Timing of cART initiation in Male and Female Migrants Living with HIV in Western Europe: an observational cohort study (1997 - 2013)

SHORT TITLE: cART initiation in migrants in Europe

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Introduction

Combined antiretroviral therapy (cART) has resulted in a drastic improvement in the prognosis of HIV infection. The COHERE collaboration has shown that subjects on cART with CD4 count greater than 500 cells/mm^3 achieve death rates close to those of the general population [1]. However, available evidence demonstrates that the effectiveness of cART depends on the timing of treatment initiation, as those who initiate at lower CD4 count experience poorer responses to treatment, and higher rates of opportunistic diseases, non-AIDS events and mortality [2-5]. Early treatment initiation therefore represents the single most important intervention able to improve the quantity and quality of life for people living with HIV.

Individuals who achieve full control of HIV infection on cART, as characterised by an undetectable viral load (VL), are now believed to be extremely unlikely to transmit HIV infection [6-7]. Thus cART is now recognised to be a key aspect of HIV control at the community level for preventing new infections and controlling the HIV epidemic [6;8-9].

Migrants represent a considerable proportion of those living with HIV in Western Europe. Of the 137,983 persons diagnosed with HIV infection in this region between 2007 and 2012, 41% were migrants [10]. Migrants from countries with high HIV prevalence are a population of special focus for the European Centre for Disease Prevention and Control (ECDC) [11]. Literature suggests that adverse socio-economic and living conditions, together with language, cultural and legal barriers, could result in later cART initiation largely through late diagnosis of HIV infection and difficulties in access to and retention in care [11-16]. Indeed, though in most European countries HIV

testing is recommended for migrants originating from areas with high HIV prevalence [17], universal access to cART is not guaranteed for undocumented migrants in many EU countries [11]. Delayed initiation of cART may place this group at a higher risk of sub-optimal health outcomes [18-19], and could facilitate ongoing HIV transmission. The objective of this work is to evaluate differences in timing of cART initiation, as measured by the CD4 cell count at cART initiation, by geographical origin, among HIV-positive men and women using data from a large European Collaboration of HIV Cohorts from 1997 to 2013.

Methods

Study population

Data were merged in 2013 in the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord (www.cohere.org), a collaboration of 40 observational cohorts of HIV-positive individuals in routine clinical care from 32 European countries. A detailed description of COHERE has been previously published [20]. Each cohort submits data in a standardised format (www.hicdep.org) to co-ordinating centres at the Copenhagen HIV Program, Denmark, or the Institut de Santé Publique, d'Epidémiologie et de Développement (Bordeaux School of Public Health), Bordeaux, France [21]. The two coordinating centres ensure adherence to strict quality assurance guidelines and perform data checks, including the removal of duplicate records. Ethics approval was granted by the ethics committees of each of the participating cohorts according to local regulations.

For this analysis, we included 24 cohorts systematically collecting geographical origin (GO) and/or ethnicity, representing 11 Western European countries (Austria, Belgium,

Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, Switzerland and the United Kingdom). Individuals were eligible if enrolled in the cohort from January 1997 to March 2013, with known GO and sex, aged between 18-75 years, not infected perinatally or following the receipt of clotting factor concentrates, and with at least one CD4+ T-cell count measurement while naïve to cART.

Variables

Follow-up was performed according to routine clinical practice within the country where the individual was followed. Data were collected at each encounter and included information on age, sex, country of origin, ethnicity, mode of HIV acquisition, cART (defined as a combination of either ≥3 drugs from ≥2 classes, or ≥3 nucleoside reverse-transcriptase inhibitors, at least one of which was tenofovir or abacavir), CD4 cell counts, plasma HIV-RNA and various serological results and initial and subsequent AIDS defining conditions.

The exposure variable GO, as reported by cohorts, was classified based on the United Nations categories (available at http://unstats.un.org). We classified persons as either native, if they were originally from the country of enrolment (NAT), or from one of seven migrant populations based on region of origin: Western Europe and other Western countries, including North America, Australia and New Zealand (WEWC); Eastern Europe (EE); North Africa and The Middle East (NAME); Sub-Saharan Africa (SSA); Latin America (LA); The Caribbean (CRB); and the rest of the Asian Continent and Oceania (ASIA/OC). The United Kingdom Collaborative HIV Cohort (UK CHIC) Study and the Swiss HIV Cohort Study (SHCS) only reported information on ethnicity to COHERE

which was mapped into GO assigning "Black Caribbean" to CRB, "Hispanic" to LA, "Asian" to ASIA/OC, "White" to NAT, and "Black" to SSA.

