Uptake of Combination Antiretroviral Therapy and HIV Disease Progression According to Geographical Origin in Seroconverters in Europe, Canada, and Australia

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(See the Editorial Commentary by Sawe, on pages 119–20.)

Background. We examined differences by geographical origin (GO) in time from HIV seroconversion (SC) to AIDS, death, and initiation of antiretroviral therapy (cART).

Methods. Data from HIV seroconverter cohorts in Europe, Australia and Canada (CASCADE) was used; GO was classified as: western countries (WE), North Africa and Middle East (NAME), sub–Saharan Africa (SSA), Latin America (LA), and Asia (ASIA). Differences by GO were assessed using Cox models. Administrative censoring date was 30 June 2008.

Results. Of 16 941 seroconverters, 15 548 were from WE, 158 NAME, 762 SSA, 349 LA, and 124 ASIA. We found no differences by GO in risks of AIDS (P = .99) and death (P = .12), although seroconverters from NAME (adjusted hazard ratio [aHR]: 0.57; 95% CI: 0.33–.94) and SSA (aHR: 0.74; 95% CI: 0.50–1.10) appeared to have lower mortality than WE. Chances of initiating cART differed by GO (P < .001): seroconverters from SSA were more likely to initiate cART than WE (aHR: 1.48; 95% CI: 1.26–1.74), but not after adjustment for CD4 at SC (aHR: 1.11; 95% CI: 0.88–1.40).

Conclusions. In settings with universal access to healthcare, GO does not play a major role in HIV disease progression.

Migrant populations, largely from sub–Saharan Africa (SSA), represent a considerable proportion of AIDS cases and human immunodeficiency virus (HIV) infections reported in the European Union and similar trends are observed in Canada [1, 2]. The annual number of incident AIDS cases in Western Europe has declined considerably since 1996, largely driven by combination antiretroviral therapy (cART), but this decline has not been observed among migrants [1]. This might be explained by a higher frequency of late HIV diagnoses and lower uptake of cART in some migrant populations. Inequity and social exclusion, along with administrative, cultural, and language barriers to HIV/AIDS care, may impair uptake and response to cART in high-income countries.

A higher frequency of delayed HIV diagnosis in migrants from SSA has been described before and after the introduction of cART [3]. Other investigators have reported no differences from the local populations for migrants from Latin America (LA) [4]. The few studies...
addressing HIV disease progression of migrants in Europe report similar progression rates to AIDS and death after adjusting for these delayed presentations [5, 6]. Müller et al. [7] have reported slower CD4 cell count declines in migrants from SSA. Migrants from SSA are infected with different HIV subtypes compared with Europeans, and data from the French National Agency for AIDS Research (ANRS) PRIMO cohort show that migrants from SSA have lower CD4 counts at the time of HIV-1 primary infection than subjects from other countries [8].

As migrants often present late for care, most of the above studies deal with advanced HIV infection using data from seroprevalent cohorts. There are no data on early HIV disease stage comparing migrant and nonmigrant groups. HIV-positive subjects from the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) Collaboration have well-defined dates of HIV seroconversion, which by definition excludes late HIV diagnoses. All data currently included in CASCADE are from countries with national health services that provide universal access to cART, although in some countries, undocumented migrants are not entitled to healthcare [9]. Our hypothesis is that there are no differences in HIV disease progression attributable to geographical origin, once adjusted by confounders recognizing some migrant groups may have more limited access to cART. In this paper, we analyze data from CASCADE to examine differences in time from HIV seroconversion to cART initiation, AIDS, and death among people of different geographical origin.

MATERIAL AND METHODS

Study Population
We analyzed data from CASCADE, a collaboration of 23 HIV seroconverter cohort studies in Europe, Australia, and Canada that enrolls seroconverters from the 1980s onward. CASCADE data were pooled in June 2011 within EuroCoord (www.EuroCoord.net). Details of CASCADE appear elsewhere [10]; briefly, all cohorts include people infected with HIV-1 for whom date of seroconversion can be reliably estimated. The date of seroconversion is estimated by various methods, most frequently as the midpoint between the last negative and first positive HIV antibody test dates with a maximum of 3 years between test dates.

