

source: https://doi.org/10.7892/boris.52904 | downloaded: 19.9.2024

Vol. 179, No. 12 DOI: 10.1093/aje/kwu076 Advance Access publication: May 12, 2014

### Practice of Epidemiology

# Social Meets Molecular: Combining Phylogenetic and Latent Class Analyses to Understand HIV-1 Transmission in Switzerland

Dorita Avila, Olivia Keiser, Matthias Egger, Roger Kouyos, Jürg Böni, Sabine Yerly, Thomas Klimkait, Pietro L. Vernazza, Vincent Aubert, Andri Rauch, Sebastian Bonhoeffer, Huldrych F. Günthard, Tanja Stadler, and Ben D. Spycher\* for the Swiss HIV Cohort Study

\* Correspondence to Dr. Ben Spycher, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, CH-3012 Bern, Switzerland (e-mail: bspycher@ispm.unibe.ch).

Initially submitted July 8, 2013; accepted for publication March 11, 2014.

Switzerland has a complex human immunodeficiency virus (HIV) epidemic involving several populations. We examined transmission of HIV type 1 (HIV-1) in a national cohort study. Latent class analysis was used to identify socioeconomic and behavioral groups among 6,027 patients enrolled in the Swiss HIV Cohort Study between 2000 and 2011. Phylogenetic analysis of sequence data, available for 4,013 patients, was used to identify transmission clusters. Concordance between sociobehavioral groups and transmission clusters was assessed in correlation and multiple correspondence analyses. A total of 2,696 patients were infected with subtype B, 203 with subtype C, 196 with subtype A, and 733 with recombinant subtypes (mainly CRF02\_AG and CRF01\_AE). Latent class analysis identified 8 patient groups. Most transmission clusters of subtype B were shared between groups of gay men (groups 1–3) or between the heterosexual groups "heterosexual people of lower socioeconomic position" (group 4) and "injection drug users" (group 8). Clusters linking homosexual and heterosexual groups were associated with "older heterosexual and gay people on welfare" (group 5). "Migrant women in heterosexual partnerships" (group 6) and "heterosexual migrants on welfare" (group 7) shared non-B clusters with groups 4 and 5. Combining approaches from social and molecular epidemiology can provide insights into HIV-1 transmission and inform the design of prevention strategies.

HIV; HIV-1 transmission; injection drug use; latent class analysis; phylogenetics; sexual orientation; socioeconomic position; Switzerland

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; LCA, latent class analysis; MCA, multiple correspondence analysis; SEP, socioeconomic position; SHCS, Swiss HIV Cohort Study.

Switzerland has been more severely affected by the human immunodeficiency virus (HIV) type 1 (HIV-1) epidemic than have other countries in Western Europe, as documented by a higher adult HIV-1 prevalence (0.4% in 2009) compared with, for example, Germany (0.1%) or the Netherlands (0.2%) (1). HIV-1 is the most common strain of the virus, while the other major strain, HIV type 2 (HIV-2), is rarely seen outside of Africa. As is typical for Western Europe, the main risk groups include gay men, injection drug users, and people acquiring HIV-1 through heterosexual intercourse. Whereas infections due to sharing of contaminated injecting equipment have been reduced considerably in Switzerland (1), the number of new infections in gay men has increased since 2000. This is probably due to continuing high-risk sexual behavior, particularly by persons who are unaware of their infection status (2). Furthermore, infections acquired abroad, either during travel or due to immigration from sub-Saharan Africa or Asia, have become important, with an increasing proportion of non-B subtypes being found among persons diagnosed in recent years (3, 4).

The rapid evolution of HIV-1 makes it possible to infer epidemiologic patterns from sequence data (5, 6). In the Swiss HIV Cohort Study (SHCS), a nationwide cohort of people living with HIV infection/acquired immunodeficiency syndrome (AIDS) in Switzerland (7), phylogenetic analyses found that the majority of clusters representing ongoing transmission in Switzerland were linked to gay men (8). Previous SHCS analyses (4, 8) focused on the main HIV transmission groups, but these consist of heterogeneous groups of patients, including young and older gay men, migrants, people of higher or lower socioeconomic position (SEP), and current and former injection drug users. An alternative approach to analyzing differences between transmission groups is to examine how relevant sociobehavioral characteristics cluster across patients. Originally developed in the social sciences, latent class analysis (LCA) (9) is increasingly being used for this purpose in medical research. The method assumes that the population is composed of distinct subpopulations (latent classes), which are not directly observed but are inferred from the observed characteristics of individuals. In the SHCS, Keiser et al. (10) recently used LCA to identify sociobehavioral groups and to examine outcomes of antiretroviral therapy across these groups.

In the present study, we sought to combine social and molecular epidemiology to investigate likely transmission patterns of HIV-1, based on phylogenetic analyses of *pol* sequences, between sociobehavioral groups identified in LCA.

