Long-term safety and effectiveness of ritonavir, nelfinavir, and lopinavir/ritonavir in antiretroviral-experienced HIV-infected children. *Pediatr Infect Dis J* 2008;**27**:431–37.

- ³⁷ Wunder DM, Bersinger NA, Fux CA *et al.* Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. *Antivir Ther* 2007;**12**:261–65.
- ³⁸ Huttner AC, Kaufmann GR, Battegay M, Weber R, Opravil M. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS* 2007;**21**:939–46.
- ³⁹ Khanna N, Opravil M, Furrer H *et al.* CD4+ T cell count recovery in HIV type 1-infected patients is independent of class of antiretroviral therapy. *Clin Infect Dis* 2008;**47**:1093–101.
- ⁴⁰ Mocroft A, Ledergerber B, Zilmer K *et al.* Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk score. *AIDS* 2007;**21**:1867–75.
- ⁴¹ Taffe P, Bucher HC, Flepp M, Battegay M. Two versus three-class antiretroviral therapy in antiretroviral-naïve patients in different time periods of the HAART era. *AIDS* 2007;**21**:537–38.
- ⁴² Vernazza P, Daneel S, Schiffer V *et al.* The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial. *AIDS* 2007;**21**:1309–15.
- ⁴³ Vo TT, Ledergerber B, Keiser O *et al.* Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. *J Infect Dis* 2008;**197**:1685–94.
- ⁴⁴ Wolbers M, Battegay M, Hirschel B *et al.* CD4+ T-cell count increase in HIV-1-infected patients with suppressed viral load within 1 year after start of antiretroviral therapy. *Antivir Ther* 2007;**12**:889–97.
- ⁴⁵ Wolbers M, Bucher HC, Furrer H *et al.* Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. *HIV Med* 2008;**9**:397–405.
- ⁴⁶ Wolbers M, Opravil M, von Wyl V *et al.* Predictors of optimal viral suppression in patients switched to abacavir, lamivudine, and zidovudine: the Swiss HIV Cohort Study. *AIDS* 2007;**21**:2201–7.
- ⁴⁷ Dunn D, Woodburn P, Duong T *et al.* Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *J Infect Dis* 2008;**197**:398–404.
- ⁴⁸ Rauch A, Nolan D, Thurnheer C *et al.* Refining abacavir hypersensitivity diagnoses using a structured clinical assessment and genetic testing in the Swiss HIV Cohort Study. *Antivir Ther* 2008;**13**:1019–28.
- ⁴⁹ Rauch A, Rickenbach M, Weber R *et al.* Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. *Clin Infect Dis* 2005;**41**:395–402.
- ⁵⁰ Sabin CA, Worm SW, Weber R *et al.* Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008;**371**:1417–26.
- ⁵¹ Periard D, Cavassini M, Taffe P *et al.* High prevalence of peripheral arterial disease in HIV-infected persons. *Clin Infect Dis* 2008;**46**:761–67.
- ⁵² Nguyen A, Calmy A, Schiffer V *et al.* Lipodystrophy and weight changes: data from the Swiss HIV Cohort Study, 2000–2006. *HIV Med* 2008;**9**:142–50.
- ⁵³ Ledergerber B, Furrer H, Rickenbach M *et al.* Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis* 2007;**45**:111–19.
- ⁵⁴ Glass TR, Weber R, Vernazza PL *et al.* Ecological study of the predictors of successful management of dyslipidemia in HIV-infected patients on ART: the Swiss HIV Cohort Study. *HIV Clin Trials* 2007;**8**:77–85.
- ⁵⁵ Sterne JA, May M, Bucher HC *et al.* HAART and the heart: changes in coronary risk factors and implications for coronary risk in men starting antiretroviral therapy. *J Intern Med* 2007;**261**:255–67.
- ⁵⁶ Wunder DM, Fux CA, Bersinger NA *et al.* Androgen and gonadotropin patterns differ in HIV-1-infected men who develop lipodystrophy during antiretroviral therapy: a case-control study. *HIV Med* 2008;**9**:427–32.
- ⁵⁷ Garbino J, Inoubli S, Mossdorf E *et al.* Respiratory viruses in HIV-infected patients with suspected respiratory opportunistic infection. *AIDS* 2008;**22**:701–5.
- ⁵⁸ Hoffmann M, Reichmuth M, Fantelli K *et al.* Conventional tuberculin skin testing versus T-cell-based assays in the diagnosis of latent tuberculosis infection in HIV-positive patients. *AIDS* 2007;**21**:390–92.
