

Ethnicity predicts viral rebound after travel to the tropics in HIV-infected travelers to the tropics in the Swiss HIV Cohort Study

HM Gebreselassie,¹ D Kraus,^{1,2,3} CA Fux,⁴ S Haubitz,^{1,4} A Scherrer,⁵ C Hatz,^{6,7} O Veit,⁷ M Stoeckle,⁸ J Fehr,⁵ S de Lucia,⁹ M Cavassini,¹⁰ E Bernasconi,¹¹ P Schmid,¹² H Furrer,¹ C Staehelin¹ For the Swiss HIV Cohort Study (SHCS)*

¹Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Switzerland, ²Institute for Social and Preventive Medicine, Bern University, Bern, Switzerland, ³Institute of Mathematics and Statistics, Masaryk University, Brno, Czech Republic, ⁴Department of Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Aarau, Switzerland, ⁵Division of Infectious Diseases and Hospital Epidemiology, Zürich University Hospital, Zürich, Switzerland, ⁶Swiss Tropical and Public Health Institute, Basel, Switzerland, ⁷Institute for Epidemiology, Biostatistics and Prevention, University of Zürich, Zürich, Switzerland, ⁸Clinic for Infectious Diseases, University Hospital Basel, Basel, Switzerland, ⁹Department of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland, ¹⁰Department of Infectious Diseases, Lausanne University Hospital, Lausanne, Switzerland, ¹¹Department of Infectious Diseases, Lugano Regional Hospital, Lugano, Switzerland and ¹²Department of Infectious Diseases, St. Gallen Cantonal Hospital, St. Gallen, Switzerland

Objectives

The number of HIV-infected individuals from developed countries travelling to tropical and subtropical areas has increased as a result of the clinical and survival benefits of combination antiretroviral therapy. The aim of our study was to describe the traveler population in the SHCS and to determine the frequency of viral rebound in virologically suppressed individuals after a travel episode to the tropics compared to non-travelers.

Methods

Swiss HIV Cohort Study participants with at least one follow-up visit between 1 January 1989 and 28 February 2015 were eligible for inclusion in the study. The primary outcome was the occurrence of viral rebound (viral load > 200 HIV-1 RNA copies/mL) after a travel episode compared with a nontravel episode in previously suppressed individuals (≤ 200 copies/mL). All virologically suppressed patients contributed multiple travel or nontravel episodes to the analysis. Logistic regression was performed including factors associated with viral rebound.

Results

We included 16 635 patients in the study, of whom 6084 (36.5%) had ever travelled to the tropics. Travel frequency increased over time, with travellers showing better HIV parameters than nontravellers [less advanced Centers for Disease Control and Prevention (CDC) stage and higher CD4 count nadir]. Viral rebound was seen in 477 (3.9%) of 12 265 travel episodes and in 5121 (4.5%) of 114 884 nontravel episodes [unadjusted odds ratio (OR) 0.87; 95% confidence interval (CI) 0.78–0.97]. Among these 477 post-travel viral rebounds, 115 had a resistance test performed and 51 (44%) of these showed new resistance mutations. Compared with European and North American patients, the odds for viral rebound were significantly lower in Southeast Asian (OR 0.67; 95% CI 0.51–0.88) and higher in sub-Saharan African (SSA) patients (OR 1.41; 95% CI 1.22–1.62). Travel further increased the odds of viral rebound in SSA patients (OR 2.00; 95% CI 1.53–2.61).

Correspondence: Dr Cornelia Staehelin, Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland. Tel: +41 31 632 01 83 or +41 31 632 27 45; fax: +41 31 632 31 76; e-mail: cornelia.staehelin@insel.ch and

Dr Hiwot Gebreselassie, Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland. Tel: +41 31 632 27 45 or +41 79 244 82 23; e-mail: mamohiwot8@gmail.com

Data were presented in part at the 15th European AIDS Conference, Barcelona, Spain, 21–24 October 2015 (Poster PE 21/21).

*See Appendix.

Conclusions

Region of origin is the main risk factor for viral rebound rather than travel *per se*. Pre-travel adherence counselling should focus on patients of SSA origin.

Keywords: adherence, HIV, travel, virological failure, visiting friends and relatives

Accepted 23 November 2016

Introduction

The number of HIV-infected individuals from developed countries travelling to tropical and subtropical areas has increased [1–4] as a result of the clinical and survival benefits of combination antiretroviral therapy (cART). The introduction of cART has shifted the motive of many travellers from taking a “last chance to travel” [5] towards tourism and visiting friends and relatives (VFR) [1]. The rate of international travellers among the HIV-infected population ranges between 20% and 46% in different studies [5–7], with some reports stating that HIV-infected individuals may be travelling more frequently and taking longer journeys than the general population [8].

The sustained effectiveness of cART depends on long-term, regular, and time-specific dosing schedules ensuring drug concentrations always well above the inhibitory concentration of the virus [9]. Consequently, adherence to cART is of paramount importance and is a strong predictor of virological failure [10–12]. Some studies have associated travelling or being away from home with non-adherence [6,13–17]. A wish for a “drug holiday” in those not travelling for VFR, and nondisclosure and fear of stigma in those travelling for VFR have been implicated as causes of nonadherence [15–17]. Other factors that negatively impact adherence to cART are sudden familial events or unstable politics leading to unexpected lengthening of stay, impaired intake because of gastroenteritis, and travel bans for HIV-positive persons. However, a Danish cross-sectional retrospective study over 2 years did not show any change in adherence in HIV-infected travellers [8], although this study may have suffered from recall and selection bias. In a study by Glass *et al.*, [10] drug holidays were reported in 3.5% of cohort visits in the Swiss HIV Cohort Study (SHCS) – the potential association with travel, however, was not looked at.

