Neighbourhood socio-economic position, late presentation and outcomes in people living with HIV in Switzerland

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\textbf{Objectives:} Inequalities and inequities in health are an important public health concern. In Switzerland, mortality in the general population varies according to the socio-economic position (SEP) of neighbourhoods. We examined the influence of neighbourhood SEP on presentation and outcomes in HIV-positive individuals in the era of combination antiretroviral therapy (cART).

\textbf{Methods:} The neighbourhood SEP of patients followed in the Swiss HIV Cohort Study (SHCS) 2000–2013 was obtained on the basis of 2000 census data on the 50 nearest households (education and occupation of household head, rent, mean number of persons per room). We used Cox and logistic regression models to examine the probability of late presentation, virologic response to cART, loss to follow-up and death across quintiles of neighbourhood SEP.

\textbf{Results:} A total of 4489 SHCS participants were included. Presentation with advanced disease [CD4\textsuperscript{+} cell count <200 cells/\mu l or AIDS] and with AIDS was less common in neighbourhoods of higher SEP: the age and sex-adjusted odds ratio (OR) comparing the highest with the lowest quintile of SEP was 0.71 [95% confidence interval (95% CI) 0.58–0.87] and 0.59 (95% CI 0.45–0.77), respectively. An undetectable viral load at 6 months of cART was more common in the highest than in the lowest quintile (OR 1.52; 95% CI 1.14–2.04). Loss to follow-up, mortality and causes of death were not associated with neighbourhood SEP.

\textbf{Conclusion:} Late presentation was more common and virologic response to cART less common in HIV-positive individuals living in neighbourhoods of lower SEP, but in contrast to the general population, there was no clear trend for mortality.

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Introduction

Inequalities and inequities in health between countries, regions and areas are an important public health concern [1–3]. Such differences are not only explained by both the characteristics and behaviours of the individuals living in an area (compositional effects) but also by the social and environmental characteristics of communities and neighbourhoods (contextual factors) [4–6], including social cohesion, health services and environmental factors. In Switzerland, mortality varies substantially across neighbourhoods of different socio-economic position (SEP) [3]. Inequalities may be particularly pronounced in patients with conditions that disproportionately affect the socially vulnerable, such as infection with the HIV.

The main risk groups for HIV infection in Switzerland are MSM, IDUs and people acquiring HIV-1 through heterosexual intercourse [7]. Infections in migrants from sub-Saharan Africa or Asia have become important in recent years [8]. HIV-positive people often have significant comorbidity but may face more barriers to access health services [9], may be more likely to be unemployed [10] and have fewer material and social resources but higher levels of psychological distress [11], and less favourable health behaviours than those free of HIV infection [12].

Late presentation with advanced immunodeficiency or clinical AIDS is an important issue for care and prevention of HIV infection. Timely diagnosis and successful treatment with potent combination antiretroviral therapy (cART) is both associated with improved prognosis and a reduction of the risk of onward transmission of HIV [13,14]. Loss to follow-up is also an issue: in the Swiss HIV Cohort (SHCS), patients who were seen regularly at a clinic were less likely to progress to AIDS [15].

We analysed data from the SHCS [16] to examine the influence of neighbourhood and individual SEP on the probability of late presentation, initiation and response to cART, loss to follow-up (LTFU) and mortality.

Materials and methods

The Swiss HIV Cohort Study

The SHCS is a nationwide, prospective cohort study of HIV-infected patients aged 16 years or older [16]. Socio-demographic, clinical and laboratory data are recorded at enrolment and in 6-monthly intervals. Clinical stage is classified according to the clinical criteria of the Centers for Disease Control and Prevention (CDC) [17]. Patients who miss follow-up visits are traced and deaths in patients lost to follow-up ascertained through municipalities and mortality records. Written informed consent is obtained from all participants. The present analysis was approved by a Federal Expert Commission.

All treatment-naive patients who started cART between 2000 and 2013 at a University clinic or Cantonal hospital and had a valid address were eligible. SHCS patients who were seen in private practices and patients infected through mother–to-child transmission were excluded. The closing date of the database was April 2013.

Neighbourhood index of socio-economic position

On the basis of Census 2000 data, the Swiss neighbourhood index of SEP is based on neighbourhoods of about 50 households [18]. Each household was spatially referenced using the geographic coordinates of the building. Areas centred on residences were then created. Boundaries changed from one building to the next and were distorted in the direction of roads with shops, amenities and public transport. The SEP of neighbourhoods was determined on the basis of rent per square metre, proportion of households headed by a person with primary education or less, proportion headed by a person in manual or unskilled occupation and mean number of persons per room [18].