- ⁵⁹ Rauch A, Gaudieri S, Evison J *et al.* Low current and nadir CD4+ T-cell counts are associated with higher hepatitis C virus RNA levels in the Swiss HIV cohort study. *Antivir Ther* 2008;**13**:455–60.
- ⁶⁰ Gasser O, Bihl FK, Wolbers M *et al.* HIV patients developing primary CNS lymphoma lack EBV-specific CD4+ T cell function irrespective of absolute CD4+ T cell counts. *PLoS Med* 2007;**4**:e96.
- ⁶¹ Khanna N, Wolbers M, Mueller NJ *et al.* JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. *J Virol* 2009;**83**:4404–11.
- ⁶² Clifford GM, Rickenbach M, Polesel J *et al.* Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *AIDS* 2008;**22**:2135–41.
- ⁶³ El Amari EB, Toutous-Trellu L, Gayet-Ageron A *et al.* Predicting the evolution of Kaposi sarcoma, in the highly active antiretroviral therapy era. *AIDS* 2008;**22**:1019–28.
- ⁶⁴ Franceschi S, Maso LD, Rickenbach M *et al.* Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *Br J Cancer* 2008;**99**:800–4.
- ⁶⁵ Gasser O, Wolbers M, Steffen I, Hirsch HH, Battegay M, Hess C. Increased Epstein-Barr virus-specific antibody-levels in HIV-infected individuals developing primary central nervous system lymphoma. *AIDS* 2007;**21**:1664–66.
- ⁶⁶ Polesel J, Clifford GM, Rickenbach M *et al.* Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS* 2008;**22**:301–6.
- ⁶⁷ Simcock M, Blasko M, Karrer U *et al.* Treatment and prognosis of AIDS-related lymphoma in the era of highly active antiretroviral therapy: findings from the Swiss HIV Cohort Study. *Antivir Ther* 2007;**12**:931–39.
- ⁶⁸ Weiser B, Philpott S, Klimkait T *et al.* HIV-1 coreceptor usage and CXCR4-specific viral load predict clinical disease progression during combination antiretroviral therapy. *AIDS* 2008;**22**:469–79.

- ⁶⁹ Bochud PY, Hersberger M, Taffe P *et al*. Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection. *AIDS* 2007;**21**:441–46.
- ⁷⁰ Colombo S, Rauch A, Rotger M *et al*. The HCP5 single-nucleotide polymorphism: a simple screening tool for prediction of hypersensitivity reaction to abacavir. *J Infect Dis* 2008;**198**:864–67.
- ⁷¹ Rauch A, Nolan D, Furrer H *et al*. HLA-Bw4 homozygosity is associated with an impaired CD4T cell recovery after initiation of antiretroviral therapy. *Clin Infect Dis* 2008;**46**: 1921–25.
- ⁷² Rotger M, Colombo S, Furrer H, Decosterd L, Buclin T, Telenti A. Does tenofovir influence efavirenz pharmacokinetics? *Antivir Ther* 2007;**12**:115–18.
- ⁷³ Rotger M, Saumoy M, Zhang K *et al*. Partial deletion of CYP2B6 owing to unequal crossover with CYP2B7. *Pharmacogenet Genomics* 2007;**17**:885–90.
- ⁷⁴ Frater AJ, Brown H, Oxenius A *et al*. Effective T-cell responses select human immunodeficiency virus mutants and slow disease progression. *J Virol* 2007;**81**:6742–51.
- ⁷⁵ Joos B, Fischer M, Kuster H *et al*. HIV rebounds from latently infected cells, rather than from continuing low-level replication. *Proc Natl Acad Sci USA* 2008;**105**: 16725–30.
- ⁷⁶ Kaiser P, Joos B, Niederost B, Weber R, Gunthard HF, Fischer M. Productive human immunodeficiency virus type 1 infection in peripheral blood predominantly takes place in CD4/CD8 double-negative T lymphocytes. *J Virol* 2007;**81**:9693–706.
- ⁷⁷ Muller V, von Wyl V, Yerly S *et al*. African descent is associated with slower CD4 cell count decline in treatment-naïve patients of the Swiss HIV Cohort Study. *AIDS* 2009;**23**:1269–76.
- ⁷⁸ Brossard P, Boulvain M, Coll O *et al*. Is screening for fetal anomalies reliable in HIV-infected pregnant women? A multicentre study. *AIDS* 2008;**22**:2013–17.
- ⁷⁹ Kahlert C, Rudin C, Kind C. Sudden infant death syndrome in infants born to HIV-infected and opiate-using mothers. *Arch Dis Child* 2007;**92**:1005–8.
- ⁸⁰ Keiser O, Gayet-Ageron A, Rudin C *et al*. Antiretroviral treatment during pregnancy. *AIDS* 2008;**22**:2323–30.