HIV infections were assumed to have been acquired after migration, as all subjects had a previous HIV-negative test almost always documented in the participating care center. We excluded children less than 15 years of age at seroconversion.

Variables and Definitions
Migrants were defined based on their geographical origin, which was derived from nationality or from country of birth/origin, and was classified as follows: western countries (WE: Europe, North America, Australia, and New Zealand), North Africa and Middle East (NAME), sub-Saharan Africa (SSA), Latin America (LA), and Asia (ASIA). As there were very few seroconverters whose country of origin was a western country different to the one reporting the case, they were included in the WE category.

Statistical Analyses
Descriptive analysis of patients’ characteristics was carried out. Differences by geographical origin in demographic and clinical characteristics were assessed through the nonparametric Kruskal-Wallis test for continuous variables and the \( \chi^2 \)-squared test for independence for categorical variables.

Last data update was June 2009 but we considered June 2008 as our date of administrative censoring.

For time-to-death analyses, individuals not known to have died by 30 June 2008 were censored on the date they were known to be alive. We used the Kaplan-Meier method to estimate the cumulative incidence of death and a Cox proportional hazards model to assess differences by geographical origin on the risk of death.

For time-to-AIDS analyses, pre-AIDS mortality was treated as a competing event, and individuals not known to have developed AIDS by 30 June 2008 were censored on their last date of assessment. The cumulative incidence of AIDS was calculated within a competing risk framework using the multiple decrement method [11, 12], and a proportional hazards model on the subdistribution hazard [13–15] was used to assess differences by geographical origin on the cumulative incidence of AIDS.

We explored whether differences by geographical origin in time to AIDS and death from seroconversion (SC) had changed over time by including interaction terms between geographical origin and calendar period at risk, pre-1997 and 1997-onward, in multivariate models.

Analyses on time-to-cART initiation from SC were restricted to people who seroconverted after 1 January 1997 and were completely antiretroviral drug–naïve at cART initiation. Death before cART initiation was treated as a competing event, and patients not known to have started cART by 30 June 2008 were censored on the date last assessed for ART. We used the multiple decrement method [11, 12] and a proportional hazards model on the subdistribution hazard [13–15] to estimate the cumulative incidence of cART initiation from HIV SC and to assess differences by geographical origin on the cumulative incidence of cART, respectively.

All models allowed for late entry, were stratified by cohort, and were adjusted for potential confounders.

In order to estimate CD4 cell count levels at cART initiation, a modified Kaplan-Meier technique was used where the time scale of the standard survival analysis was replaced by a reverse CD4 scale [16]. This way, one can estimate the CD4 cell count (and the corresponding 95% confidence interval [CI]) at which
the probability of starting cART equals 50% using all available information (ie, from both those who initiated cART and those who remained cART-free until the end of follow-up).

We assessed differences by geographical origin in the proportion of seroconverters with staggered entries into the cohort (ie, presence of a lag between SC and enrolment into the cohort) and in their staggered times (ie, time between SC and enrolment into the cohort). We explored the immunological, virological, and clinical status of subjects lost to follow-up according to their geographical origin. Patients were considered lost to follow-up if they had not had a visit in the recruiting center in the previous 2 years.

The Wald test was used to derive \( P \) values. All statistical analyses were performed by using Stata software (Version 11.0, College Station, TX).