Geocoding

Patient addresses were coded in ArcGIS 10 software (Esri) using the GeoPost database (Esri, Zurich, Switzerland), which includes data on the exact geographical coordinates of buildings. On the basis of the geocode, the Swiss SEP neighbourhood index was allocated to each study participant. The study number and neighbour SEP index, but not geocodes or addresses, left clinics for further analyses.

Definition of outcomes and variables

We considered seven outcomes: late presentation; presentation with advanced HIV disease; presentation with AIDS-defining illness; time to start of cART; virologic response to cART; LTFU; and mortality. Late presentation was defined as a person with HIV first presenting for care with a CD4+ cell count less than 350 cells/μl or with an AIDS-defining event [19]. Presentation with advanced HIV disease was defined as presentation with a CD4+ cell count less than 200 cells/μl or with AIDS: patients presenting with advanced disease are a subgroup of late presenters. First, presentation for care was defined as the date of the first positive HIV test or first CD4+ cell count recorded in the database, whichever came first. Time to start of cART in ART-naive patients was related to the time from presentation to the start of therapy. Virologic response to cART was defined as a viral load less than 50 copies/ml at 6 months among ART-naive patients followed for at least
6 months. The viral load measurement closest to 6 months of follow-up within a window of ±3 months was used. A patient was considered LTFU if the last visit was more than 14 months before the closing date of the database and the patient was not known to have died. Only patients with more than 14 months of potential follow-up, before closure of the database, were included in the analysis of LTFU.

Causes of deaths were classified according to the Causes of Death in HIV (CoDe) protocol (Version 2.3) [20], or based on ICD-10 codes from the death certificate (Table S1, http://links.lww.com/QAD/A603). We considered patients as exposed to hepatitis C virus (HCV) if they had positive anti-HCV or HCV-RNA tests and exposed to hepatitis B virus (HBV) in the presence of positive anti-HBc, HBs-antigen or HBV-DNA tests.

Statistical analysis
We used descriptive statistics to examine patient characteristics across quintiles of neighbourhood SEP. We used logistic regression (late presentation outcomes, virologic response) and Cox proportional hazards models (time to start of cART, LTFU and death from all causes). In Cox models, time was measured from enrolment to the time the outcome occurred or the last follow-up visit. In patients starting cART at enrolment, we added 1 day of follow-up. Schoenfeld’s test was used to assess the proportional hazard assumption [21]. Models were adjusted for age and sex. In additional analyses, variables associated with individual-level SEP and variables that may mediate effects of SEP were also included: education (compulsory school, vocational training, higher education, other/unknown), occupation (self-employed/higher management, middle management, employee, apprentice/trainee/student, other/unknown), smoking (current smoker, other/unknown), source of income (salaried work, welfare benefits, support from family or partner, other/unknown), transmission group (heterosexual, MSM, IDU, other/unknown), region of origin (Switzerland, North–West Europe, Southern Europe, sub-Saharan Africa, Latin America, Asia/ Eastern Europe, other/unknown).

We imputed missing baseline CD4⁺ cell counts and viral load values based on characteristics at baseline and whether or not the patient died. Analyses were run on each of 20 imputation datasets and combined with Rubin’s rule [22]. We calculated mortality rates per quintiles of the neighbourhood index of SEP both for the SHCS and the general population. We used the Swiss National Cohort, a census-based cohort of the entire Swiss population [23].

Analyses were done in Stata (Stata Corp., College Station, Texas, USA, version 12.0) and R (R Foundation for Statistical Computing, Vienna, Austria, version 3.0.2). Results are presented as odds ratios (ORs) and hazard ratios, with 95% confidence intervals (CIs).

Results
A total of 6825 patients were enrolled into the SHCS since 1 January 2000 of whom 2336 patients were excluded, mainly because they were seen in associated clinics and private practices wherein geocoding of addresses was not possible. Excluded patients were more likely to be MSM, to have higher education and to be in salaried work than included patients (Table S2, http://links.lww.com/QAD/A603). A total of 4489 patients (69.7% male) were included in the analyses of mortality with a median follow-up time of 5.4 years [interquartile range (IQR) 2.8–8.7 years]. Fewer patients were included in the analyses of other outcomes: 4218 for late presentation, 4177 patients for presentation with advanced disease, 4477 patients for LTFU, 3863 ART-naïve patients for time to starting cART and 2694 ART-naïve patients for virologic response at 6 months. Supplemental Figure S1, http://links.lww.com/QAD/A603 shows the selection of patients for the different analyses. Only three CD4⁺ cell counts and 54 viral loads at enrolment and 246 CD4⁺ cell counts and 268 viral loads at the start of cART were missing and imputed.

