

Longer Term Clinical and Virological Outcome of Sub-Saharan African Participants on Antiretroviral Treatment in the Swiss HIV Cohort Study

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Objectives: Persons from sub-Saharan Africa (SSA) are increasingly enrolled in the Swiss HIV Cohort Study (SHCS). Cohorts from other European countries showed higher rates of viral failure among their SSA participants. We analyzed long-term outcomes of SSA versus North Western European participants.

Design: We analyzed data of the SHCS, a nation-wide prospective cohort study of HIV-infected adults at 7 sites in Switzerland.

Methods: SSA and North Western European participants were included if their first treatment combination consisted of at least 3 antiretroviral drugs (cART), if they had at least 1 follow-up visit, did not report active injecting drug use, and did not start cART with CD4 counts >200 cells per microliter during pregnancy. Early

viral response, CD4 cell recovery, viral failure, adherence, discontinuation from SHCS, new AIDS-defining events, and survival were analyzed using linear regression and Cox proportional hazard models.

Results: The proportion of participants from SSA within the SHCS increased from 2.6% (<1995) to 20.8% (2005–2009). Of 4656 included participants, 808 (17.4%) were from SSA. Early viral response (6 months) and rate of viral failure in an intent-to-stay-on-cART approach were similar. However, SSA participants had a higher risk of viral failure on cART (adjusted hazard ratio: 2.03, 95% confidence interval: 1.50 to 2.75). Self-reported adherence was inferior for SSA. There was no increase of AIDS-defining events or mortality in SSA participants.

Conclusions: Increased attention must be given to factors negatively influencing adherence to cART in participants from SSA to guarantee equal longer-term results on cART.

Key Words: adherence, cohort study, HIV infection, migrants, sub-Saharan Africa, viral failure

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INTRODUCTION

In the last 10 years, HIV risk groups and transmission patterns have changed substantially in Western Europe. Currently, heterosexual transmission and transmission between men who have sex with men equally account for about 35% of new HIV cases.¹ The heterosexual subepidemic is mainly driven by patients who originated in countries with a generalized epidemic, in particular from sub-Saharan Africa (SSA). In some European countries, 60%–70% of new HIV cases with heterosexual transmission were from SSA.^{1–4} In Switzerland, about 43% of new infections were acquired through heterosexual transmission, and within this group, 32% originated from SSA.⁵ By comparison, only 0.9% of the resident population in Switzerland have an African nationality.⁶ In response to this development, several studies have aimed to assess the level of and response to HIV care among migrant groups. A previous study within the Swiss HIV Cohort Study (SHCS) already documented the increasing proportion of SSA participants.⁷ This was mainly due to persons seeking asylum or immigrating to Switzerland for marriage.⁸ Equal uptake of combination antiretroviral therapy

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C.S. and H.F. designed the study. C.S., O.K. and H.F. conducted the statistical analyses and drafted the article together. All authors contributed data, critically revised the article, and approved its final version.

The members of the Swiss HIV Cohort Study are listed in Appendix I.

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(cART), progression to AIDS, and mortality could be demonstrated.⁷ Other studies in Europe showed increased rates of viral failure among HIV participants from SSA or non-European origin.^{9–11} These results prompted us to analyze the long-term immunological, virological, and clinical outcome on cART in SSA versus North Western European (NWE) participants in the SHCS.

METHODS

The Swiss HIV Cohort Study

The SHCS (<http://www.shcs.ch>) is a national prospective cohort study of HIV-infected participants aged 16 years and older followed up at outpatient clinics of 5 university hospitals and 2 cantonal hospitals in Switzerland.¹² It was set up in 1988, though some data going back to 1981 were collected retrospectively. A comparison with official AIDS notifications and deaths indicated that about 70% of all participants living with AIDS in Switzerland participate in the study.¹² Data collection and study procedures are standardized. Detailed information on demographics, mode of HIV acquisition, risk behaviors, clinical events, treatments, and adherence to treatment are collected at registration and then at 6 monthly intervals.

HIV-1 RNA (Roche Amplicor HIV-1 Monitor assay), CD4 counts, and other laboratory parameters are also measured every 6 months. Clinical AIDS diagnoses are recorded according to the 1993 Centers for Disease Control and Prevention criteria.¹³

Participants are grouped into geographical regions according to their nationality at entry into the study. The regions correspond to a simplified version of the UNAIDS

regions.¹⁴ For this study, participants from SSA were compared with participants from NWE (excluding the Southern European countries Italy, Spain, and Portugal).