**RESULTS**

Of 16 941 seroconverters included in the analyses of time to death, 15 548 (91.8%) were from WE, 158 (0.9%) from NAME, 762 (4.5%) from SSA, 349 (2.1%) from LA, and 124 (0.7%) from ASIA. Of 5775 patients with ethnicity data available, 96.8% of those from WE were of white ethnicity compared with 12.9% among those from SSA; 86.4% of seroconverters from SSA were black. The proportion of seroconverters from SSA enrolled into CASCADE rose steadily over time, from 0.8% before 1990 to 2.9% in 1990–1999 and 7.9% in 2000–2008. The proportion of women was around 20–24% in seroconverters from WE, LA, and ASIA, but was as high as 38% in NAME and exceeded that of the proportion of men in SSA, 63.1%. The proportion of seroconverters heterosexually infected was greatest among seroconverters from SSA. Of those 3331 seroconverters with a known HIV subtype, 91.5% of those from WE were infected with a B subtype compared with 18.1% among those from SSA; 86.4% of seroconverters from SSA were black. The proportion of seroconverters from SSA enrolled into CASCADE rose steadily over time, from 0.8% before 1990 to 2.9% in 1990–1999 and 7.9% in 2000–2008. The proportion of women was around 20–24% in seroconverters from WE, LA, and ASIA, but was as high as 38% in NAME and exceeded that of the proportion of men in SSA, 63.1%. The proportion of seroconverters heterosexually infected was greatest among seroconverters from SSA. Of those 3331 seroconverters with a known HIV subtype, 91.5% of those from WE were infected with a B subtype compared with 18.1% among those from SSA. Among 6303 seroconverters with information on CD4 cell counts within 6 months from SC, median (interquartile range [IQR]) CD4 cell count (cells/\( \mu L \)) at SC was 362 (253–530) in seroconverters from SSA compared with 545 (393–730) in those from WE (Table 1).

There were 2269 deaths among the 16 941 seroconverters included in the analyses of time to death from any cause: 2195 (14%) in seroconverters from WE, 13 (8%) in NAME, 26 (3%) in SSA, 25 (7%) in LA, and 10 (8%) in ASIA. In the crude analysis, there were significant differences by geographical origin in the risk of death (\( P = .003 \)): seroconverters from SSA (HR: 0.50; 95% CI: 0.34–0.74) and NAME (HR: 0.62; 95% CI: 0.36–1.08) had a reduced risk of death than those from WE (Figure 1A). Although after adjustment for sex, exposure category, age at SC (continuous), and calendar period in a multivariate Cox regression model, the overall difference by geographical origin became not significant (\( P = .12 \)), NAME retained a lower risk of death (adjusted hazard ratio [aHR]: 0.57; 95% CI: 0.33–0.94), which was in the limit of statistical significance in SSA (aHR: 0.74; 95% CI: 0.50–1.10) (Table 2). The most important confounder was calendar period at risk, characterized by an 81% reduction in the risk of death in the cART era compared with the pre-cART era (data not shown).

In the analysis of progression to AIDS, we excluded 354 individuals for having an AIDS diagnosis prior to or at enrolment, 159 because the date of last clinical visit was the same as the date of enrolment, and 4 because the date of AIDS was missing. Of 16 424 seroconverters included, 2806 developed AIDS: 2677 in WE, 27 in NAME, 53 in SSA, 34 in LA, and 35 in ASIA. In seroconverters from SSA, the most frequent first AIDS-defining events were tuberculosis (16, 30.2%) and Kaposi’s sarcoma (7, 13.2%). Pneumocystis jiroveci pneumonia (425, 15.9%), Kaposi’s sarcoma (336, 12.6%), and candidal oesophagitis (283, 10.6%) occurred most often in seroconverters from WE. A total of 667 (4.1%) seroconverters died without an AIDS diagnosis: 4.3% in WE, 1.3% in NAME, 1.3% in SSA, 2.7% in LA, and 2.5% in ASIA. In the crude analysis, there were significant differences by geographical origin in the risk of AIDS (\( P = .043 \)), with seroconverters from SSA experiencing a lower risk of AIDS compared with those from WE (HR: 0.65; 95% CI: 0.49–0.86; Figure 1B). After adjustment for sex, exposure category, age at SC (continuous), and calendar period at risk in a multivariate proportional hazards model on the subdistribution hazard, these differences were no longer present (\( P = .99 \); Table 2).

The most important confounder for the risk of AIDS, similar to that observed for the risk of death, was calendar period at risk; a 75% reduction in the risk of AIDS was seen in the cART era (data not shown).

We failed to find any evidence suggesting a change over calendar period in the effect of geographical origin in the risk of AIDS (\( P = .27 \)) or death (\( P = .93 \); data not shown).