In addition to reports of an association of lower adherence with travel, associations of an increase in viral load (VL) or a decrease in CD4 counts with travel have been reported in only a few studies [13,14,17].

This study had two aims: (1) to describe the characteristics of the population in the SHCS travelling to the tropics, using a descriptive analysis at the patient level, and (2) to determine the frequency and risk factors of

viral rebound following a travel episode *vs.* a nontravel episode if the VL at the beginning of the episode was suppressed, using a regression analysis at the episode level.

Within the traveller population, we focused on frequent travellers and those originating from tropical regions, such as sub-Saharan Africa (SSA), Southeast Asia (SEA; this also includes the entire Indian subcontinent and China), and Latin America and the Caribbean (LAC).

Methods

The study was based on prospectively collected data from individuals who were enrolled in the SHCS and followed through 6-monthly visits at one of the seven participating out-patient clinics (Basel, Berne, Geneva, Lausanne, Lugano, St Gallen and Zurich) or associated clinics and private practices (www.shcs.ch).

At every visit, patients are asked verbally whether they have travelled to the tropics in the past 6 months. The tropics are not defined geographically in the SHCS database. However, the term is often used colloquially as a generic word for subtropical and tropical regions. There is no additional information on the number of travel episodes since the last cohort visit nor on travel destination.

Definitions

Traveller: a patient with at least one travel episode to the tropics during the whole follow-up period in the cohort.

Frequent traveller: an individual in the top quarter of participants in terms of number of travel episodes.

Visiting friends and relatives (VFR): origin of the traveller in SSA, SEA or LAC was taken as a proxy for VFR.

An episode under study was defined as a unit bounded by a visit with suppressed viraemia (termed the ‘pre-visit’) and a subsequent visit (termed the ‘post-visit’). Episodes during which travel occurred were defined as travel episodes, and episodes without travel were defined as non-travel episodes. Nontravel episodes were contributed by travelers and nontravellers.

Virological suppression: a VL of ≤ 200 HIV-1 RNA copies/mL for the main analysis and ≤ 50 copies/mL for the sensitivity analysis, while the patient was on cART.

Virological rebound: a VL > 200 copies/mL [18,19] for the main analysis and > 50 copies/mL for the sensitivity analysis in a previously suppressed individual.

Virological failure: viral rebound with subsequent treatment change in the SHCS reported as being attributable to virological failure.

Combination antiretroviral treatment (cART): a combination of at least three antiretroviral compounds.

Robust ART: any cART including at least one nonnucleoside reverse transcriptase inhibitor (NNRTI), ritonavir-boosted protease inhibitor (PI/r) or integrase strand transfer inhibitor (INSTI), or maraviroc (MVC).

Nonadherence: history of any follow-up visit at which adherence to cART was suboptimal, that is, missing more than one dose of cART in the preceding month.

Descriptive analysis

The descriptive analysis described the traveller and non-traveller populations in the SHCS. Eligible individuals were all SHCS participants with at least one follow-up visit from 1 January 1989 to 28 February 2015. Basic demographic characteristics including region of origin and HIV-specific data were used to describe the population. Patients were assigned to one of four categories according to region of origin: patients in the reference group (Eur-NAM) had a nontropical origin in Europe, North America, North Africa, the Middle East, Central Asia, Australia or New Zealand, and the other three groups consisted of patients from SSA, SEA and LAC, respectively. In univariable analyses, the χ^2 test was used for categorical data and the Wilcoxon rank-sum test for continuous data to compare the travelling and nontravelling populations. The statistical package used was STATA Version 13 (StataCorp LLC, College Station, TX, USA).

Primary outcome analysis

The main outcome of the study was the rate of viral rebound in a travel episode *vs.* a nontravel episode as well as risk factors thereof. Episodes (with travellers contributing to travel and nontravel episodes and nontravellers contributing only to nontravel episodes) were included if they met the following two criteria. (1) The patient was on cART with suppressed viraemia at the pre-visit. Viraemia was considered to be suppressed if (a) VL was detectable and < 200 copies/mL (or 50 copies/mL in the sensitivity analysis) or (b) VL was undetectable and the detection limit was \leq 200 copies/mL (or \leq 50 copies/mL in the sensitivity analysis). (2) There was a VL determination at the post-visit. Patients with unrecorded region of origin or who were on dual or mono ART or

enrolled in a structured treatment interruption study were excluded. Any patient with suppressed viraemia in the cohort could have travel and nontravel follow-up episodes and could thus contribute multiple episodes to the regression analysis.