Selection of Study Population

We included all HIV-1–positive participants from SSA and NWE who had started a triple cART without any prior pretreatment and who had at least 1 follow-up visit since the start of the SHCS till the closure of the database in February 2010 (Fig. 1). Participants who started treatment with unboosted saquinavir were excluded, as the outcome on a regimen with this unboosted protease inhibitor (PI) is known to be significantly worse than on other unboosted PI regimens due to its low bioavailability.^{15,16} In addition, we excluded participants with ongoing injecting drug use. Unless noted otherwise, women who started cART during pregnancy with CD4 counts >200 cells per microliter were excluded for all analyses, as it was common practice to stop cART after pregnancy in women with a CD4 count above the threshold set by the respective guidelines for a start of cART.

Definitions

Treatment combinations containing a ritonavir-boosted protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (NNRTI) were grouped together as potent cART.

Coinfection with hepatitis B (HBV) or hepatitis C virus (HCV) was defined as positive hepatitis B surface antigen or hepatitis C antibodies at any time during follow-up.

Treatment Periods were grouped into early cART (<year 2000) or late cART period (≥2000).

We grouped reasons for discontinuing participation from the SHCS (apart from death) as follows: moved to another

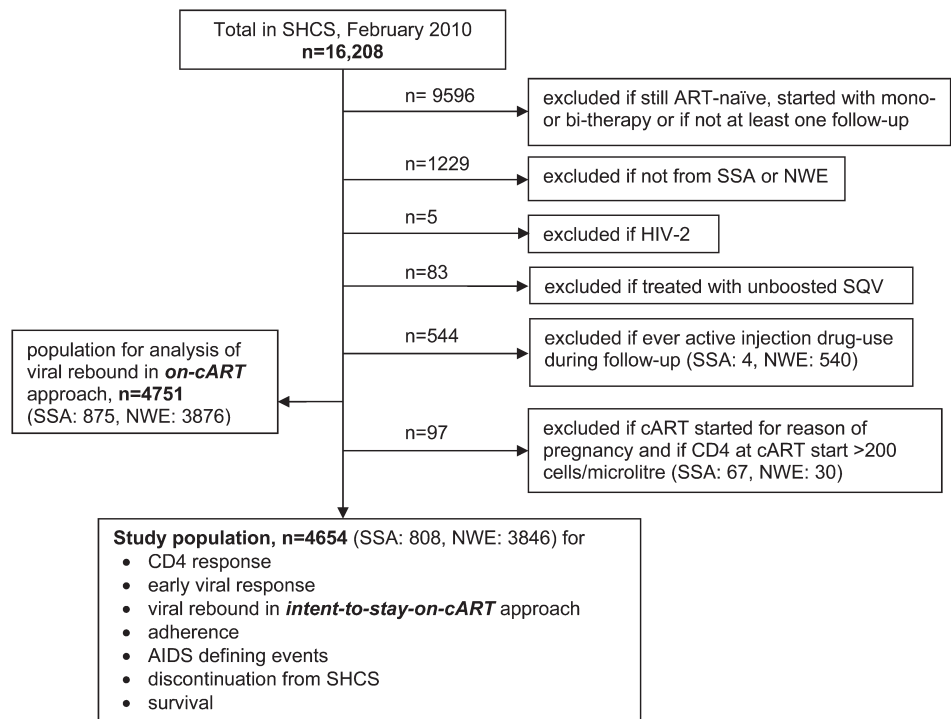


FIGURE 1. Selection of study population.

country, patient's wish to discontinue, lost to follow-up (no visit for at least 14 months), other reasons.

Self-reported adherence is assessed at every cohort visit for the 4 weeks immediately preceding the visit. Adherence is grouped using following options in increasing order of adherence: missed more than 1 dose in a row (drug holiday); missed ≥ 2 doses; missed ≥ 1 dose, never missed a dose. Adherence within the SHCS is described in more detail in the study by Glass et al.¹⁷ For this study, adherence was assessed at the last visit in the study period.