#### METHODS

#### Study population

Established in 1988, the SHCS is an ongoing nationwide, prospective Swiss cohort study that includes information on over 15,000 patients (7). A comparison of cohort data with official AIDS notifications indicated that approximately 70% of all persons living with HIV/AIDS in Switzerland participate in the SHCS (11). A recent comparison with drugsales data showed that 75% of antiretroviral drug prescriptions in Switzerland can be attributed to study participants (7). Sequence data from routine viral-load tests and systematic retrospective sequencing from the SHCS sample repository are available for about 70% of the enrolled patients. Since the year 2000, a questionnaire on sociodemographic and behavioral data has been completed by the treating physician at the time of study enrollment and during semiannual visits. All participants provided informed consent.

#### Identification of sociobehavioral groups

We used LCA (9, 12) to identify groups of patients with similar sociodemographic and behavioral characteristics. This analysis was an update of Keiser et al.'s previously published LCA (10). We included all persons who enrolled in the SHCS between 2000 and 2011. The LCA included the following categorical variables at cohort registration: sex, age (in categories: <25, 25–34, 35–44, 45–54, or  $\geq$ 55 years), region of origin (Switzerland and northwestern Europe, Southern Europe, sub-Saharan Africa, Latin America, or Asia and Eastern Europe), level of education (compulsory schooling, vocational training, or higher education), occupation (self-employed, apprentice or trainee, higher-level management, middle- or lower-level management, employee, or house-wife/homemaker), main source of income (salaried work,

support from family or partner, or welfare benefits), sexual orientation (heterosexual, bisexual, or homosexual), main sexual partnership pattern (no partner, unprotected sex with stable partner, protected sex with stable partner, unprotected sex with occasional partner, or protected sex with occasional partner), history of injection drug use (never, ever, or current user), and alcohol consumption (severe, moderate, or light, according to World Health Organization criteria (13)). These variables cover all demographic, socioeconomic, and behavioral factors on which data are collected in the SHCS and which, in our view, might be associated with HIV transmission. To characterize patient groups identified by LCA, the SEP of patients was defined as higher or lower, based on educational attainment and occupation.

LCA assumes that the population consists of subpopulations (latent classes) that differ in their distributions of the included variables, and that within latent classes these variables are independent. We used the Bayesian Information Criterion to select the number of classes, thus balancing parsimony and model fit (12). For each patient, we computed posterior probabilities of belonging to the different latent classes of a fitted model. We allocated individuals to the groups for which they had the highest posterior membership probability (12). We fitted the LCA models using Mplus, version 6.1 (14). More details on the LCA are provided in the Web Appendix (available at http://aje.oxfordjournals.org/).

#### **Phylogenetic analysis**

All laboratories performing genotypic resistance testing in Switzerland participate in the SHCS drug resistance database (15). These laboratories sequence at least the full protease enzyme and part of the reverse transcriptase enzyme using inhouse methods (16) or commercial assays (ViroSeq, version 1 (PE Biosystems, Rotkreuz, Switzerland); ViroSeq, version 2 (Abbott AG, Baar, Switzerland); or vircoTYPE HIV-1 Assay (Virco BVBA, Mechelen, Belgium)). For the phylogenetic analysis, we included all patients for whom sequence data were available. In the case of multiple sequences, the oldest sequence was retained.

In order to identify domestic transmission clusters, we first split the data into the major subtypes. Within a subtype, we then randomly selected the same number of sequences from other countries using the Los Alamos Sequence Database (8, 17). Viral sequences from domestic transmission chains are expected to cluster with SHCS sequences rather than with Los Alamos sequences, while sequences from infections acquired abroad will not show such clustering. Antiretroviral treatment may lead to convergent evolution, thus distorting phylogenetic analyses. Therefore, we removed all major amino-acid positions associated with antiretroviral drug resistance, following the International AIDS Society (IAS)–USA guidelines (18).

We inferred the maximum-likelihood tree per major subtype with a GTRCAT model implemented in RaxML (19) and used 100 bootstrap trees to define the strength of support for nodes in the maximum-likelihood tree. A subtype K Los Alamos sequence was used as the outgroup—that is, a reference group that is related to all sequences but whose relationship is expected to be less close than any of the other sequences. Trees were plotted with FigTree software (http://tree.bio.ed. ac.uk/software/figtree/). For every subtype, the maximumlikelihood tree was explored using the *ape* package in R (20). We inferred transmission clusters as described by Hue et al. (6) and as in previous SHCS publications (4, 8). SHCS clusters were defined as clusters with greater than 70% bootstrap support and more than 70% of persons from the SHCS.

# Concordance of sociobehavioral groups and phylogenetic clusters

We cross-tabulated sociobehavioral groups (columns) against SHCS phylogenetic clusters (rows) and analyzed the table in 2 ways. First, we calculated pairwise Pearson correlation coefficients for correlations between columns—that is, the correlation between each pair of sociobehavioral groups regarding the frequency with which they appeared in the different clusters. A substantial correlation between 2 groups indicates that patients from these groups appear in the same phylogenetic clusters, suggesting between-group transmission. Coefficients up to 0.4 were considered to reflect weak correlations, coefficients between 0.4 and 0.7 to reflect strong correlations.