Logistic regression was fitted to indicators of viral rebound (RNA > 200 or > 50 copies/mL, respectively) at the end of a follow-up episode, resulting in binary outcomes. Regression models included constant covariables (sex, region of origin, mode of HIV transmission and indicators of nonadherence), time-updated covariables evaluated either at the beginning of the follow-up episodes [calendar date (per 1-year increment), age, base 2 logarithm of CD4 count, use of robust cART, current injecting drug use (IDU), and history of cART change after treatment failure] or at the end of a follow-up episode (travel indicator), and interaction terms between the region of origin and travel. In all regression models, we accounted for the within-patient correlation of outcomes using generalized estimating equations; standard errors were obtained from sandwich estimators.

We analysed treatment change and the emergence of resistance in travellers who fulfilled either or both of the following criteria: (1) persistent VL > 200 copies/mL at the second post-travel visit ("post-travel visit 2") or (2) treatment switch between the pre-travel visit and the immediate post-travel visit ("post-travel visit 1") or between post-travel visit 1 and post-travel visit 2. For these patients, the resistance database was searched for any resistance test and emergence of new resistance mutations between the pre-travel visit and post-travel visit 1 and between post-travel visit 1 and post-travel visit 2.

We considered a *P*-value of < 0.05 as significant. This part of the statistical analysis was performed in R (version 3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Descriptive analysis

We analysed data for 16 635 patients in the SHCS with at least one follow-up visit from 1 January 1989 to 28 February 2015. There were 6084 (36.5%) patients who had ever travelled to the tropics, with a total of 21 118 travel episodes. The percentage of participants travelling per regional category varied substantially from 31.2% for those in the Eur-NAM category to 80.7% for those in the SEA category. Figure 1 shows a sharp decline in the percentage of travellers per follow-up year from 1989 to 1992, followed by a nonconstant increase from 1992 to 2014. With the exception of the Eur-NAM group (84% of

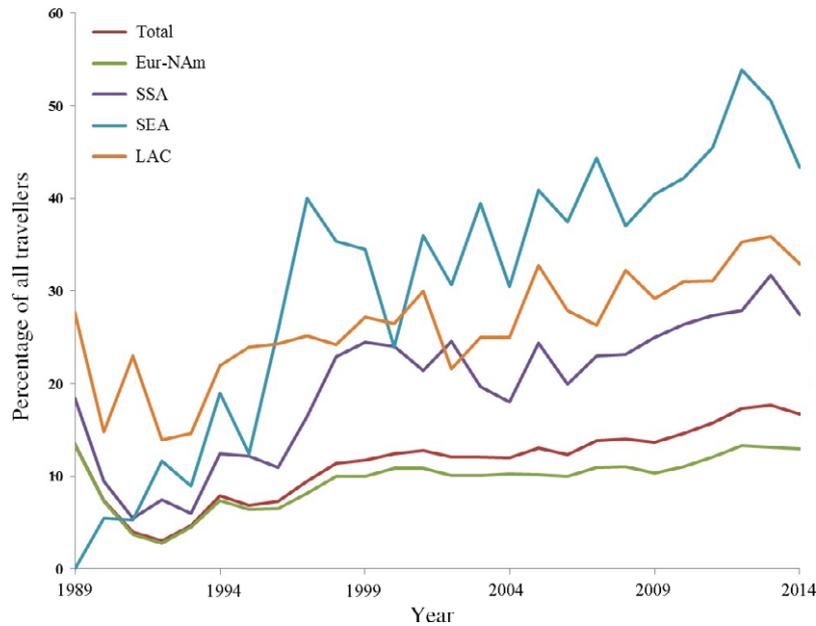


Fig. 1 Percentage of HIV-infected individuals in the SHCS, by region of origin per total population, travelling to the tropics from 1989–2015 X-axis: Five years period interval Y-axis: percentage of travelers by region of origin within the SHCS per follow up year. Eur-NAm, Europe, North America, North Africa, the Middle East, Central Asia, Australia or New Zealand; SSA, sub-Saharan Africa; SEA, Southeast Asia; LAC, Latin America and the Caribbean.

cohort participants), which showed only a marginal increase in the percentage of travellers over time, all regional categories had a marked yearly increment in the

percentage of travellers: from 18.5% in 1992 to 27.5% in 2014 for SSA, from 11.7% in 1992 to 43.3% in 2014 for SEA, and from 27.7% in 1992 to 33.0% in 2014 for LAC.

Table 1 Characteristics of HIV-infected individuals in the Swiss HIV Cohort travelling or not travelling to the tropics from 1989 to 2014

Variable	Travellers	Nontravellers	Total	P-value
Total [n (%)]	6082 (36.5)	10 553 (63.5)	16 635	
Sex [n (%)]				
Male	4111 (34.45)	7817 (65.5)	11 928	< 0.001
Female	1971 (41.9)	2736 (58.1)	4707	
Age at inclusion in the SHCS (years) [median (IQR)]	34.8 (29.0–42.2)	34 (28.5–41.9)		< 0.001
Length of follow-up (years) [median (IQR)]	10.7 (4.7–16.1)	4.9 (2.0–11.0)		< 0.001
Region of origin [n (%)]				< 0.001
Eur-NAm*	4384 (31.2)	9672 (68.8)	14 056	
SSA	968 (60.2)	640 (39.8)	1608	
SEA	325 (80.7)	78 (19.3)	403	
LAC	405 (71.3)	163 (28.7)	568	
Mode of transmission				< 0.001
MSM	2374 (37.6)	3935 (62.4)	6309	
Heterosexual	2598 (46.5)	2988 (53.5)	5586	
IDU	847 (20.8)	3222 (79.2)	4069	
Others	263 (39.2)	408 (60.8)	671	
CDC stage at last follow-up				< 0.001
A	2952 (41.0)	4254 (59.0)	7206	
B	1515 (37.7)	2507 (62.3)	4022	
C	1615 (29.9)	3792 (70.1)	5407	
CD4 count nadir (cells/ μ L) [median (IQR)]	178 (69–283)	143 (30–280)		< 0.001
RNA max. (copies/mL) [median (IQR)]	111 050 (30 700–328 000)	113 000 (29 623–345 123)		0.79
Number of travel episodes per person [median (IQR)]	2 (1–4)	NA		