For time-to-cART analyses, we excluded 8945 individuals that seroconverted prior to 1 January 1997, 380 that were pre-treated at cART initiation, 1142 that initiated cART at enrolment, and 139 in which the date of enrolment was the same as the date last assessed for ART. Of 6335 seroconverters included, 3422 initiated cART during follow-up: 2981 in WE, 25 in NAME, 302 in SSA, 82 in LA, and 32 in ASIA. A total of 226 (3.6%) seroconverters had an AIDS diagnosis prior to or at cART initiation (3.6% in WE, 6.2% in NAME, 4.0% in SSA, 2.0% in LA, and 4.9% in ASIA), and 52 (0.8%) died before initiating cART (0.9% in WE, 0% in NAME, 0.2% in SSA, 0.5% in LA, and 1.6% in ASIA). There were differences by geographical origin in the median (95% CI) CD4 cell count (cells/\( \mu L \)) at cART initiation (\( P < .001 \)): 272 (267–279) in seroconverters from WE, 252 (183–286) in NAME, 236 (224–251) in SSA, 232 (199–260) in LA, and 195 (161–220) in ASIA.
The time from HIV seroconversion to cART initiation was significantly shorter in seroconverters from SSA as compared with those from WE (Figure 1C). In a multivariate proportional hazards model on the subdistribution hazards adjusting for sex, age at SC (continuous), exposure category, calendar year of SC (‘97–’98, ‘99–’00, ‘01–’04, and ‘05–’08), AIDS diagnosis prior to enrolment, and acute HIV infection (gap interval between the last negative and the first positive HIV antibody test below 30 days or laboratory evidence of seroconversion), seroconverters from SSA were more likely to initiate cART compared with those from WE (aHR: 1.48; 95% CI: 1.26–1.74). After additional adjustment for CD4 cell count at SC in the subset of 3021 seroconverters for whom information on CD4 counts within 6 months from SC was available, this difference became of small magnitude and was no longer statistically significant (aHR: 1.11; 95% CI: 0.88–1.40). In a sensitivity analysis, patients starting cART at enrolment were included and nominally given 1 day in the analyses of time to cART initiation from SC; the results did not change.

In the subset of people with ethnicity data available, adjusting for ethnicity (white, black, and other) did not lead to changes in the main results for the 3 outcomes studied. However, because of lower numbers and colinearity, confidence intervals were very wide.
DISCUSSION

We found no evidence of a difference in time to cART initiation, AIDS, and death following HIV seroconversion for people of different geographical origins living in industrialized countries. However, migrants from NAME and from SSA exhibit lower mortality rates than seroconverters from western countries, which are in the limit of statistical significance.

Our results provide more convincing evidence regarding previous findings reported by some groups in a European setting. Del Amo and colleagues [5] found similar rates of HIV progression in patients of African and European origin followed up in London before cART was available. In the cART era, Staehelin et al. [6] showed similar prognosis between SSA patients and Northwest European patients, despite lower baseline CD4 cell count in SSA patients.

It is noteworthy that, although adjustment for known risk factors of survival considerably reduced differences in time to death among people of different geographical origin, seroconverters from SSA still had better survival than seroconverters from WE that were in the limit of statistical significance. This may be explained by differential ascertainment of deaths for migrants and nonmigrants, as well as by 2 forms of selection bias that need to be considered in migrant populations: the “healthy migrant effect” and the “salmon bias” [17].

The healthy migrant effect, widely reported in HIV-negative populations, is caused by migrants having better health than the autochthonous populations, as their main drive to migrate is to work, thus selecting the fittest. The salmon bias is caused by the unhealthy ones returning home to die. In our study, though, the longer survival in seroconverters from SSA does not seem to be attributable to selective losses of rapid progressors, differential losses to follow-up, or systematic losses of sicker people, but the healthy migrant effect is not possible to rule out.

Although seroconverters from SSA were lost to follow-up at slightly lower CD4 cell counts than those from WE, the absolute difference was low and therefore not enough to explain the observed findings. Finally, differential ascertainment of deaths through linkage with external national and regional registries may have a lower yield for foreign surnames and cannot be ruled out, as the spelling and surname order for foreign surnames is prone to errors.