New AIDS-defining events were defined as any new or relapsing AIDS-defining event occurring later than 1 month after the initiation of cART.

Statistical Analysis

Continuous data were compared using the Wilcoxon rank-sum test, categorical data with the χ^2 test.

CD4 response was measured as increase from baseline to 1 year and to 5 years after cART start. Linear regression analysis was used to adjust for baseline variables.

We used Kaplan–Meier graphs and Cox proportional hazard models to estimate hazard ratios (HRs) of the following endpoints: virologic suppression (HIV-1 RNA \leq lower limit of detection of the respective test), viral failure (first of 2 consecutive HIV RNA measurements >400 copies per milliliter after prior viral suppression to below the lower limit of detection of the respective test), time to new AIDS-defining event, and time to death from all causes.

For the analysis of viral rebound, we distinguished 2 approaches in analogy to clinical trials:

In the intent-to-stay-on-cART approach, we included all participants who had ever started cART and ignored any subsequent treatment changes, interruptions, or stops with the exception of participants enrolled in a trial for structured interruption of treatment. These participants were censored at the first treatment stop within a structured interruption of treatment trial.

In the on-cART approach, all participants who had ever started cART were analyzed, including women who had started in the context of pregnancy. However, in this analysis, participants were censored at first treatment stop or interruption.

For time-to-event analyses, time was measured from the start of cART or from time of viral suppression to the time the event occurred, the time of the last follow-up visit, or the time of cART stop or interruption (for the on-cART approach), whichever came first.

Multivariable analyses were adjusted for the following variables: sex, age at cART start (grouped in decades), CD4 at treatment start (square root transformed), HIV viral load (per log₁₀ increase), AIDS at treatment start, HBV, and HCV infection, and antiretroviral treatment variables (early versus late cART period; potent versus other cART).

Data were analyzed using Stata version 10.1 (College Station, TX).

RESULTS

Between 1981 and 2010, an 8-fold increase (2.6% before 1995 to 20.8% in 2005–2009) in the proportion of SSA

participants enrolled in the SHCS was observed. Median duration of follow-up was significantly shorter in SSA than in NWE individuals (4.3 versus 5.6 years). Of the 16,208 participants registered in the SHCS, 4656 participants were included into this study, 17.4% (n = 808) were from SSA (Fig. 1).

Patient characteristics are shown in Table 1. SSA participants were more likely to be female, infected by heterosexual contact and to present with advanced disease. They were less likely to be infected with HCV but more likely with HBV. At cART start, they had lower CD4 counts and HIV RNA levels. Participants from SSA were more likely to be started on a regimen containing an NNRTI. In both patient groups, there was a shift from unboosted PI-based regimens in the early cART period toward combinations with an NNRTI or a boosted PI in the late cART period.

CD4 Response and Early Viral Response

SSA origin continued to be associated with lower CD4 counts up to 5 years after cART initiation even after adjustment for all covariables: median (interquartile range) CD4 increase (in cells/ μ L) 1 year after cART start was +158 (71–239) in SSA and +166 (78–271) in NWE (adjusted $P < 0.001$, n = 3119) and +260 (128–413) and +273 (132–446) at 5 years (adjusted $P = 0.002$, n = 1753).

An equal number of participants from each group reached HIV viral load values below the limit of detection at 6 months (61% in SSA and 60% in NWE, adjusted $P = 0.16$).

Viral Failure

In the intent-to-stay-on-cART approach, there was a trend toward a higher rate of viral failure in SSA [adjusted HR 1.2, 95% confidence interval (CI) 1.0 to 1.45] (Fig. 2).

In the on-cART analysis, there was strong evidence that participants from SSA had a greater risk of viral failure than participants from NWE (adjusted HR: 2.03, 95% CI: 1.5 to 2.75). Lower CD4 counts at start of cART were associated with an increased risk of viral failure although higher viral load was not. On treatment, men had a higher risk for viral failure. Starting cART after the year 2000 and with a regimen containing an NNRTI or ritonavir-boosted protease inhibitor was clearly associated with reduced viral failure.