Figure 1 shows a colour-coded map of the 1 298 079 neighbourhoods and their index of SEP. Neighbourhoods of higher SEP (in shades of green) are concentrated in the urban centres, most notably in Zurich, Geneva, Basel, Lausanne, Bern, Lugano and surroundings; and along some of the lakes, for example, Lake Geneva and Lake Zurich. Neighbourhoods of lower SEP (in shades of red) dominate the regions north of the Alps, the area north of the lakes of Neuchâtel and Bienne in the West of the country and the valleys of the Alps. Clear differences in neighbourhood SEP are also seen within cities, at the level of streets (Figure S2, http://links.lww.com/QAD/A603).

There were substantial and statistically significant differences in patient characteristics across quintiles of neighbourhood SEP (Table 1). Fewer women lived in neighbourhoods in the highest quintile of SEP than the lowest quintile. The proportion of patients with a history of IDU decreased with increasing SEP of neighbourhoods, whereas more MSM lived in high SEP neighbourhoods. Patients living in neighbourhoods of higher SEP had higher educational levels, were more likely to work in managerial positions, less likely to smoke and more likely to be Swiss citizens than those living in neighbourhoods of lower SEP. Important differences across neighbourhood SEP were also seen in clinical characteristics (Table 2). For example, the percentage of patients presenting with CDC clinical stage C, exposure to HBV or HCV increased with decreasing SEP of neighbourhoods, whereas the median CD4⁺ cell count at start of cART decreased from 259 to 220 cells/µl.

At enrolment, there were 2571 (61.0%) late presenters, 1452 (34.8%) presenters with advanced HIV disease and
691 (15.4%) patients with AIDS. A total of 3496 ART-naive patients started cART. Median time from enrolment to start of therapy was 11 days (IQR 1 day to 14.5 months). After starting cART, 2046 (76.0%) patients suppressed viral replication by 6 months, 166 (3.7%) were lost to follow-up and 246 (5.4%) patients died. Presentation with advanced disease was less common in neighbourhoods of higher SEP: the age-adjusted and sex-adjusted OR comparing the highest with the lowest quintile of the neighbourhood SEP index was 0.71 (95% CI 0.58–0.87, \( P = 0.003 \) from test of trend) (Table 3). For presentation with AIDS, the corresponding OR was 0.59 (95% CI 0.45–0.77, \( P = 0.0002 \)). Patients living in neighbourhoods in the highest quintile of SEP were more likely to suppress viral replication at 6 months after starting cART than those living in neighbourhoods from the lowest quintile: OR 1.52 (95% CI 1.14–2.04, \( P = 0.05 \)). There was little evidence for a trend for time to start of cART, LTFU and mortality (Table 3). Associations persisted but were attenuated and no longer statistically significant when additionally adjusting for individual-level variables transmission group, region of origin, education, occupation, smoking and source of income (supplemental Table S3, http://links.lww.com/QAD/A603). The exception was late presentation with AIDS (\( P = 0.03 \)).

The mortality rate from all causes was 999 per 100 000 (95% CI 778–1284) in the lowest quintile of neighbourhood SEP and 959 per 100 000 (95% CI 716–1285) in the highest quintile, with no clear trend across levels of neighbourhood SEP (\( P = 0.65 \), Fig. 2). In the general population, mortality clearly varied across neighbourhood SEP: the rate per 100 000 declined from 419 (95% CI 415–423) to 347 (95% CI 343–351) per 100 000 when moving from the lowest to the highest quintile of neighbourhood SEP (\( P < 0.001 \), Fig. 2). The standardized mortality ratio (SMR) comparing mortality in the SHCS with mortality in the general population was 3.91 (95% CI 3.45–4.43).

The majority of deaths in the SHCS (193, 78.5%) related to causes other than AIDS. There was some evidence for a higher proportion of deaths from AIDS in the lower than the higher quintiles of SEP, and a trend in the same direction for deaths of unknown causes, but differences in the distribution of causes of death overall were not statistically significant (\( P = 0.11 \), supplemental Table S4, http://links.lww.com/QAD/A603).

**Discussion**

We examined whether the SEP of neighbourhoods of residence influenced presentation and outcomes in HIV-infected patients in Switzerland. Compared with patients living in neighbourhoods of lower SEP, those residing in areas of higher SEP had higher educational attainment, were more likely to be MSM, to live in urban...
centres and to occupy managerial positions. The proportion of patients with a history of IDU and the proportion exposed to HBV or HCV decreased with increasing SEP of neighbourhoods, whereas the median CD4^+ cell count increased with higher SEP. Late presentation and presentation with advanced HIV disease were more common in neighbourhoods of lower SEP, and virologic response to cART more likely in neighbourhoods of higher SEP, but there was little evidence of an association with mortality.