- ⁸¹ Gredig D, Niederost S, Rickenbach M. Parents living with HIV in a high-income country: do patients need specific support? *Swiss Med Wkly* 2008;**138**:38–46.
- ⁸² Sendi P, Brouwer WB, Bucher HC, Weber R, Battegay M. When time is more than money: the allocation of time between work and leisure in HIV-infected patients. *Soc Sci Med* 2007;**64**:2355–61.
- ⁸³ Conen A, Fehr J, Glass TR *et al*. Self-reported alcohol consumption and its association with adherence and outcome of antiretroviral therapy in the Swiss HIV Cohort Study. *Antivir Ther* 2009;**14**:349–57.
- ⁸⁴ Staehelin C, Rickenbach M, Low N *et al*. Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: access to antiretroviral therapy, disease progression and survival. *AIDS* 2003;**17**:2237–44.
- ⁸⁵ Weber R, Huber M, Rickenbach M *et al*. Uptake of and virological response to antiretroviral therapy among HIV-infected former and current injecting drug users and persons in an opiate substitution treatment programme: the Swiss HIV Cohort Study. *HIV Med* 2009;**10**: 407–16.
- ⁸⁶ Taffe P, May M. A joint back calculation model for the imputation of the date of HIV infection in a prevalent cohort. *Stat Med* 2008;**27**:4835–53.
- ⁸⁷ Keiser O, Orrell C, Egger M *et al*. Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. *PLoS Med* 2008;**5**:e148.
- ⁸⁸ Sabin CA, d'Arminio Monforte A, Friis-Moller N *et al*. Changes over time in risk factors for cardiovascular disease and use of lipid-lowering drugs in HIV-infected individuals and impact on myocardial infarction. *Clin Infect Dis* 2008;**46**:1101–10.
- ⁸⁹ Friis-Moller N, Reiss P, Sabin CA *et al*. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007;**356**:1723–35.
- ⁹⁰ Mugavero MJ, May M, Harris R *et al*. Does short-term virologic failure translate to clinical events in antiretroviral-naïve patients initiating antiretroviral therapy in clinical practice? *AIDS* 2008;**22**:2481–92.
- ⁹¹ Pantazis N, Touloumi G, Vanhems P, Gill J, Bucher HC, Porter K. The effect of antiretroviral treatment of different durations in primary HIV infection. *AIDS* 2008;**22**: 2441–50.
- ⁹² Monforte A, Abrams D, Pradier C *et al*. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* 2008;**22**: 2143–53.
- ⁹³ Ceccherini-Silberstein F, Cozzi-Lepri A, Ruiz L *et al*. Impact of HIV-1 reverse transcriptase polymorphism F214L on virological response to thymidine analogue-based regimens in antiretroviral therapy (ART)-naïve and ART-experienced patients. *J Infect Dis* 2007;**196**: 1180–90.
- ⁹⁴ ART-C. Importance of baseline prognostic factors with increasing time since initiation of highly active antiretroviral therapy: collaborative analysis of cohorts of HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2007;**46**: 607–15.
- ⁹⁵ De Wit S, Sabin CA, Weber R *et al*. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care* 2008;**31**: 1224–29.
- ⁹⁶ Martin MP, Qi Y, Gao X *et al*. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. *Nat Genet* 2007;**39**:733–40.
- ⁹⁷ ART-C. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008;**372**: 293–99.
- ⁹⁸ Mocroft A, Phillips AN, Gatell J *et al*. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet* 2007;**370**:407–13.
- ⁹⁹ May M, Sterne JA, Sabin C *et al*. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS* 2007;**21**:1185–97.
- ¹⁰⁰ Damond F, Benard A, Ruelle J *et al*. Quality control assessment of human immunodeficiency virus type 2 (HIV-2) viral load quantification assays: results from

- an international collaboration on HIV-2 infection in 2006. *J Clin Microbiol* 2008;**46**:2088–91.
- ¹⁰¹ Mocroft A, Staszewski S, Weber R *et al.* Risk of discontinuation of nevirapine due to toxicities in antiretroviral-naïve and -experienced HIV-infected patients with high and low CD4+ T-cell counts. *Antivir Ther* 2007;**12**: 325–33.
- ¹⁰² Brinkhof MW, Egger M, Boulle A *et al.* Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. *Clin Infect Dis* 2007;**45**: 1518–21.
- ¹⁰³ SMART/INSIGHT, D:A:D. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008;**22**:F17–24.
- ¹⁰⁴ Veit O, Niedrig M, Chapuis-Taillard C *et al.* Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* 2009;**48**: 659–66.