The incidence of patients with viral failure among SSA versus NWE were as follows: at 12 months, 4.5% (95% CI: 3.2 to 6.4) versus 2.9% (2.4 to 3.5); 24 months, 9.8% (7.6 to 12.5) versus 6.9% (6.0 to 7.9); 36 months, 13% (10.3 to 16.2) versus 8.7% (7.7 to 9.8); 48 months, 15.3% (12.3 to 19.0) versus 9.9% (8.7 to 11.1); and 60 months, 16.5% (13.3 to 20.5) versus 12% (10.7 to 13.4).

In a sensitivity analysis, only data from NWE and SSA participants with heterosexual transmission were analyzed; the results did not change materially: in the intent-to-stay-on-cART approach, the adjusted HR was 1.25 (95% CI: 1.0 to 1.56); in the on-cART approach the adjusted HR was 1.92 (95% CI: 1.3 to 2.8).

Adherence

In the last recorded study visit, participants from SSA reported worse adherence compared with NWE: missed ≥ 1

TABLE 1. Baseline Characteristics

	SSA	NWE	P
Study participants, no. (%)	808 (17.4)	3846 (82.6)	<0.001
Women, no. (%)	526 (65.1)	834 (21.7)	
Mode of HIV transmission			
Heterosexual	720 (89.1)	1308 (34.0)	<0.001
MSM	17 (2.1)	1868 (48.6)	
IVDU	7 (0.9)	512 (13.3)	
Blood products	19 (2.4)	24 (0.6)	
Perinatal/other/unknown	45 (5.6)	134 (3.5)	
Age at start cART (yrs)	32 (27–37)	39 (34–47)	<0.001
CD4 at start cART (c/μL), median (IQR)*	197 (112–296)	219 (104–335)	0.009
Log HIV RNA at start cART (copies/mL), median (IQR)†	4.7 (3.8–5.2)	4.9 (4.2–5.4)	<0.001
CDC stage at start cART‡ A	539 (67.5%)	2403 (63.5%)	<0.001
B	96 (12.0%)	719 (19.0%)	
C	164 (20.5%)	660 (17.5%)	
Coinfection with hepatitis B virus	75 (9.3%)	117 (4.6%)	<0.001
Coinfection with hepatitis C virus§	26 (3.3%)	697 (18.4%)	<0.001
Follow-up after start cART, median yrs (IQR)	4.3 (1.8–7.7)	5.6 (2.2–9.9)	<0.001
Duration of first cART treatment, excluding treatment stops for SITT, mean months (IQR)	15.6 (4.0–36.6)	21.3 (6.4–45.7)	<0.001
Duration of first cART treatment if treatment started > 1.1.2000 (excluding stops for SITT), mean months (IQR)	12.3 (3.0–32.8)	12.3 (3.4–29.3)	0.8
Initial treatment combination			
3 NRTI	25 (3.1%)	84 (2.2%)	<0.001
2 NRTI + PI	217 (26.9%)	1379 (35.9%)	
2 NRTI + r/PI	221 (27.4%)	1150 (29.9%)	
2 NRTI + NNRTI	333 (41.2%)	1139 (29.6%)	
Initial treatment combination if cART start >1.1.2000 (n = 3041)			
3 NRTI	22 (3.5%)	65 (2.7%)	<0.001
2 NRTI + PI	88 (14.0%)	240 (10.0%)	
2 NRTI + r/PI	202 (32.1%)	1011 (41.9%)	
2 NRTI + NNRTI	311 (49.4%)	1041 (43.2%)	

Missing values:

*510.

†530

‡73

§85.

IVDU, injecting drug use; IQR, interquartile range; MSM, men who have sex with men; NRTI, nucleotide reverse transcriptase inhibitor; NNRTI non-nucleotide reverse transcriptase inhibitor; r/PI, ritonavir-boosted protease inhibitor; SITT, structured intermittent treatment trials.

dose 21.6% versus 16.1%, missed ≥ 2 doses 8.6% versus 5.1%, missed more than 1 dose in a row 5.2% versus 2.5% ($P < 0.001$ for each of the comparisons). Of the participants who experienced viral failure, 32.3% SSA versus 21.9% NWE reported having missed ≥ 1 dose ($P = 0.002$); 17.7% SSA versus 8.3% NWE reported having missed ≥ 2 doses ($P < 0.001$), and 9% SSA versus 5.2% NWE ($P = 0.05$) reported missing more than 1 dose in a row.