Our study showed that, in the crude analyses, seroconverters from SSA were more likely to initiate cART and at a more advanced HIV infection than seroconverters from WE. The shorter time to cART initiation in seroconverters from SSA was mostly attributable to lower values of CD4 cell counts at HIV SC.
Table 2. Differences in Time From HIV SC to AIDS, Death, and cART Initiation Among People of Different Geographical Origin, CASCADE Collaboration

<table>
<thead>
<tr>
<th>Geographical Origin</th>
<th>Death</th>
<th>Progression to AIDS</th>
<th>Initiation of cART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)^a</td>
<td>P</td>
<td>Adjusted HR (95% CI)^b</td>
</tr>
<tr>
<td>WE</td>
<td>1.00 (0.33–0.94)</td>
<td>.12</td>
<td>1.00 (0.68–1.46)</td>
</tr>
<tr>
<td>NAME</td>
<td>0.57 (0.33–0.94)</td>
<td></td>
<td>1.00 (0.68–1.46)</td>
</tr>
<tr>
<td>SSA</td>
<td>0.74 (0.50–1.10)</td>
<td></td>
<td>1.03 (0.77–1.37)</td>
</tr>
<tr>
<td>LA</td>
<td>1.05 (0.71–1.55)</td>
<td></td>
<td>0.99 (0.70–1.40)</td>
</tr>
<tr>
<td>ASIA</td>
<td>0.81 (0.45–1.44)</td>
<td></td>
<td>1.11 (0.66–1.86)</td>
</tr>
</tbody>
</table>

Abbreviations: WE, western countries; NAME, North Africa and Middle East; SSA, sub-Saharan Africa; LA, Latin America; ASIA, Asia; HIV, human immunodeficiency virus; SC, seroconversion; cART, combination antiretroviral therapy; HR, hazard ratio; CI, confidence interval.

^a Adjusted HRs are derived from a Cox proportional hazards model, including geographical origin, sex, age at SC (continuous), exposure category, and calendar period (pre-1997 and 1997 onward), and stratified by cohort.

^b Adjusted HRs are derived from a proportional hazards model on the subdistribution hazard, including geographical origin, sex, age at SC (continuous), exposure category, and calendar period (pre-1997 and 1997 onward), and stratified by cohort.

^c Adjusted HRs are derived from a proportional hazards model on the subdistribution hazard, including geographical origin, sex, age at SC (continuous), exposure category, calendar year of SC ('97–'98, '99–'00, '01–'04, and '05–'08), AIDS diagnosis prior to enrolment, and acute HIV infection, and stratified by cohort.

^d Adjusted for all the above factors and additionally for CD4 within 6 months from SC (<200, 200–350, and ≥350), and stratified by cohort.

Similar observations have been reported in Africans living in London [18, 19] and France [20], in nonwhite patients in a Danish cohort [21], in nonindigenous patients in a Dutch cohort [22], and in sub-Saharan migrants in the Swiss HIV cohort [6, 23]. In this respect, it is reassuring that initiation of cART does not seem to be delayed in HIV-infected migrants compared with nonmigrants. It is worth highlighting that these analyses were conducted in seroconverters, which represent a minority of the HIV-infected population. These data support that strategies to encourage HIV diagnosis soon after seroconversion are key to guarantee access to cART for migrant populations, too.

Defining who is a migrant is a difficult task; HIV-positive migrants encompass diverse populations from different countries and ethnic backgrounds and HIV exposure risks [24–26]. Inevitably, there is bound to be a certain degree of non-differential misclassification. Regarding the external validity of these findings, seroconverters represent only a very small fraction of the HIV-positive population in Europe. We are aware that data of age and timing of migration would have been very important to interpret our findings, but they are very difficult to obtain in designs such as ours. What is reassuring, though, is that once people are diagnosed, there seems to be no differences in the uptake of cART, calling for more intensive efforts to diagnose people early and link them into care. The European Centre for Disease Prevention and Control HIV testing guidance released on 1 of December 2010 identifies migrants as one of the key populations to reach by HIV testing programs [27].

In summary, this is the first study that has looked at differences by geographical origin in cART uptake and HIV disease progression in seroconverters, and our data suggest that in settings with universal access to healthcare, geographical origin does not seem to play a major role in the HIV disease progression.

Notes

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