Second, we used multiple correspondence analysis (MCA) to obtain a 2-dimensional representation of columns and rows and their interdependencies (21). In MCA plots, sociobehavioral groups lie close together if their members appear in the same phylogenetic clusters, while phylogenetic clusters are

positioned close to each other if they have a similar composition of sociobehavioral groups (21). In the full-dimensional MCA representation, of which we display only the 2 main dimensions, phylogenetic clusters are positioned at the barycenter (center of gravity) of the sociobehavioral groups they consist of, with the sociobehavioral groups having weights equal to their proportion in the phylogenetic cluster. Analyses were conducted for all subtypes, subtype B, and non-B subtypes.

### RESULTS

#### Study population

All 6,027 patients who enrolled in the SHCS from 2000 to 2011 were included in the LCA analyses. Among these persons, 4,013 patients (66.6%) had viral sequence data available and 3,581 patients (59.4%) had eligible subtypes; 1,662 patients (27.6%) were part of an SHCS cluster (Figure 1). Patients with viral DNA sequences were similar to all patients enrolled in the SHCS with respect to age and sex, history of injection drug use, self-reported sexual contacts, region of origin, and main source of income (Table 1). The proportion of heterosexual patients was higher among those included in the phylogenetic analyses (54.8% vs. 37.5% among all patients). As expected, patients included in SHCS clusters were more likely to be from Switzerland or northwestern Europe in comparison with all patients. They were also more likely to be gay men and to report former or current injection drug use (Table 1).



Figure 1. Selection of populations for an analysis of likely human immunodeficiency virus (HIV) type 1 transmission patterns in the Swiss HIV Cohort Study, 2000–2011. The numbers of patients included in the latent class analysis, the phylogenetic analysis, and the cluster analysis are shown.

	Latent Class Analysis ( <i>n</i> = 6,027)		Phylogen Analysis ( <i>n</i> =	etic 4,013)	Analysis of SHCS Clusters ( <i>n</i> = 1,662)		
	No.	%	No.	%	No.	%	
No. of women	1,766	29.3	1,104	27.5	327	19.7	
Median age, years	37 (35–45) <sup>a</sup>		37 (35–45)		37 (35–45)		
Region of origin							
Switzerland or northwestern Europe	3,761	62.4	2,578	64.2	1,234	74.2	
Southern Europe	461	7.6	308	7.7	135	8.1	
Sub-Saharan Africa	977	16.2	596	14.9	90	5.4	
Latin America	250	4.1	157	3.9	44	2.6	
Asia or Eastern Europe	392	6.5	254	6.3	114	6.9	
Other or unknown	186	3.1	120	3.0	45	2.7	
Occupation							
Student or trainee	162	2.7	121	3.0	40	2.4	
Employee	2,569	42.6	1,931	48.1	836	50.3	
Middle or lower management	520	8.6	413	10.3	181	10.9	
Higher management	209	3.5	157	3.9	66	4.0	
Self-employed	599	9.9	447	11.1	179	10.8	
Housewife/homemaker	230	3.8	154	3.8	41	2.5	
Other or unknown	1,738	28.8	790	19.7	319	19.2	
Main source of income							
Salaried work	3,554	59.0	2,464	61.4	1,095	65.9	
Support from family or partner	656	10.9	399	9.9	117	7.0	
Welfare benefits	1,756	29.1	1,119	27.9	443	26.7	
Other or unknown	61	1.0	31	0.8	7	0.4	
Sexual orientation							
Homosexual	2,260	37.5	1,563	38.9	754	45.4	
Bisexual	338	5.6	236	5.9	109	6.6	
Heterosexual	3,393	56.3	2,199	54.8	793	47.7	
Unknown	36	0.6	15	0.4	6	0.4	
Sexual contacts							
No partner	1,042	17.3	647	16.1	232	14.0	
Unprotected sex with stable partner	1,185	19.7	796	19.8	308	18.5	
Protected sex with stable partner	1,135	18.8	695	17.3	278	16.7	
Unprotected sex with occasional partner	1,089	18.1	822	20.5	389	23.4	
Protected sex with occasional partner	985	16.3	687	17.1	302	18.2	
Unknown	591	9.8	366	9.1	153	9.2	
History of injection drug use							
Never user	5,149	85.4	3,445	85.8	1,354	81.5	
Former user	646	10.7	380	9.5	204	12.3	
Current user	232	3.8	188	4.7	104	6.3	

 Table 1.
 Characteristics of Patients Included in the Latent Class Analysis, the Phylogenetic Analysis, and the Analysis of SHCS Clusters, Swiss HIV Cohort Study, 2000–2011

Abbreviations: HIV, human immunodeficiency virus; SHCS, Swiss HIV Cohort Study.

<sup>a</sup> Numbers in parentheses, interquartile range (25th–75th percentiles).