Discontinuation From the SHCS

Over the study period, 21.9% ($n = 177$) of SSA and 13.4% ($n = 517$) of NWE stopped participating in the SHCS ($P < 0.001$). In both groups, loss to follow-up was the main reason: 83 SSA (10.3%) and 239 NWE (6.2%). The next predominant reason in SSA ($n = 50$, 6.2%) was move to a foreign country. There was no difference between the patient groups regarding participants' wish to discontinue in the study.

AIDS-Defining Events After Treatment Start and Survival

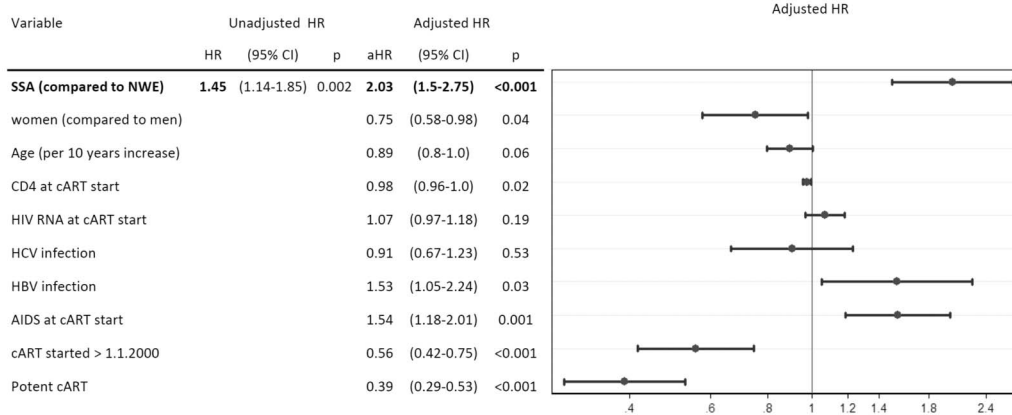
In the multivariable analysis, there was no statistically significant difference in the incidence of AIDS-defining events between both populations (adjusted HR for SSA: 1.35, 95% CI: 0.96 to 1.94).

Among participants from SSA, there were 23 deaths in 4071 person-years, in NWE 340 in 23,601 person-years. In the unadjusted model the mortality rate per 100 person-years was lower for SSA (0.6; 95% CI: 0.4 to 0.8) than for NWE (1.4, 95% CI: 1.3 to 1.6), (Fig. 2). After adjusting for all covariables, the effect of region of origin disappeared (HR: 0.75, 95% CI: 0.45 to 1.26).

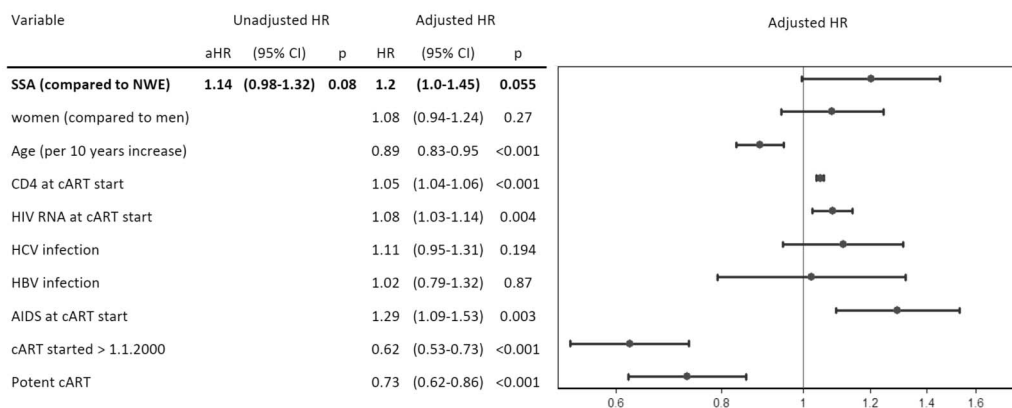
DISCUSSION

We demonstrated similar outcomes of the African participants under cART as compared with their NWE

A Risk factors associated with viral failure in the on-cART approach
(n= 4751 for selected population, n=4032 for model)



B Risk factors associated with viral failure in the intent-to-stay-on-cART approach
(n=4654 for selected population, n=3937 for model)