CDC, Centers for Disease Control and Prevention; IQR, interquartile range; SSA, sub-Saharan Africa; SEA, Southeast Asia; LAC, Latin America and Caribbean; MSM, men who have sex with men; IDU, injecting drug use; NA, not applicable; SHCS, Swiss HIV Cohort Study. Bold text indicates significant values.

*Combined group of patients from nontropical countries, including Europe, North America, North Africa, the Middle East, Central Asia, Australia and New Zealand.

There were between 1 and 30 travel episodes per traveller (median 2), with a mean of 0.5 trips/person/year. The majority of travellers (81.1%) reported one to five travel episodes to the tropics. Travellers had a less advanced median clinical Centers for Disease Control and Prevention (CDC) stage and a higher median CD4 count nadir than nontravellers (Table 1). VFR constituted the reason for travel in 27.9% of all travellers, accounting for 32.9% of all travel episodes to the tropics.

Frequent travellers accounted for 9.7% of all SHCS participants and 22.1% of all travellers, with 18.9% of patients in the Eur-NAM group, 25.7% of those in the SSA group, 30% of those in the LAC group, and 38.9% of those in the SEA group being frequent travellers.

Primary outcome

In total, our analysis included 127 149 follow-up episodes, 12 265 (9.6%) of which were travel episodes. Viral rebound was seen in 477 (3.9%) of these 12 265 travel episodes, and in 5121 (4.5%) of the remaining 114 884 nontravel episodes. The unadjusted odds ratio (OR) for viral rebound in a travel *vs.* nontravel episode was 0.87 [95% confidence interval (CI) 0.78–0.97]. At the patient level, this translated into a total of 10 945 patients who contributed at least one episode with pre-visit suppressed viraemia to this analysis. Of these, 3858 (35.2%) patients contributed at least one travel episode, and 405 (10.5%) of them experienced at least one post-travel viral rebound. There was no clustering of patients with frequent rebounds in the traveller or nontraveller patient group: no viral rebound was recorded in 67% of travellers and 66% of nontravellers, one viral rebound was recorded in 20% of travellers and 22% of nontravellers, two rebounds were recorded in 8% of travellers and 7% of nontravellers, and at least three viral rebounds were recorded in 4% of each group. In a subanalysis restricted to nontravel episodes (depicting everyday conditions), the OR for viral rebound in travellers *vs.* nontravellers was 0.82 (95% CI 0.76–0.88).

The multivariable logistic regression analysis predicting the binary outcome of viral rebound > 200 copies/mL showed the following significant protective factors (Table 2; Fig. 2): later years within the SHCS, older age, being of SEA origin, higher CD4 count and use of robust cART. Factors associated with a higher rate of viral rebound were being female, a history of virological failure, reported nonadherence, current IDU use and being of SSA origin. Travel was a significant additional risk factor only in patients of SSA origin (OR 1.30; 95% CI

Table 2 Odds ratio for a viral load (VL) > 200 copies/mL at a post-travel visit if VL was suppressed at the pre-travel visit

Variable	Odds ratio (95% CI)	P-value
Years since inclusion in SHCS (per 1-year follow-up)	0.85 (0.84–0.86)	< 0.001
Female sex	1.12 (1.01–1.23)	0.025
Age (per 10-year increment)	0.89 (0.86–0.93)	< 0.001
Region of origin		
Eur-NAM	1	
SSA	1.41 (1.22–1.62)	< 0.001
SEA	0.67 (0.51–0.88)	0.004
LAC	1.18 (0.94–1.48)	0.155
Mode of transmission		
MSM	0.94 (0.84–1.04)	0.244
IDU	1.09 (0.97–1.21)	0.149
Other	1.05 (0.84–1.30)	0.675
CD4 (per doubling)*	0.91 (0.87–0.96)	< 0.001
Use of robust cART	0.91 (0.84–0.97)	0.008
History of ART failure	1.77 (1.61–1.95)	< 0.001
Overall nonadherence	1.37 (1.26–1.49)	< 0.001
Current IDU use	1.54 (1.28–1.86)	< 0.001
Travel as a covariable, per region of origin		
Eur-NAM	0.91 (0.79–1.05)	0.205
SSA	1.30 (1.02–1.65)	0.033
SEA	0.87 (0.53–1.42)	0.574
LAC	0.93 (0.61–1.41)	0.731
Comparing only travel episodes between regions of origin		
Eur-NAM	1	
SSA	2.00 (1.53–2.61)	< 0.001
SEA	0.64 (0.40–1.04)	0.069
LAC	1.20 (0.79–1.83)	0.389

ART, antiretroviral therapy; CI, confidence interval; cART, combination antiretroviral therapy; Eur-NAM, Europe, North America, North Africa, the Middle East, Central Asia, Australia and New Zealand; SSA, sub-Saharan Africa; SEA, Southeast Asia; LAC, Latin America and Caribbean; MSM, men who have sex with men; IDU, injecting drug use.