#### Sociobehavioral groups

The LCA identified 8 distinct sociobehavioral groups, which are described in Appendix Table 1 and Web Table 1. A comparison of fit statistics for models with 1–10 classes

and model results for the selected 8-class model are given in Web Tables 2 and 3, respectively. Three of the 8 groups were dominated by gay men but differed with respect to age, SEP, migrant status, and sexual partnership patterns. These 3 groups are numbered 1–3 and are described as "gay and bisexual men of lower SEP," "gay and heterosexual men of higher SEP," and "young gay migrant men," respectively. Groups 4–7 were dominated by people who acquired HIV heterosexually. These groups again differed in terms of age, SEP, migrant status, and partnership type, and additionally with regard to dependence on welfare benefits. These 4 groups are described as "heterosexual people of lower SEP," "older heterosexual and gay people on welfare benefits," "migrant women in heterosexual partnerships," and "heterosexual migrants on welfare benefits." Group 8 consisted of people with former or current injection drug use ("injection drug users"). The posterior probabilities of belonging to the different latent classes ranged from 0.78 among gay and heterosexual men of higher SEP to 0.98 among injection drug users.

#### Phylogenetic analysis

Of the 4,013 patients with phylogenetic data, 2,696 (67.2%) were infected with HIV-1 subtype B. Other major subtypes included CRF02\_AG (n = 272; 6.8%), CRF01\_AE (n = 214; 5.3%), C (n = 203; 5.1%), and A (n = 196; 4.9%). The remaining subtypes were poorly represented (<2%) and were excluded (Figure 1). The maximum-likelihood phylogenetic trees for all of the major subtypes (A, B, C, CRF02\_AG, and CRF01\_AE) are shown in Web Figures 1–5.

The prevalences of the different subtypes across the 8 sociobehavioral groups are shown in Figure 2. Subtype B dominated in the 3 groups of gay men (87%–94%). Injection drug users had the highest prevalence of subtype B (95%), whereas heterosexual migrants on welfare benefits had the lowest prevalence (11%). Subtypes of African origin (A, 02\_AG, and C) dominated the latter group (85%) and were also highly prevalent among migrant women in heterosexual partnerships (56%). The subtype of Asian origin (01\_AE) was also prevalent among migrant women in partnerships (20%), older heterosexual and gay people on welfare benefits (9%), and heterosexual people of lower SEP (8%).

#### **Phylogenetic clusters**

We identified 195 SHCS clusters including a total of 1,964 sequences, of which 1,662 belonged to SHCS patients. There were 140 B subtype clusters and 55 clusters of non-B subtypes: subtypes A (11 clusters), C (13 clusters), 01\_AE (14 clusters), and 02\_AG (17 clusters). The mean number of SHCS patients in SHCS clusters was larger for B clusters than for non-B clusters (subtype B: 10.0 (range, 2–150); subtype A: 6.2 (range, 2–21); subtype C: 3.1 (range, 2–7); subtype 01\_AE: 6.9 (range, 2–21); subtype 02\_AG: 3.6 (range, 2–8)). Thirteen B clusters had over 20 SHCS sequences.

### Concordance of sociobehavioral groups and phylogenetic clusters

Table 2 shows Pearson correlation coefficients for correlations between sociobehavioral groups and phylogenetic clusters for all virus subtypes, the B subtype, and non-B subtypes (95% confidence intervals for these coefficients are reported in Web Table 4). When all subtypes were included in the



Figure 2. Distribution of subtypes of human immunodeficiency virus (HIV) type 1 across 8 sociobehavioral groups in the Swiss HIV Cohort Study, 2000–2011. A) Gay and bisexual men of lower socioeconomic position (SEP); B) gay and heterosexual men of higher SEP; C) young gay migrant men; D) heterosexual people of lower SEP; E) older heterosexual and gay people on welfare benefits; F) migrant women in heterosexual partnerships; G) heterosexual migrants on welfare benefits; H) injection drug users.

analyses, moderate or strong correlations were found between the groups of gay men (groups 1–3; r = 0.59-0.77). Somewhat weaker correlations were observed between these groups and the group of hetero- and homosexual people on welfare benefits (group 5; r = 0.34-0.67). The latter group was also correlated with heterosexual people of lower SEP (group 4; r = 0.75) and injection drug users (group 8; **Table 2.** Pearson Correlation Coefficients for Correlations Between Pairs of Sociobehavioral Groups Across Swiss Transmission Clusters (AllSubtypes, B Subtype Only, and Non-B Subtypes), Swiss HIV Cohort Study, 2000–2011