Geocoding of patients’ addresses allowed us to assign an index of neighbourhood SEP [18] to over 90% of eligible patients. The index was constructed using both

| Table 1. Patient characteristics at enrolment by neighbourhood socioeconomic position. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Characteristic                  | 1 (22.5%)                       | 2 (19.3%)                       | 3 (19.7%)                       | 4 (20.0%)                       | 5 (18.5%)                       |
| No. of participants            | 1011                            | 864                             | 885                             | 897                             | 832                             |
| No. of women                   | 392                             | 277                             | 252                             | 269                             | 269                             |
| Median (IQR) age (years)       | 36 (30–43)                      | 36 (30–44)                      | 37 (32–46)                      | 37 (30–44)                      | 38 (32–45)                      |
| Injection drug use             | Never                           | 827                             | 715                             | 762                             | 775                             |
| HIV transmission groups        | HET                             | 559                             | 422                             | 397                             | 354                             |
| Stable partner only            | 496                             | 395                             | 370                             | 395                             | 395                             |
| Middle/lower management        | 102                             | 109                             | 119                             | 829                             | 849                             |
| Education                       | Compulsory school               | 380                             | 287                             | 238                             | 225                             |
| Secondary sources              | Salaried work                   | 462                             | 461                             | 515                             | 559                             |
| Main source of income          | Never                           | 424                             | 331                             | 329                             | 354                             |
| Level of urbanization          | Urban                           | 504                             | 424                             | 474                             | 465                             |
| Smoking status                 | Never                           | 424                             | 331                             | 329                             | 354                             |
| Geographic region              | Switzerland, North-West Europe  | 498                             | 487                             | 551                             | 539                             |
| Current                        | 455                             | 406                             | 411                             | 404                             | 335                             |
| Occupation^a                    | Self-employed                   | 76                               | 66                               | 67                               | 85                               |
| Higher management              | 14                               | 21                               | 27                               | 31                               | 34                               |
| Middle/lower management        | 63                               | 56                               | 67                               | 83                               | 84                               |
| Education                       | Compulsory school               | 380                             | 287                             | 238                             | 225                             |
| Secondary sources              | Salaried work                   | 462                             | 461                             | 515                             | 559                             |
| Main source of income          | Never                           | 424                             | 331                             | 329                             | 354                             |
| Level of urbanization          | Urban                           | 504                             | 424                             | 474                             | 465                             |

Analysis based on a total of 4489 patients. Numbers (percentages) are shown. P values from Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables. Quintile 1 describes neighbourhoods of lowest SEP, quintile 5 neighbourhoods of highest SEP. IQR, interquartile range.

^aCurrent or last held profession.
Table 2. CD4+ cell count, clinical stage and prevalence of exposure hepatitis B and C at enrolment and at start of combination antiretroviral therapy by quintile of neighbourhood socio-economic position.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neighbourhood socio-economic position (quintile)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At enrolment (n = 2648)</td>
<td>Median CD4+ cell count (IQR), cells/µl</td>
<td>355 (193–551)</td>
<td>350 (201–508)</td>
<td>378 (216–522)</td>
<td>372 (235–542)</td>
<td>361 (215–520)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>CDC clinical stage C</td>
<td>9.3% (54/578)</td>
<td>11.5% (59/512)</td>
<td>6.9% (42/521)</td>
<td>8.1% (42/521)</td>
<td>6.2% (32/518)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Median HIV-RNA log10 (IQR), copies/ml</td>
<td>4.6 (3.9–5.1)</td>
<td>4.6 (3.9–5.1)</td>
<td>4.6 (3.9–5.1)</td>
<td>4.6 (3.9–5.1)</td>
<td>4.6 (3.9–5.1)</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Exposure to hepatitis B</td>
<td>17.6% (52/300)</td>
<td>19.2% (55/291)</td>
<td>15.2% (38/251)</td>
<td>16.0% (38/238)</td>
<td>13.4% (38/281)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Exposure to hepatitis C</td>
<td>18.0% (51/284)</td>
<td>16.3% (41/250)</td>
<td>11.8% (27/230)</td>
<td>12.8% (27/214)</td>
<td>7.5% (27/364)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At the start of cART (n = 3496)</td>
<td>Median CD4+ cell count (IQR), cells/µl</td>
<td>220 (120–330)</td>
<td>223 (122–337)</td>
<td>252 (133–362)</td>
<td>253 (136–360)</td>
<td>259 (146–363)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CDC clinical stage C</td>
<td>19.5% (57/294)</td>
<td>19.5% (57/294)</td>
<td>15.7% (41/258)</td>
<td>16.0% (41/256)</td>
<td>15.1% (41/268)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Median HIV-RNA log10 (IQR), copies/ml</td>
<td>4.8 (4.0–5.3)</td>
<td>4.8 (4.0–5.3)</td>
<td>4.8 (4.0–5.3)</td>
<td>4.8 (4.0–5.3)</td>
<td>4.8 (4.0–5.3)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Exposure to hepatitis B</td>
<td>17.4% (36/207)</td>
<td>18.8% (36/194)</td>
<td>15.6% (29/185)</td>
<td>15.4% (29/185)</td>
<td>14.1% (29/206)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Exposure to hepatitis C</td>
<td>12.2% (27/222)</td>
<td>12.6% (27/222)</td>
<td>9.0% (20/222)</td>
<td>9.7% (20/213)</td>
<td>5.6% (20/359)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Analyses based on patients who were ART-naïve at enrolment or start of therapy. Quintile 1 describes neighbourhoods of lowest SEP, quintile 5 neighbourhoods of highest SEP. P values from tests of trend. IQR, interquartile range.