Bold text indicates significant values.

*base 2 logarithm of CD4 counts.

1.02–1.65; $P = 0.033$); the effect of travel was insignificant in patients from other regions (Fig. 2a).

In an equivalent model comparing patients of Eur-NAM origin with those from other regions within travel and nontravel episodes (Fig. 2b), SSA origin was a risk factor for viral rebound in nontravel episodes (OR 1.41; 95% CI 1.22–1.62; $P < 0.001$) and even more so in travel episodes (OR 2.00; 95% CI 1.53–2.61; $P < 0.001$). SEA origin was significantly protective in nontravel episodes, with an OR of 0.67 (95% CI 0.51–0.88; $P = 0.004$), with no significant effect in travel episodes.

We conducted a further comparison between all VFR travelers in one group (all regions combined, however SSA being the dominant patient group contributing 57% of all VFR travelers) versus nontravelers. Travel was not an additional risk factor for viral rebound compared with nontravel episodes. However, being in the VFR group was a significant risk factor for viral rebound compared with being of Eur-NAM origin in both travel and nontravel

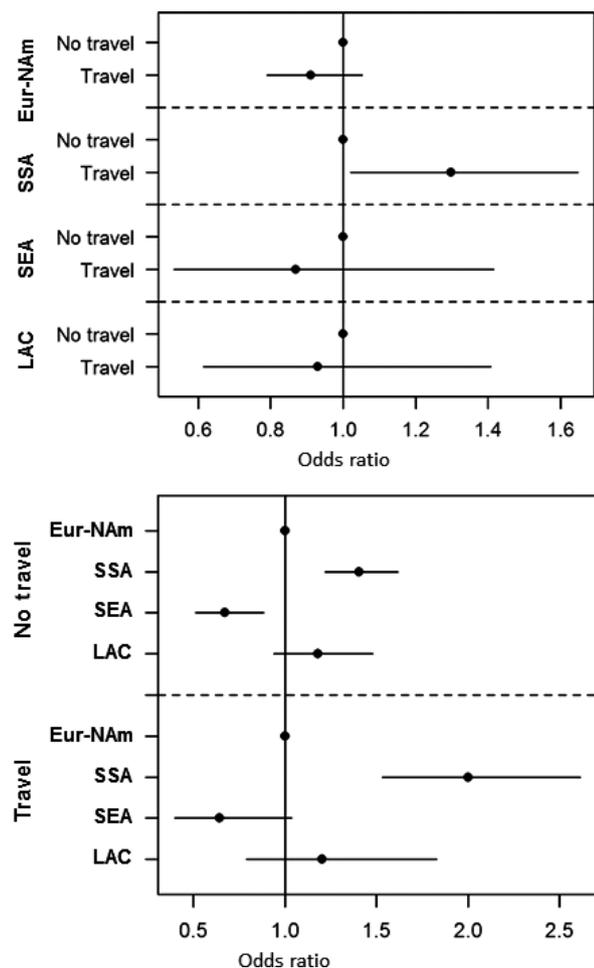


Fig. 2 Adjusted odds ratio of having HIV RNA above 200 c/mL after a previously suppressed VL. Top panel (a): the effect of travel separately in the different regional groups. Bottom panel (b): the effect of region of origin separately in travel and non-travel episodes. Models further adjusted for covariates listed in Table 2. Eur-NAm, Europe, North America, North Africa, the Middle East, Central Asia, Australia or New Zealand; SSA, sub-Saharan Africa; SEA, Southeast Asia; LAC, Latin America and the Caribbean.

episodes, with ORs of 1.20 (95% CI 1.07–1.36; $P = 0.002$) and 1.41 (95% CI 1.12–1.78; $P = 0.004$), respectively.

In a further subgroup analysis, being a frequent traveller was not a risk factor for viral rebound compared with the nontraveller and non-frequent-traveller populations.

Among the 477 travel episodes with viral rebound, in 247 the patient either had persistent viral rebound at post-travel visit 2 or had changed treatment. Treatment change occurred in 89 of these 247 episodes (36%).

In the above selected 247 travel episodes, with all regional categories combined, the following results were obtained for the analysis of resistance emergence: between the pre-travel visit and post-travel visit 1, a total

of 56 resistance tests were performed and 21 (37%) of these tests showed the emergence of at least one new resistance mutation. Between post-travel visit 1 and post-travel visit 2, another 59 resistance tests were performed, 30 (51%) of which demonstrated the emergence of a new resistance mutation.

Sensitivity analyses

Sensitivity analyses were performed on 116 054 episodes (with a pre-visit VL of ≤ 50 copies/mL), of which 11 363 (9.8%) were travel episodes. Viral rebound to > 50 copies/mL was reported in 810 (7.1%) travel episodes and in 7913 (7.6%) nontravel episodes (OR 0.94; 95% CI 0.86–1.02).