C Risk factors associated with mortality
(n= 4654 for selected population, n=3937 for model)

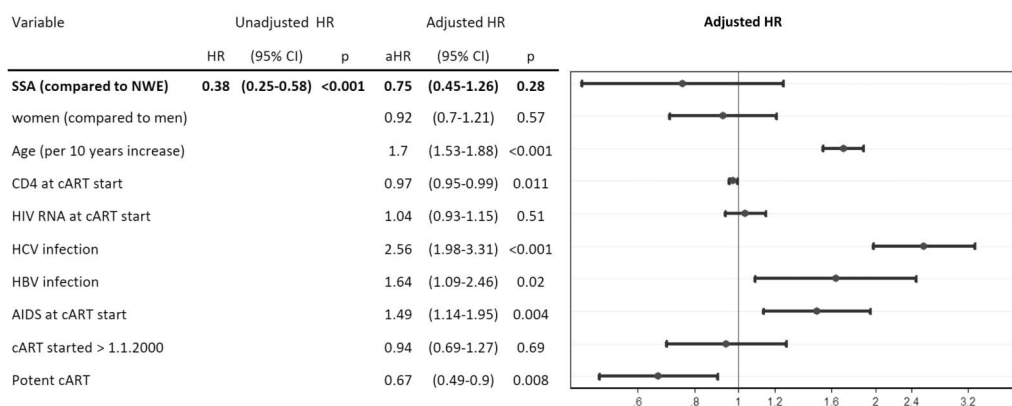


FIGURE 2. Cox regression analyses of factors associated with viral failure and death. Unadjusted and adjusted hazard ratios (HR and aHR) are given. Potent cART = triple antiretroviral treatment containing at least 1 NNRTI or 1 boosted PI. CD4 at cART start: square root transformed. HIV RNA at cART start: per log 10 increase.

contemporaries with regard to initial viral suppression and subsequent viral failure in the intent-to-stay-on-cART analysis. However, we noticed a doubled risk of viral failure for SSA participants who remained on treatment compared with their NWE counterparts. Further points of concern are higher rates of self-reported nonadherence and loss to follow-up. The increase in viral failure on treatment raises concerns about long-term stability of cART in the SSA subpopulation, which—as in other European countries—is an increasingly important minority in Switzerland. Fortunately, so far this has not translated into increased mortality.

Virological and Clinical Outcome

We found no difference in initial viral response to below the lower limit of detection. For the long-term analysis, however, there was a trend toward increased viral failure in the intent-to-stay-on-cART analysis. In the on-cART analysis, there was even a significant 2-fold elevated risk for SSA to develop viral failure.

In the Netherlands, 2 studies showed a higher risk of failure to achieve early viral suppression among HIV participants of non-Dutch population groups. Nellen et al⁹ showed no differences between patient groups in reaching viremia <400 copies per milliliter or in CD4 recovery. However, a significantly higher proportion of African participants failed to achieve viral suppression to below 50 copies per milliliter. Participants from sub-Saharan Africa progressed faster to AIDS and death. The other Dutch cohort study by van den Berg et al¹⁰ demonstrated a 4.6-fold higher risk of early failure to achieve undetectable viral load for non-Europeans. Of the non-European patients who failed, 80% were Africans. Poor adherence seemed to be the main reason for failure. However, once treatment was successful in the early phase, there were similar response rates among both patient groups later. A study conducted in London among African patients¹¹ showed good initial viral suppression and CD4 recovery, however, a significantly higher rate of viral rebound in patients from SSA.

We documented lower baseline CD4 counts among SSA participants as is seen in other European countries.^{9,11,18} Lower baseline and on-treatment CD4 counts have been associated with an increased risk of viral failure,¹⁹ demonstrating the role of CD4 cells not only as target cells of the HIV virus but also as key players in the control of HIV. In our on-cART analysis, lower baseline CD4 counts were also associated with increased viral failure, which goes in line with this finding. The lower CD4 lymphocyte gain in SSA, although statistically significant, is small and of questionable clinical relevance because we observed no difference in incidence of opportunistic diseases.