individual-level information on education and occupation, and household-level information on rent and crowding. The small size of neighbourhoods is a strength: previous analyses of regional health disparities were generally based on larger administrative areas with arbitrary, fixed boundaries, for example municipalities, census units or, in Switzerland, cantons [24]. Although the importance of analyses based on a finer resolution has been highlighted [5,25], such analyses are not possible in many countries.

Areas centred on the residence of individuals, with sliding rather than fixed boundaries, define neighbourhoods that should capture the environmental and social conditions to which an individual is exposed to. It therefore seems likely that the neighbourhoods and their index of SEP reflect contextual neighbourhood effects, as well as compositional effects that stem from the population characteristics of residents in the neighbourhoods [26]. Indeed, associations with neighbourhood SEP persisted when adjusting models for individual-level variables such as education, occupation, source of income or smoking, although they were attenuated.

Established in 1988, the SHCS is one of the longest running HIV cohort studies worldwide [16]. About 70% of patients living with AIDS are enrolled in the SHCS and 70% of the antiretroviral drugs sold in the country are prescribed within the study [16,27]. We had to exclude patients seen in private practices who were better educated and more likely to be in salaried work than the patients included in our study. Other limitations include the relatively small number of patients and events, which meant that the statistical power to detect or exclude differences was limited for some outcomes. For example, when comparing mortality of those living in neighbourhoods in the highest quintile of SEP with those in the lowest quintile, results were compatible with almost a 40% lower and a 60% higher mortality. Finally, the number of deaths was too small to allow detailed analyses of cause-specific mortality. The Danish HIV Cohort study recently reported that mortality was higher in patients with low educational attainment compared with patients with high attainment, particularly for smoking and alcohol-related causes [28].

A county-level analysis in the United States of America showed that in the cART era, survival decreased with an increasing proportion of people living below the poverty level and with the level of unemployment in the counties [29]. Another study examined racial/ethnic disparities in mortality among people living with AIDS in San Francisco [30]. Delayed initiation of cART or no treatment in black people living with AIDS was strongly associated with neighbourhood SEP. Indeed, the disparity in mortality between black and white people disappeared when neighbourhood SEP was included in model [30]. Our study showed little difference in mortality across levels of SEP of neighbourhoods in patients enrolled in the SHCS. One explanation might be the unrestricted access to healthcare in Switzerland: health insurance is compulsory for all residents, covers HIV treatment and care, and is subsidized in those with low incomes [31]. Of note, in British Columbia, where healthcare is also universal, survival differences were nevertheless observed across levels of neighbourhood SEP [32].
To our knowledge, this is the first study examining the association between neighbourhood SEP and late presentation, as defined by a European working group [19]. A recent analysis of 23 cohort studies by the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) found that although late presentation had decreased since 2000, particularly in MSM, it remained an important problem across Europe. Late presentation was associated with increased mortality in some, but not all regions [33].

In conclusion, our study shows that in Switzerland, residence in neighbourhoods of low SEP is associated with late presentation of HIV-positive people and presentation with advanced disease. However, the late presentation to care did not translate into increased mortality in subsequent years.

Acknowledgements

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Conflicts of interest
There are no conflicts of interest.

References