At the patient level, this amounted to 10 659 persons contributing to the sensitivity analyses. Of these, 3699 (34.7%) contributed at least one travel episode, and 661 (17.9%) of these had at least one post-travel rebound.

In the multivariable logistic regression analysis predicting the binary outcome of viral rebound > 50 copies/mL, being on robust cART, higher CD4 count and female sex lost their significant effects, while homosexual transmission was significantly protective (OR 0.92; 95% CI 0.84–1.00). The effects of other protective or detrimental factors, including the region of origin, remained unchanged.

Discussion

The proportion of SHCS participants travelling to the tropics has increased substantially since the late 1990s, with patients originating from tropical countries contributing over-proportionately to these figures. This trend is a reflection of the general success of cART, although travellers are still characterized by significantly better HIV-related parameters than nontravellers.

Our primary outcome showed that around 10% of travellers with a pre-travel VL < 200 copies/mL and 18% of those with a pre-travel VL < 50 copies/mL experienced viral rebound above these respective thresholds after a travel episode. Viral rebound was not more common in travel episodes than in nontravel episodes. The travelling population even showed a lower risk for viral rebound when not travelling than the nontravelling patients, indicating that the traveling population was in better health overall than the nontravelling population.

However, evident risk factors for viral rebound after travel were being of SSA origin, current IDU, being younger, having a lower CD4 count, a history of ART failure, using nonrobust cART, and demonstrating poor overall adherence.

The increasing trend for patients of non-Eur-NAM origin within the SHCS to travel is a reflection of the growing number of migrant populations in Switzerland, as is observed world-wide. Typically, migrant populations travel back to the tropics for VFR [20–23] and rarely as tourists. Given the database limitations, we could not ascertain destination of travel within our study. In spite of being a minority within the general population, travellers for VFR comprised the majority of travellers in the USA as well as in Europe [24–26]. Our findings show that the travelling population had higher nadir CD4 counts and less advanced CDC stages, hence showing the “healthy traveller effect”, as was previously seen in the cohort in the pre-cART era [27]. Despite the benefits of cART for all patients, travelling evidently still appears to be an activity enjoyed by those who can afford to take greater risks.

Post-travel viral rebound (> 200 copies/mL) was documented in 477 (3.9%) travel episodes in 405 (10.5%) pre-travel virologically suppressed travellers. In a French study in sub-Saharan African immigrants, viral rebound to > 50 copies/mL was detected at the post-travel visit in 23 (11.5%) of 200 patients who were virologically suppressed at the pre-travel visit. These patients reported a “during trip” nonadherence rate of 11.5% [13]. A small cohort study of HIV-infected Hajj pilgrims from Nigeria on ART showed that a high proportion of patients reported nonadherence: 16 of 31 (55%), with ART failure occurring in 15 of 31 (48.4%) of these patients [14]. We used a very conservative definition for nonadherence as a covariable, by classifying patients as “nonadherent” if they ever indicated having missed more than one dose in a month. In this study, indication of nonadherence increased the odds of having viral rebound > 200 copies/mL by 37%. However, as adherence is only assessed for the 4 weeks immediately preceding the respective follow-up visit, nonadherence during travel could not be fully reflected.

Both the main and the sensitivity analyses revealed that being of SSA origin was linked to a higher risk for viral rebound in travel and nontravel episodes. Patients from SEA had the most stable viral control in travel and nontravel episodes compared with all other regions. When all VFR travellers were analysed together, being a VFR traveller compared with being in the Eur-NAM comparator group was a significant risk factor for viral rebound in travel and particularly in nontravel episodes. This result was, however, driven by the fact that 57% of VFR travellers in this study were of SSA origin. VFR travellers were thus not a uniform group, but the group effect was dominated by the influence of patients from SSA. Possibly, reasons for this difference within the VFR traveller group between SSA patients on the one hand and SEA and LAC patients on the other hand may be that stigma and denial

are still most frequently experienced by SSA patients. Previous studies have underlined self-perceived family support and/or the family’s and the household’s knowledge of the patient’s HIV status as being the most relevant factors for adherence in VFR travellers [13,28]. Despite the growing proportion of VFR travellers world-wide [29], their uptake of pre-travel advice is low [5,6,30]. Taking together the higher risk of viral rebound, as seen in SSA patients in our study, and the data on the risky sexual behaviour of travellers [6,31–33], this may have an impact on HIV transmission in the visited country.

Other factors that should not be ignored regarding ART adherence in travellers are an insufficient supply of medication, lack of availability of the same drugs in the area of destination, unexpected familial events and unstable politics leading to an unexpected prolongation of stay, gastrointestinal upset caused by traveller’s diarrhoea and travel bans for HIV-positive persons [34].

The lack of any negative effect of travel *per se* on viral rebound was a positive and unexpected finding. The finding of virological failure mainly in SSA participants, however, is in line with the findings of previous studies within the SHCS. In these studies, we showed an increasing proportion of SSA participants within the SHCS, and, while initial cART uptake and viral response were similar to those in European patients [35], on longer term analysis SSA participants showed a higher rate of viral rebound on cART [36]. Possibly the more fragile status of most SSA patients in Swiss society, relative to patients from LAC or SEA, may help to explain their inferior viral control, both in nontravel and in travel episodes. While patients from SEA and LAC mainly migrated to Switzerland because of marriage, SSA patients mainly migrated to Switzerland as asylum seekers.