	Sociobehavioral Group							
Sociobehavioral Group	1) Gay and Bisexual Men of Lower SEP	2) Gay and Heterosexual Men of Higher SEP	3) Gay Migrant Men	4) Heterosexual People of Lower SEP	5) Older Heterosexual and Gay People on Welfare Benefits	6) Migrant Women in Heterosexual Partnerships	7) Heterosexual Migrants on Welfare Benefits	
All subtypes								
<ol> <li>Gay and heterosexual men of higher SEP</li> </ol>	0.77 <sup>a</sup>							
3) Gay migrant men	0.65 <sup>a</sup>	0.59 <sup>a</sup>						
4) Heterosexual people of lower SEP	0.17	0.49 <sup>a</sup>	0.17					
<ol> <li>Older heterosexual and gay people on welfare benefits</li> </ol>	0.48 <sup>a</sup>	0.67 <sup>a</sup>	0.34 <sup>a</sup>	0.75 <sup>a</sup>				
6) Migrant women in heterosexual partnerships	-0.07	0.08	0.12	0.43 <sup>a</sup>	0.28			
<ol> <li>Heterosexual migrants on welfare benefits</li> </ol>	-0.02	0.07	0.04	0.30	0.24	0.35		
8) Injection drug users	0.11	0.45 <sup>a</sup>	0.11	0.91 <sup>a</sup>	0.65 <sup>a</sup>	0.34	0.24	
B subtype								
<ol> <li>Gay and heterosexual men of higher SEP</li> </ol>	0.76 <sup>a</sup>							
3) Gay migrant men	0.68 <sup>a</sup>	0.62 <sup>a</sup>						
4) Heterosexual people of lower SEP	0.18	0.51 <sup>a</sup>	0.17					
<ol> <li>Older heterosexual and gay people on welfare benefits</li> </ol>	0.52 <sup>a</sup>	0.71 <sup>a</sup>	0.36	0.77 <sup>a</sup>				
<ol> <li>6) Migrant women in heterosexual partnerships</li> </ol>	0.03	0.33	0.04	0.75 <sup>a</sup>	0.49 <sup>a</sup>			
<ol> <li>Heterosexual migrants on welfare benefits</li> </ol>	0.21	0.40	0.26	0.67 <sup>a</sup>	0.53 <sup>a</sup>	0.61 <sup>a</sup>		
8) Injection drug users	0.09	0.45 <sup>a</sup>	0.11	0.93 <sup>a</sup>	0.69 <sup>a</sup>	0.75 <sup>a</sup>	0.67 <sup>a</sup>	
Non-B subtypes								
<ol> <li>Gay and heterosexual men of higher SEP</li> </ol>	0.47 <sup>a</sup>							
3) Gay migrant men	0.23	0.15						
4) Heterosexual people of lower SEP	-0.14	0.15	0.14					
<ol> <li>Older heterosexual and gay people on welfare benefits</li> </ol>	0.02	0.34	0.12	0.49 <sup>a</sup>				
<ol> <li>6) Migrant women in heterosexual partnerships</li> </ol>	-0.1	-0.08	0.53 <sup>a</sup>	0.47 <sup>a</sup>	0.22			
<ol> <li>Heterosexual migrants on welfare benefits</li> </ol>	-0.17	-0.05	-0.04	0.19	0.15	0.13		
8) Injection drug users	-0.15	-0.13	-0.12	0.04	-0.12	-0.13	-0.13	

Abbreviations: HIV, human immunodeficiency virus; SEP, socioeconomic position; SHCS, Swiss HIV Cohort Study.

<sup>a</sup> Value > 0.4.

r = 0.65). Migrant women in heterosexual partnerships (group 6) were moderately associated with heterosexual people of lower SEP (group 4; r = 0.43). Heterosexual migrants receiving welfare benefits (group 7) were only weakly associated with the other groups with predominantly heterosexual orientation (r = 0.24-0.35). Finally, injection drug users showed a strong association with heterosexual people of lower SEP (r = 0.91).

When analyses were restricted to subtype B, correlations tended to get stronger. In particular, correlations involving the groups of migrants and those including injection drug users became more prominent. Many correlations disappeared or weakened when analyses were restricted to non-B subtypes, while 1 new association (between migrant women in heterosexual partnerships and homosexual young migrant men) emerged for non-B subtypes (r = 0.53) (Table 2).

#### Geometric representation of data using MCA

Associations between sociobehavioral LCA groups and SHCS phylogenetic clusters are shown geometrically in Figure 3 for all HIV-1 subtypes (part A), subtype B (part B), and non-B subtypes (part C). In all analyses, the first 2 axes explained over 50% of the association (as measured by the  $\chi^2$  metric) between sociobehavioral groups and phylogenetic clusters. In the analysis of all subtypes, the 3 groups dominated by homosexual men (groups 1-3) are located in close vicinity around a concentration of clusters with sequences almost entirely from these groups. To the bottom right are clusters containing predominantly sequences from heterosexual people of lower SEP (group 4) and injection drug users (group 8). In between, in the vicinity of hetero- and homosexual people on welfare benefits (group 5), there is another concentration of phylogenetic clusters containing sequences of both homosexual and heterosexual patient groups. Smaller clusters with sequences from the 2 heterosexual migrant groups are found towards the upper right corner (groups 6 and 7). Thus, axis 1 distinguished phylogenetic clusters dominated by men who have sex with men from clusters dominated by heterosexuals and injection drug users, while axis 2 distinguished small clusters involving heterosexual



Axis 1 (28%)