Statistical Analysis

All analyses were stratified by sex. Individuals were followed-up until they either experienced the event of interest (cART initiation) or were right-censored due to loss to follow-up, death or administrative censoring (ranging from September 2009 to July 2013). To assess the cumulative probability of cART initiation as the CD4 count decreased we used the method proposed by Phillips et al [22], using time-to-event analysis methods, but with the time scale substituted by a reversed scale of CD4 cell counts. In this framework, individuals are assumed to be at risk of initiating cART from the CD4 count origin, here set artificially to be 2000 cells/mm^3, down to the minimum recorded CD4 count during their follow-up, respecting the monotonically changing nature of time. As discussed by Phillips et al, the method is insensitive to the choice of the CD4 count origin as long as it is higher than the highest recorded value. Kaplan-Meier methods were used to estimate the median CD4 count at cART initiation, this is, the CD4 levels at which the probability of starting cART is 50%, and 95% Confidence Intervals (95%CI). Hazard Ratios (95%CI) of cART initiation for migrants from each GO compared to the native population were estimated using multivariable Cox regression. As the effect of each GO on the probability of initiating cART may vary depending on the immunological status at entry into care, an interaction between GO and first recorded CD4 cell count after recruitment (<100; 100-250; 250-350; 350-500; >500) was explored using the likelihood-ratio test (LRT). Wald test was used to derive p-values for Hazard Ratios.

All models were adjusted for the following potential confounders chosen a priori and measured at cohort entry: age (years: <25; 25-35; 35-50;≥50) , HIV acquisition group [men who have sex with men (MSM), heterosexual transmission (HTX), persons who inject drugs users or other (PWID/OTH), and unknown (UNK)], HIV-RNA levels (log_{10} copies/ml: <4; 4-5; ≥5; unknown), AIDS diagnosis at recruitment (no; yes), co-infection with hepatitis C virus (HCV, RNA and/or antibody: positive; negative), or hepatitis B virus (HBV, DNA and/or any antibody excluding surface antibody: positive; negative); and calendar period (1997-1999; 2000-2003; 2004-2008; 2009-2013). Due to the high proportion of individuals with unknown HCV and HBV status at baseline (over 60% for both viruses), where this information was missing, data generated during follow-up was assumed to represent the status at baseline.

Sensitivity analyses were performed to assess the impact of the diverse assumptions: (a) using last (instead of minimum) measured CD4 count for those initiating cART; (b) accounting for left censoring, allowing individuals to enter the risk set at their first observed measure of CD4 count (only patients with more than one distinct CD4 count while cART-naïve could be included); (c) modelling CD4 count trajectories using a piecewise linear mixed-effects model with random intercepts and random slopes for the square root transformation of the CD4 cell count, and predicting the CD4 count at the date of cART initiation or right censoring [23]; (d) excluding the three cohorts that only included HIV seroconverters (defined as patients with a negative test within 3 years of their first HIV positive result and therefore less likely to have late diagnosis) - PRIMO, SEROCO and CASCADE; (e) excluding UK CHIC and SHCS to assess the impact of possible misclassification in deriving GO from ethnicity; (f) restricting the analysis to

individuals recruited in the cohort after 2004, when the recommendation to start cART below 350 CD4 cells/mm^3 became widespread in Western Europe; (g) excluding the HBV core antibody as a sole criteria for HBV coinfection; (h) considering only known HBV status at maximum 1 month after cohort entry for classification of HBV coinfection; (i) grouping transmission routes defined as "other" with unknown (instead of PWID), to evaluate the impact of misclassification of this category.

Analyses were conducted using STATA (V.12.0MP, Stata Corporation, College Station, Texas, USA).

Results

A total of 151 674 individuals were included in this analysis of which 110 592 (72.9%) were men and 45.412 (29.9%) were migrants. Among women, the proportion of migrants was higher (n=21 490; 52.3%) than among men (n=23 922; 21.6%). Migrants from SSA accounted for the largest migrant group (9.4% of men and 39.4% of women), followed by LA (3.8%) and WEWC (2.5%) in men and CRB (3.4%) and LA (2.7%) in women. Patient characteristics varied by geographical origin and sex (Table 1).