Our analysis thus adds another facet to understanding cART uptake in patients from SSA; in this population, travel appears to accentuate pre-existing weaknesses in viral control.

Development of resistance to ART has been described after travel in other studies [17,37]. In this study, we appreciate that an important percentage (37–51%) of all participants with a resistance test performed after a travel episode demonstrated the emergence of new resistance mutations. So, while travelling might have broadened horizons, it also narrowed future ART options.

The strengths of our study lie in the large sample size, the comprehensive set of data with a long follow-up period for the study population, and the comparison of HIV-infected travellers *vs.* nontravellers at the RNA level, which is a more objective measure than self-reported adherence. The limitations of our study were: (1) the travel question in the SHCS questionnaire does not enquire about the frequency of

travel in the preceding 6 months, the length of stay during travel or the travel destination; (2) the information on adherence was not specific to the travel period itself; and (3) because of the variable time lag between the travel episode and the post-travel RNA determination, rebounds could have been missed as the VL might have normalized again after the return of the traveller and re-uptake of cART.

In conclusion, travelling is increasingly popular among HIV-infected individuals, and is mainly done by HIV-positive patients with preserved immunity. SSA HIV-positive travellers were at highest risk of viral rebound even in nontravel episodes, but especially in travel episodes. Treatment change and emergence of resistance after post-travel viral rebound occurred in a substantial percentage of patients. Thus, advice about travel should be an integral part of pre-ART and on-ART adherence counselling in this particular at-risk population. Travelling in general, however, is not *per se* a risk factor for loss of viral control.

Acknowledgements

We are grateful to the SHCS scientific committee for approving the project and to all the patients who participate in the SHCS.

Conflicts of interest and sources of funding

This study was financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant #148522), by SHCS project #782 and by the SHCS research foundation. The data are gathered by the five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in <http://www.shcs.ch/180-health-care-providers>). Data on emergence of resistance were extracted from the SHCS Drug Resistance database. Work on this database is supported by the Swiss National Science Foundation (grants 33CS30_148522 and 320030_159868); the Swiss HIV Cohort Study (projects 470, 528, 569 and 683); the SHCS Research Foundation; the Yvonne-Jacob Foundation; Gilead, Switzerland (unrestricted grant to the SHCS Research Foundation); and the University of Zurich's Clinical Research Priority Program (Viral infectious diseases: Zurich Primary HIV Infection Study). None of the authors declare any conflicts of interest with regard to this paper.

Appendix : Members of the Swiss HIV Cohort Study group

V. Aubert, M. Battegay, E. Bernasconi, J. Böni, D. L. Braun, H. C. Bucher, A. Calmy, M. Cavassini, A. Ciuffi, G.

Dollenmaier, M. Egger, L. Elzi, J. Fehr, J. Fellay, H. Furrer (Chairman of the Clinical and Laboratory Committee), C. A. Fux, H. F. Günthard (President of the SHCS), D. Haerry (deputy of the "Positive Council"), B. Hasse, H. H. Hirsch, M. Hoffmann, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, T. Klimkait, R. D. Kouyos, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, C. Marzolini, K. J. Metzner, N. Müller, D. Nicca, G. Pantaleo, P. Paioni, A. Rauch (Chairman of the Scientific Board), C. Rudin (Chairman of the Mother & Child Substudy), A. U. Scherrer (Head of Data Centre), P. Schmid, R. Speck, M. Stöckle, P. Tarr, A. Trkola, P. Vernazza, G. Wandeler, R. Weber and S. Yerly.

References

- 1 Elfrink F, van den Hoek A, Sonder GJ. Trends and characteristics among HIV-infected and diabetic travelers seeking pre-travel advice. *Travel Med Infect Dis* 2014; 12: 79–83.
- 2 Aung AK, Trubiano JA, Spelman DW. Travel risk assessment, advice and vaccinations in immunocompromised travellers (HIV, solid organ transplant and haematopoietic stem cell transplant recipients): a review. *Travel Med Infect Dis* 2015; 13: 31–47.
- 3 Franco-Paredes C, Hidron A, Tellez I, Lesesne J, Del Rio C. HIV infection and travel: pretravel recommendations and health-related risks. *Top HIV Med* 2009; 17: 2–11.
- 4 Hochberg NS, Barnett ED, Chen LH *et al.* International travel by persons with medical comorbidities: understanding risks and providing advice. *Mayo Clin Proc* 2013; 88: 1231–1240.
- 5 Kemper CA, Linett A, Kane C, Deresinski SC. Frequency of travel of adults infected with HIV. *J Travel Med* 1995; 2: 85–88.
- 6 Salit IE, Sano M, Boggild AK, Kain KC. Travel patterns and risk behaviour of HIV-positive people travelling internationally. *CMAJ* 2005; 172: 884–888.
- 7 Schuhwerk MA, Richens J, Zuckerman JN. HIV and travel. *Travel Med Infect Dis* 2006; 4: 174–183.
- 8 Nielsen US, Jensen-Fangel S, Pedersen G *et al.* Travelling with HIV: a cross sectional analysis of Danish HIV-infected patients. *Travel Med Infect Dis* 2014; 12: 72–78.
- 9 Gunthard HF, Aberg JA, Eron JJ *et al.* Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA panel. *JAMA* 2014; 312: 410–425.
- 10 Glass TR, Battegay M, Cavassini M *et al.* Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* 2010; 54: 197–203.