Figure 3. Concordance between sociobehavioral groups and human immunodeficiency virus (HIV) type 1 (HIV-1) phylogenetic clusters in the Swiss HIV Cohort Study (results from multiple correspondence analysis), 2000–2011. A) All HIV-1 subtypes; B) subtype B; C) non-B subtypes. The figure shows the 2 main axes explaining most of the associations between the sociobehavioral groups and the phylogenetic clusters, as measured by the  $\chi^2$  metric (percentage in parentheses). The proximity between sociobehavioral groups (circles) reflects their tendency to co-occur in the same phylogenetic clusters, while phylogenetic clusters (squares) are positioned in the proximity of the groups for which they contain the most sequences. The 8 sociobehavioral groups are numbered as: 1) gay and bisexual men of lower socioeconomic position (SEP); 2) gay and heterosexual men of higher SEP; 3) young gay migrant men; 4) heterosexual people of lower SEP; 5) older heterosexual and gay people on welfare benefits; 6) migrant women in heterosexual partnerships; 7) heterosexual migrants on welfare benefits; and 8) injection drug users.

migrant groups from the large clusters involving heterosexual Swiss-dominated groups. Patterns were similar when the analysis was restricted to B subtypes, with a reduced representation of migrant groups (Figure 3, part B).

The picture changed when we focused on non-B subtypes: The 2 heterosexual migrant groups (groups 6 and 7) and the heterosexual men and women of lower SEP (group 4) were now closely associated, with many shared phylogenetic clusters (Figure 3, part C). The hetero- and homosexual people on welfare benefits (group 5) were found in the vicinity. Furthermore, homosexual migrant men (group 3) and homo- and heterosexual men of higher SEP (group 2) were represented both in said clusters and in the few clusters associated with injection drug users (group 8).

#### DISCUSSION

By combining sociobehavioral data with phylogenetic transmission clusters, we characterized the Swiss HIV epidemic in greater depth and identified possible routes of HIV transmission between groups. These groups were described not only by sexual orientation or injection drug use but also by socioeconomic and migrant status or main source of income. We found phylogenetic clusters that were shared between homosexual and heterosexual patient groups, suggesting that there is transmission between these subepidemics. In particular, the group of older heterosexual and gay people on welfare benefits might act as a bridge between homosexual and heterosexual clusters, whereas injection drug users were associated with heterosexual people of lower SEP. Domestic transmission of non-B subtypes happened primarily through heterosexual contact with migrants: Migrant women in partnerships and single migrants on welfare shared phylogenetic clusters with heterosexual people of lower SEP and older hetero- and homosexual people supported by welfare.

#### Limitations

Much of the information used to define the sociobehavioral groups was self-reported and therefore potentially biased. For example, unprotected sex and sex between men may have been underreported, and protected and heterosexual sex may have been overreported. Reporting behavior may have differed by socioeconomic or migrant status. Collection of some of the sociodemographic information commenced in 2000, which limited the size and period covered by the study, and some relevant information was missing—for example, information on commercial sex work.

Sequences were available for only about 70% of patients included in the LCA, but patients with sequences were similar to all patients. Routine resistance testing in drug-naive patients was introduced from 2003 onwards. Patients who started antiretroviral therapy earlier and whose antiretroviral treatment never failed did not have a resistance test. Furthermore, patients presenting to health-care providers with AIDS-defining conditions often receive antiretroviral therapy in the hospital, and their virus levels are often undetectable by the time they are enrolled in the SHCS. We assigned patients to sociobehavioral groups based on the highest membership probabilities, thus ignoring membership uncertainty. However,

because mean membership probabilities for the most likely class were high (>0.76; Web Table 3), we do not think this had a major impact on our results. The phylogenetic analysis was limited by common caveats, such as incompleteness of transmission chains and sampling, as well as temporal biases affecting the proportion of subtypes. The high national representativeness of the data set makes such biases less likely. Bootstrap support in the best trees was low in many of the clusters; this could have resulted in loss of domestic clusters. The size of clusters was typically small for non-B subtypes, which limited statistical power to detect associations between sociobehavioral groups for these subtypes.

Finally, we interpreted co-occurrence in the same phylogenetic cluster as indicating increased likelihood of transmission between 2 individuals. We acknowledge that there might be assortative mixing among patients whose viral sequences are in the same phylogenetic cluster. For instance, a phylogenetic cluster with sequences from both gay men and heterosexual people is compatible with both frequent mixing between these groups and predominant mixing within groups, with few transmissions between groups.

## Comparison with previous studies of HIV-1 transmission in Switzerland

Kouyos et al. (8) previously investigated subtype B transmission in Switzerland using data from the SHCS and similar phylogenetic methods. As in the present study, they found that most domestic transmission clusters fell into one of 2 broad groups: those dominated by homosexual transmission among men and those dominated by transmission through heterosexual contact and injection drug use. Their analysis did not allow a more detailed characterization of the patient groups involved. For example, the analysis could not identify the different migrant groups associated with the gay male epidemic and the heterosexual epidemic. Von Wyl et al. (4) found that the epidemic of non-B subtypes was primarily maintained through reintroduction from abroad but that domestic heterosexual transmission also played a role. Their results are in line with the findings of the present study, which additionally showed that this epidemic specifically involves Swiss or European people of lower SEP and migrant women in stable partnerships, but also migrants without stable partnerships.