The cumulative probability of cART initiation and median CD4 counts at cART initiation are shown in Figure 1. Median CD4 count falls far below 250 cells/mm^3 in all groups, and with the exception of EE, it was lower in all migrant groups than in native population, especially in men. The lowest medians (95% CI) were estimated for men from SSA [161(158-167) cells/mm^3] and CRB [161(150-174) cells/mm^3], and for women from ASIA/OC [185(165-197) cells/mm^3].

Adjusted Hazard Ratios (95%CI) for the effect of GO on the probability of starting cART as compared to native population are shown in Table 2 and Figure 2. Where the

likelihood-ratio test showed an interaction between GO and CD4 count at recruitment HR (95%) for GO is shown stratified by CD4 at recruitment.

Migrant men, with the exception of LA, had a lower probability of initiating cART compared to natives; the effect was strongest for CRB men, who had a 23% (18-27%) lower probability of initiating cART. However, these HRs varied depending on CD4 count at recruitment (overall interaction p-value<0.01), with the effect of GO being greater at higher CD4 count at recruitment (Figure 2). The heterogeneity of strata was only statistically significant for EE, SSA and CRB men, so CD4 count strata-specific aHR (95%CI) are provided in Table 2 for these groups. For men recruited at >500 cells/mm^3, the probability of initiating cART was 45% (36-53%) lower for CRB, 30% (17-40%) lower for EE and 25% (19-30%) lower for SSA compared to natives.

In women, overall, most migrant groups' CD4 count at cART initiation did not differ to those in native women except for SSA, whose probability was 3% (0-6%) higher, and LA, whose probability was 7% (0-13%) lower. Again, the effect was heterogeneous depending on the CD4 count at recruitment (overall interaction p-value<0.01), specifically for SSA, CRB, WEWC and NAME women; CD4-count strata-specific aHR (95%CI) are provided in Table 2 for these groups. For SSA and CRB women recruited at CD4 count>500 cells/mm^3 the probability of initiating cART compared to native women was 31% (24-38%) and 14% (0-29%) higher, respectively; in contrast, the effect was reversed or disappeared among women who entered into care at lower CD4 count, reaching a 9% (4-14%) lower probability for SSA women with CD4<100 cells/mm^3 at recruitment.

In some of the sensitivity analyses (Appendix Table 1) the lower probability of cART initiation in LA men reached statistical significance [in analyses (a) (c), (d) and (e)]. Some other differences were found, especially when using the modelled instead of the observed CD4 count [analysis (c)], and although the direction of the effect was preserved, some effects were no longer statistically significant, such as the previously described associations for EE and ASIA/OC men, and WEWC and NAME women.

Discussion

This is the first study to analyse the CD4 count at cART initiation in migrants from a wide range of geographical origins living with HIV in Western Europe. The CD4 cell counts at which the probability of having initiated treatment was 50%, was below 250 cells/mm^3 for all groups. Our results show that the majority of migrant men, particularly those from Sub-Saharan Africa, initiate cART at lower CD4 count than native men, with the gap tending to be wider in men recruited at CD4 count ≥350 cells/mm^3. In contrast, women appeared to initiate cART at similar CD4 count compared to native women, most likely reflecting HIV testing and cART initiation to prevent mother to child transmission in the context of antenatal care. In Sub-Saharan African and Caribbean women the probability of initiating cART was, in fact, higher than among natives when women were linked to care at CD4 count ≥350 cells/mm^3, although the effect disappeared or was even reversed for those linked to care at very low CD4 count.

Later cART initiation in migrants can result in worse health outcomes [2-5;18-19;24], but is also of public health concern [8], as it facilitates ongoing transmission of HIV within the community, thus compromising the 90-90-90 target set by UNAIDS that

relies on equitable access to cART for key populations worldwide [25]. Inequalities in timing of cART initiation may be explained by different factors associated with late diagnosis of HIV infection [12;26-30], impaired linkage and retention in clinical care [13-15;31-32] or to barriers to accessing antiretroviral drugs themselves [8;11; 13]. Disentangling the contribution of each of these factors is difficult.