One of the most important factors for continued viral suppression is to maintain good adherence to ART intake.^{20–22} In our study, participants from SSA were more likely to report nonadherence than their NWE counterparts. This corresponds to an earlier study showing a higher rate of nonadherence in non-whites.¹⁷ In Switzerland, health insurance is mandatory; premiums are per-capita based. Maintenance of drug supply and clinical services are guaranteed through the basic health insurance. However, health insurance premiums are costly,

and some participants struggle to access social service schemes which would subsidize their premiums. In addition, contextual or individual factors such as language barriers with dependency on translators, difficulties understanding the Swiss health system or instability of legal status may account for lower drug adherence.

The increase in long-term viral failure in SSA patients has fortunately not resulted in an increase in AIDS events or deaths. This confirms earlier findings within the SHCS⁷ and gives a cautiously optimistic perspective over a longer period of time, though the “natural history” of uncontrolled viremia is development of resistance and an increased risk of mortality.^{20,23,24}

Discontinuation From the SHCS

In the current study, 177 (21.9%) participants from SSA and 517 (13.4%) from NWE stopped participating in the SHCS, the main reason for both groups being loss to follow-up, yet with a significantly higher proportion among SSA. The next main reason for discontinuation of SSA participants within the SHCS was move to another country followed by their wish to discontinue. Reasons for loss to follow-up can only be speculated upon. In a single SHCS centre study of migrants,⁸ 64.8% of the SSA participants migrated to Switzerland in quest of asylum, whereas 24.2% came to get married within Switzerland. At the end of the study, the majority of those who had left the country had been denied asylum. It is very likely, therefore, that SSA participants, who no longer turn up for regular visits, are facing legal issues related to their residence status.

Strengths and Limitations

The main strengths of this study lie within the structures of the SHCS, which is a large and representative cohort with regular follow-up visits and structured questionnaires and clinical assessments. We may, therefore, expect our findings to be robust and generalizable for participants within similarly structured settings. Another strength of the study was the exclusion of participants who reported active intravenous drug use because they were likely to bias the results with a predicted inferior outcome and were almost exclusively in the NWE group.

There are several limitations mostly inherent to the observational nature and the long history of the SHCS. We did not measure drug levels as a marker of adherence. Information on clade of HIV virus and genotype mutations is also missing in this analysis. Data collection is not as rigid as in an interventional trial; therefore, missing data is a relevant issue. Seven hundred seventeen participants (15%) had ≥ 1 missing parameter, of these, 21% were from SSA. Mainly, participants enrolled before January 1, 2000, had missing data as follows: 43% in our study compared with 35% of all SHCS participants. This is a voluntary cohort with written informed consent, so participants with the most fragile legal status may not want to enter such a cohort as was demonstrated in a cross-sectional study in the SHCS centres, which showed that clinic attendees from SSA, particularly men, were less likely to participate and were thus underrepresented in the SHCS.²⁵

In conclusion, we observe—as do other European cohorts—an increased rate of viral failure of SSA participants on medium to long-term cART. In this and in a previous study within the SHCS,¹⁷ markers of self-reported adherence were consistently worse for SSA than for NWE participants. This finding is disturbing; particularly in the context of available universal access to health care in Switzerland. It has to be concluded, therefore, that other factors, such as socioeconomic factors beyond access to health care, difficulties with residence status, financial instability, and cultural and language barriers act as hindrances to optimal compliance in SSA participants within the SHCS.

Involving HIV physicians to inform about HIV and available health services at the immigration centre may reduce the barrier to request HIV services. Including an analysis of social and financial parameters in the clinical file through the social worker²⁶ and involving male intercultural mediators and translators to reach SSA men may be possible interventions to increase adherence and retention and thus increase rates of long-term viral suppression among SSA participants.

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APPENDIX I: MEMBERS OF THE SHCS

The members of the SHCS are Barth J, Battegay M, Bemasconi E, Böni J, Bucher HC, Bürgisser P, Burton-Jeangros C, Calmy A, Cavassini M, Dubs R, Egger M, Elzi L, Fehr J, Fischer M, Flepp M, Francioli P (President of the SHCS), Furrer H (Chairman of the Clinical and Laboratory Committee), Fux C, A, Gorgievski M, Günthard H (Chairman of the Scientific Board), Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Müller N, Nadal D, Pantaleo G, Rauch A, Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother and Child Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Telenti A, Trkola A, Vernazza P, and von Wyl.