#### Possible mechanisms

Transmission between groups of gay men and different heterosexual groups, as indicated by our data, would likely occur through men who have sex with both men and women. All groups dominated by homosexual men included a minority of men reporting a bisexual orientation (8.5%-11.1%). Bisexual orientation was rarely reported among the other groups, with the exception of the older heterosexual and gay people on welfare (6.6% bisexual) and injection drug users (3.8% bisexual). Switzerland lacks a dedicated survey of sexual behavior, such as the British National Survey of Sexual Attitudes and Lifestyles (22), but based on other surveys (23), the prevalence of bisexuality reported by some groups (e.g., people of lower SEP (0.1%)) was lower than anticipated and thus compatible with underreporting. The largest clusters of heterosexual transmission were of the B subtype and dominated by heterosexual people of lower SEP and injection drug users. Heterosexual people of lower SEP also played an important role in the transmission of non-B subtypes while injection drug users did not, suggesting that among heterosexuals, those who engage in sex with migrants are different from those engaging in contact with injection drug users. It seems likely that there is more heterogeneity with respect to sexual mixing between predominantly heterosexual groups, which was not fully captured by our sociobehavioral classification.

The group of older heterosexual and gay men is of particular interest, for several reasons. It was represented in both the heterosexual clusters involving injection drug users and the smaller clusters involving migrant groups, but it was also represented in clusters dominated by men who have sex with men. This heterogeneous group of older HIV-1-positive people is rapidly growing in Switzerland and elsewhere (24) and includes both people who are aging with the disease and people who acquired the infection later in life. These men may perceive themselves to be less at risk for HIV (24), and they may be socially more isolated than younger men and therefore more vulnerable (25). Some of their contacts with either young homosexual migrants or young migrant women may involve commercial sex. The lower-SEP groups may be more vulnerable and more difficult to reach, and these groups also included many older people. Migrants are another fast-growing segment of the Swiss HIV-positive population. Although many infections are probably acquired abroad, our data showed that different groups of gay men and heterosexual groups shared phylogenetic clusters with migrant groups, suggesting that there is domestic propagation, perhaps driven to some extent by commercial sex and older men.

#### Conclusions

In this study, LCA enabled us to characterize the subgroups involved in the Swiss HIV epidemic in greater detail than in previous phylogenetic studies of this Swiss cohort (4, 8), while the phylogenetic analyses uncovered associations between sociobehavioral groups not previously documented. The combination of social science and epidemiologic tools in this study represents a novel approach, which should help inform the development of strategies to prevent the spread of HIV in Switzerland. In particular, specific HIV prevention strategies for older men, bisexual men, and migrants-strategies that respect the human rights of HIV-positive people and avoid stigmatization-should be prioritized. Indeed, qualitative research into the needs and preferences of the groups identified in this study is a logical next step, to ensure that any targeted health promotion programs are not inadvertently stigmatizing (26).

#### **ACKNOWLEDGMENTS**

Author affiliations: Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Dorita Avila, Olivia Keiser, Matthias Egger, Ben D. Spycher); Institute for Integrative Biology, ETH Zurich, Zurich, Switzerland (Dorita Avila, Sebastian Bonhoeffer); Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa (Matthias Egger); Institute of Medical Virology, Swiss National Center for Retroviruses, University of Zurich, Zurich, Switzerland (Jürg Böni); Laboratory of Virology, Department of Genetics and Laboratory Medicine, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Geneva, Switzerland (Sabine Yerly); Department of Biomedicine, Faculty of Medicine, University of Basel, Basel, Switzerland (Thomas Klimkait); Division of Infectious Diseases, Cantonal Hospital St. Gallen, St. Gallen, Switzerland (Pietro L. Vernazza); Division of Immunology and Allergy, Department of Laboratory Medicine, Lausanne University Hospital, Lausanne, Switzerland (Vincent Aubert); Department of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland (Andri Rauch); Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland (Huldrych F. Günthard, Roger Kouvos); and Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland (Tanja Stadler).

T.S. and B.S. contributed equally to this work.

This work was funded within the framework of the Swiss HIV Cohort Study (SHCS), supported by the Swiss National Science Foundation (grants 33CS30-134277, 33CS30-148522, and PZ00P3-136820 to T.S., grant 324730-130865 to H.F.G., and SHCS projects 470, 528, 569, and 687), the SHCS Research Foundation, the European Community's Seventh Framework Program (grant FP7/2007-2013), the Collaborative HIV and Anti-HIV Drug Resistance Network (grant 223131 to H.F.G.), and the Yvonne-Jacob Foundation (grant A/B1113 to H.F.G.), as well as an anonymous research grant from the Union Bank of Switzerland (grant DRDB8910 to H.F.G.), an unrestricted research grant to the SHCS Research Foundation from Gilead Sciences Switzerland Sàrl (Zug, Switzerland), and the University of Zurich's Clinical Research Priority Program: Viral Infectious Diseases-ZPHI Study. O.K., R.K., and B.D.S. were supported by Swiss National Science Foundation fellowships (grants 32333B\_131629/1, PZ00P3\_142411, PZ00P3\_ 147987/1, and PZ00P3 136820, respectively).