Several barriers have been postulated to explain these gaps, including factors at structural, health care and community levels. Social exclusion, racism and discrimination, economic instability, precarious working conditions, higher geographical mobility and administrative and legal frameworks, with fear of discrimination or deportation after a positive diagnosis, have all been reported as barriers [12-14;26;33-35]. Fear of disclosure, language barriers and cultural differences in settings where translators and cultural mediators are not available, may also contribute to higher disengagement from HIV care [14;36]. In addition, it is likely that personal choices and prescribing physicians' views are influenced by health literacy and socio-economic status, which tend to be lower in most migrant groups [13]. The fact that migrants may already arrive to the destination country with HIV infection has also been discussed as contributing to late diagnosis and treatment. However, there is growing evidence that a significant proportion of HIV infections in migrants were acquired after their arrival into Western Europe [37-40].

Legal barriers deserve a special mention [8;14]. A recent ECDC report shows how 14 out of 29 EU/EEA countries denied access to cART for undocumented migrants in 2014 [11]. Furthermore, the austerity measures adopted following the economic crisis, with the reduction in the provision of essential services for migrants, have further

contributed to widening the gap [33;41]. In some countries such as Spain, repeated changes in legislation have generated confusion and uncertainty, even among health providers, around who can access what services free of charge, acting as deterrents for the adequate use of available services or denials to people who should be entitled to them [32;42].

In our study, we tried to discriminate the effects of delay in diagnosis and delay in initiation of treatment allowing for a differential effect of GO according to the CD4 count at which the person was recruited into the cohort, a surrogate for HIV diagnosis. Groups diagnosed later in the course of HIV infection (with CD4<350 cells/mm^3) tended to have similar probabilities of initiating cART than natives, while differences were indeed found for those diagnosed earlier. At higher CD4 count, guidelines did not consistently recommend initiation of cART and we may observe higher clinical variability, with the decision influenced by a wider range of determinants. The above mentioned barriers may have a greater impact in this situation and probably result in the later cART initiation observed in migrant men in our study. Future analyses will need to evaluate whether the differences observed in this study remain in the current context where guidelines recommend immediate cART, irrespective of CD4 cell count. Women, however, seem to be protected to a certain degree by HIV testing and treatment to decrease mother to child transmission in the context of antenatal care. This is reinforced by the consolidated practice of universal screening in pregnant women in the European context [12], and by the widely known and accepted legal framework that recognizes the right to free and accessible healthcare for pregnant women independent of their administrative status [26]. The high acceptability of

antenatal services among migrant women importantly contributes to the relatively high coverage, although gaps have been reported to persist for undocumented women [43]. This results in some migrant women, such as those from Sub-Saharan Africa or the Caribbean, having an even higher probability than natives of initiating cART when diagnosed at a high CD4 count. The notable exception is Latin American women, who exhibit a globally lower initiation of treatment, something that has not been previously explored in the literature and which merits further investigations.

Consistent with our results, a recent study found the likelihood of cART initiation in migrant men from Sub-Saharan Africa living in France was 15% lower than in French population when diagnosed between 350-500 cells/mm^3, with the difference widening with earlier diagnosis; in contrast, no difference was found in other migrant groups [16]. Other studies have failed to find any evidence of delayed initiation of cART in migrants, although lack of stratification by sex or CD4 count at diagnosis [18;44] and restriction to individuals with known date of seroconversion [45] may partially explain the discrepancy of results.

A limitation of this study was that we were unable to control for the heterogeneity of cART initiation recommendations across participating countries and throughout the study period. The composition of the COHERE collaboration has been changing throughout the time and the analysis of temporal trends may be biased by the incorporation or finalisation of specific cohorts within the collaboration. However, between 2004 and 2013 the recommendation to start cART at a CD4 count of 350 cells/mm^3 or below was widespread, and analysis restricted to years after 2004 led to similar conclusions.

Another limitation relates to the lack of information on the administrative and legal status, which could better identify the role of legal barriers and the risk of undocumented migrants, and on the socioeconomic status, which could lie on the pathway of the observed effects of GO. Our results are based in ad-hoc cohort studies, and has the advantage of achieving a large sample size. The composition of the migrant population and their characteristics in our study were similar to those reported by the European Centre for Disease Prevention and Control HIV surveillance system [10]. The study is specific to the Western European region and results are thus not generalizable to other geographical regions.

In summary, we have highlighted late initiation of cART in the migrant population in Western Europe, and differences in timing of cART initiation for some groups within migrant communities, specially for men. Addressing existing barriers to access HIV testing and care, and ensuring universal and free access to cART is important if we are to advance the e-limination of inequities and in the control of the HIV epidemic in Western Europe.

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