- 11 Robbins GK, Cohn SE, Harrison LJ *et al.* Characteristics associated with virologic failure in high-risk HIV-positive participants with prior failure: a post hoc analysis of ACTG 5251. *HIV Clin Trials* 2016; **17**: 165–172.
- 12 Bangsberg DR, Perry S, Charlebois ED *et al.* Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* 2001; **15**: 1181–1183.
- 13 Abgrall S, Fugon L, Lele N *et al.* Visiting one's native country: the risks of nonadherence in HIV-infected sub-Saharan migrants—ANRS VIHVO study. *J Int Assoc Provid AIDS Care* 2013; **12**: 407–413.
- 14 Habib AG, Abdulmumini M, Dalhat MM, Hamza M, Ilyasu G. Anti-retroviral therapy among HIV infected travelers to Hajj pilgrimage. *J Travel Med* 2010; **17**: 176–181.
- 15 Sellier P, Clevenbergh P, Ljubicic L *et al.* Comparative evaluation of adherence to antiretroviral therapy in sub-Saharan African native HIV-infected patients in France and Africa. *Clin Infect Dis* 2006; **43**: 654–657.
- 16 Taylor BS, Reyes E, Levine EA *et al.* Patterns of geographic mobility predict barriers to engagement in HIV care and antiretroviral treatment adherence. *AIDS Patient Care STDS* 2014; **28**: 284–295.
- 17 Woolley I, Bialy C. Visiting friends and relatives may be a risk for non-adherence for HIV-positive travellers. *Int J STD AIDS* 2012; **23**: 833–834.
- 18 Antiretroviral Therapy Cohort C, Vandenhende MA, Ingle S *et al.* Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS* 2015; **29**: 373–383.
- 19 Boillat-Blanco N, Darling KE, Schoni-Affolter F *et al.* Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. *Antivir Ther* 2015; **20**: 165–175.
- 20 Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. *JAMA* 2004; **291**: 2856–2864.
- 21 Centers for Disease Control and Prevention. *Health Information for International Travel: The Yellow Book 2016*. Oxford, Oxford University Press; 2016.
- 22 Fenner L, Weber R, Steffen R, Schlagenhauf P. Imported infectious disease and purpose of travel, Switzerland. *Emerg Infect Dis* 2007; **13**: 217–222.
- 23 Leder K, Tong S, Weld L *et al.* Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. *Clin Infect Dis* 2006; **43**: 1185–1193.
- 24 LaRocque RC, Rao SR, Lee J *et al.* Global TravEpiNet: a national consortium of clinics providing care to international travelers—analysis of demographic characteristics, travel destinations, and pretravel healthcare of high-risk US international travelers, 2009–2011. *Clin Infect Dis* 2012; **54**: 455–462.
- 25 Leder K, Torresi J, Libman MD *et al.* GeoSentinel surveillance of illness in returned travelers, 2007–2011. *Ann Intern Med* 2013; **158**: 456–468.
- 26 Schlagenhauf P, Weld L, Goorhuis A *et al.* Travel-associated infection presenting in Europe (2008–12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. *Lancet Infect Dis* 2015; **15**: 55–64.
- 27 Furrer H, Chan P, Weber R, Egger M, Swiss HIVCS. Increased risk of wasting syndrome in HIV-infected travellers: prospective multicentre study. *Trans R Soc Trop Med Hyg* 2001; **95**: 484–486.
- 28 Nachega JB, Stein DM, Lehman DA *et al.* Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Res Hum Retroviruses* 2004; **20**: 1053–1056.
- 29 Hill DR. The burden of illness in international travelers. *N Engl J Med* 2006; **354**: 115–117.
- 30 Bialy C, Horne K, Dendle C *et al.* International travel in the immunocompromised patient: a cross-sectional survey of travel advice in 254 consecutive patients. *Intern Med J* 2015; **45**: 618–623.
- 31 Vivancos R, Abubakar I, Hunter PR. Foreign travel, casual sex, and sexually transmitted infections: systematic review and meta-analysis. *Int J Infect Dis* 2010; **14**: e842–e851.
- 32 Matteelli A, Odolini S. Travel, syphilis and HIV. *Travel Med Infect Dis* 2014; **12**: 5–6.
- 33 Crougns M, Van den Ende JJ. Away from home: travel and sex. *Lancet Infect Dis* 2013; **13**: 184–185.
- 34 Chang F, Prytherch H, Nesbitt RC, Wilder-Smith A. HIV-related travel restrictions: trends and country characteristics. *Glob Health Action* 2013; **6**: 20472.
- 35 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**: 2237–2244.
- 36 Staehelin C, Keiser O, Calmy A *et al.* Longer term clinical and virological outcome of sub-Saharan African participants on antiretroviral treatment in the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* 2012; **59**: 79–85.
- 37 Mahto M, Ponnusamy K, Schuhwerk M *et al.* Knowledge, attitudes and health outcomes in HIV-infected travellers to the USA. *HIV Med* 2006; **7**: 201–204.