We thank the SHCS physicians and nurses for excellent patient care; the resistance laboratories for high-quality genotypic drug resistance testing; SmartGene, Inc. (Zug, Switzerland), for technical support; Brigitte Remy, Dr. Martin Rickenbach, Dr. Franziska Schoeni-Affolter, and Yannick Vallet from the SHCS Data Center in Lausanne for data management; and Daniele Perraudin and Mirjam Minichiello for administrative assistance.

The SHCS investigators: V. Aubert, J. Barth, M. Battegay, E. Bernasconi, J. Böni, H. C. Bucher, C. Burton-Jeangros, A. Calmy, M. Cavassini, M. Egger, L. Elzi, J. Fehr, J. Fellay, H. Furrer (Chairman of the Clinical and Laboratory Committee), C. A. Fux, M. Gorgievski, H. Günthard (President of the SHCS), D. Haerry (deputy of the "Positive Council"), B. Hasse, H. H. Hirsch, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, T. Klimkait, R. Kouyos, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, K. Metzner, N. Müller, D. Nadal, G. Pantaleo, A. Rauch (Chairman of the Scientific Board), S. Regenass, M. Rickenbach (head of the Data Center), C. Rudin (Chairman of the Mother & Child Substudy), F. Schöni-Affolter, P. Schmid, D. Schultze, J. Schüpbach, R. Speck, C. Staehelin, P. Tarr, A. Telenti, A. Trkola, P. Vernazza, R. Weber, and S. Yerly.

None of the funding bodies played any role in the study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

Conflict of interest: none declared.

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(Appendix follows)

			Characteristic								
Sociobehavioral Group	No. of Participants	% of Participants	Median Age, years (IQR <sup>b</sup> )	% Women	Region of Origin	Education	Occupation	Main Source of Income	Sexual Orientation	Sexual Partnership Pattern	Substance Use
1) Gay and bisexual men of lower SEP	1,478	24.5	37 (31–42)	0	85% were from Switzerland or Northern or Western Europe.		77% had vocational training; 52% worked as manual or nonmanual employees.		85% homosexual; 11% bisexual	67% reported occasional partners, and 34% reported unprotected sex with occasional partners.	
2) Gay and heterosexual men of higher SEP	873	14.5	43 (37–49)	0	85% were from Switzerland or Northern or Western Europe.	97% had a university degree.	Most (66%) worked in middle or higher management or were self- employed.		73% homosexual; 17% heterosexual	54% reported occasional partners, with 29% reporting unprotected sex with occasional partners.	
3) Young gay migrant men	316	5.2	30 (26–34)	0	63% were migrants from Latin America, Asia, or Eastern Europe.	67% had compulsory schooling only or vocational training, with a substantial proportion (17%) still in training.			83% homosexual	49% reported stable partnerships; 21% reported unprotected sex with occasional partners.	
4) Heterosexual people of lower SEP	1,089	18.1	39 (33–44)	47	25% were from sub-Saharan Africa or Southern Europe.	62% had vocational training or compulsory schooling only.	58% worked as manual or nonmanual employees.		99% heterosexual	65% had stable partners; 9% reported unprotected sex with occasional partners.	11% reported a history of injection drug use.
5) Older heterosexual and gay people on welfare benefits	443	7.4	59 (52–64)	24	90% were from Switzerland or Northern or Western Europe.			74% depended on welfare benefits and were out of work.	76% heterosexual; 23% homosexual or bisexual	Many (43%) reported having no partner; some (12%) reported unprotected sex with occasional partners.	
											Table continues

Appendix Table 1. Characteristics of the 8 Sociobehavioral Groups Identified by Latent Class Analysis in the Swiss HIV Cohort Study<sup>a</sup>

Appendix Table 1. Continued

			Characteristic									
Sociobehavioral Group	No. of Participants	% of Participants	Median Age, years (IQR <sup>b</sup> )	% Women	Region of Origin	Education	Occupation	Main Source of Income	Sexual Orientation	Sexual Partnership Pattern	Substance Use	
6) Migrant women in heterosexual partnerships	546	9.1	31 (27–36)	100	Most were from sub-Saharan Africa (50%) or Asia and Eastern Europe (24%).	60% had compulsory schooling only.		Most relied on support from their partners.	98% heterosexual	87% reported stable partnerships, with only a few (2%) reporting unprotected sex with occasional partners.		
7) Heterosexual migrants on welfare benefits	578	9.6	31 (27–36)	61	92% were from sub-Saharan Africa.	68% had compulsory schooling only.		78% depended on welfare benefits.	97% heterosexual	47% reported no stable partner; 18% reported sex with occasional partners.		
8) Injection drug users	704	11.7	36 (31–41)	35	Mainly Switzerland or Northern or Western Europe (79%)			84% depended on welfare benefits.	94% heterosexual	20% reported sex with occasional partners.	60% reported former injection drug use; 32% reported current use, and the remainder reported no use.	

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; SEP, socioeconomic position. <sup>a</sup> See Web Appendix 1 and Web Table 1 for a detailed compilation of the variables used to define these groups. <sup>b</sup> 25th–75th percentiles.