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SHORT COMMUNICATION

Children living with HIV in Europe: do migrants have worse treatment outcomes?

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Abstract

Objectives: To assess the effect of migrant status on treatment outcomes among children living with HIV in Europe.

Methods: Children aged < 18 years at the start of antiretroviral therapy (ART) in European paediatric HIV observational cohorts where ≥ 5% of children were migrants (defined as born abroad) were included. Three outcomes were considered: (i) severe immunosuppression-for-age; (ii) viraemic viral load (≥ 400 copies/mL) at 1 year after ART initiation; and (iii) AIDS/death after ART initiation. The effect of migrant status was assessed using univariable and multivariable logistic and Cox models.

Results: Of 2620 children included across 12 European countries, 56% were migrants. At ART initiation, migrant children were older than domestic-born children (median 6.1 vs. 0.9 years, $p < 0.001$), with slightly higher proportions being severely immunocompromised (35% vs. 33%) and with active tuberculosis (2% vs. 1%), but a lower proportion with an AIDS diagnosis (14% vs. 19%) (all $p < 0.001$). At 1 year after beginning ART, a lower proportion of migrant children were viraemic (18% vs. 24%) but there was no difference in multivariable analysis ($p = 0.702$), and no difference in severe immunosuppression ($p = 0.409$). However, there was a trend towards higher risk of AIDS/death in migrant children (adjusted hazard ratio = 1.51, 95% confidence interval: 0.96–2.38, $p = 0.072$).

Conclusions: After adjusting for characteristics at ART initiation, migrant children have virological and immunological outcomes at 1 year of ART that are comparable to those who are domestic-born, possibly indicating equity in access to healthcare in Europe. However, there was some evidence of a difference in AIDS-free survival, which warrants further monitoring.

KEYWORDS
children, Europe, HIV, migrant, mortality

INTRODUCTION

Migrants are a key population affected by HIV across Europe [1]. Migrant adults diagnosed with HIV in Europe are more likely to have advanced disease with low CD4 count and/or AIDS diagnoses at first presentation or at initiation of antiretroviral therapy (ART) compared with their domestic-born counterparts [2–4]. Once on treatment, they may experience a higher risk of disease progression and poorer retention in care [5–8].

There are, however, few comparable data in children living with HIV in Europe. With improved access to prevention of vertical transmission services in Europe over the last two decades, fewer children born domestically have HIV, and an increasing proportion of children living with HIV in Europe in recent years were born abroad, mostly in sub-Saharan Africa [9,10]. Understanding the health outcomes of this group is therefore of increasing importance. The largest European study to date investigating outcomes in migrant children is from the Netherlands. That study reported a higher risk of low CD4 count at diagnosis but comparable immunological and virological outcomes on ART in those born in sub-Saharan Africa compared with domestic-born children [11]; however it was limited by inclusion of patients from only one country, so further research across Europe is required.

In this study, we utilized patient-level data from paediatric HIV observational cohorts in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) to describe characteristics of migrant and domestic-born children receiving routine HIV care across Europe, and to assess the effect of migrant status on immunological and virological outcomes after ART initiation and AIDS-free survival.

METHODS

The inclusion criteria for this analysis were age < 18 years and treatment-naïve at initiation of combination antiretroviral therapy (ART) [defined as three or more drugs from two or more classes (excluding unboosted protease inhibitors (PIs)), or three or more nucleoside reverse transcriptase inhibitors (NRTIs) including abacavir] from 1996 onwards, with follow-up data through to 1 October 2016.

Migrant status was defined as having been born outside of the country of the cohort versus domestic-born, and children with unknown migrant status were excluded. This analysis was restricted to cohorts where ≥ 5% of patients were migrants (12 cohorts of 16 were included; excluded cohorts were from Romania, Russia, Thailand, Ukraine). Individual patient-level demographic, clinical and ART-related data were pooled using a modified HIV Cohort Data Exchange Protocol (www.hicdep.org).

Univariable and multivariable analysis was used to explore the effect of migrant status on three outcomes: (i) severe immunosuppression and (ii) non-suppressed viral load (VL) at 1 year after ART initiation, using logistic regression; and (iii) among children AIDS-free at the start of ART, AIDS-free survival after ART initiation, using Cox models.

Severe immunosuppression for age was based on the World Health Organization (WHO) definition: CD4 < 25% for children aged < 1 year; < 20% for 1 to < 3 years; < 15% for 3 to < 5 years; < 200 cells/μL or < 15% for ≥ 5 years [12]. Non-suppressed VL was defined as ≥ 400 HIV RNA copies/mL, and ≥ 50 copies/mL in sensitivity analyses. The closest CD4 and VL measurements to 1 year after ART initiation, within a window between 9 and 15 months, were used. Patients with < 1 year of follow-up after ART initiation were excluded from this analysis.

Analysis of AIDS-free survival was restricted to children who were AIDS-free at ART initiation. We assessed time to first AIDS-defining event [Centers for Disease Control and Prevention (CDC) 2014 definition [13]] or death as a combined outcome due to few events. Children were considered at risk from ART initiation and were censored at the earliest of last visit in paediatric care or 21st birthday. In sensitivity analysis, children with prior AIDS diagnoses were included, with an outcome of new AIDS event/death.

In multivariable analyses, estimates of the effect of migrant status were adjusted for the following potential confounders: sex; year of birth; mode of HIV acquisition; initial ART regimen; region; calendar year, age, weight-for-age *z*-score (WAZ), and severe immunosuppression at ART initiation. For WAZ and severe immunosuppression, measurements between 6 months before and 1 month after ART initiation were used. WAZ was based on the British 1990 growth charts [14]. Interactions between migrant status and year of birth, and non-proportional hazards for the analysis of AIDS-free survival were considered. Missing CD4 and weight values at ART initiation were imputed, with 20 imputed datasets created, applying Rubin's rules [15]. Sensitivity analyses compared outcomes among migrants born in sub-Saharan Africa against those who were domestic-born. All analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Of 2651 children followed in the eligible cohorts, 31 (1%) were excluded due to unknown migrant status. Of the remaining 2620, 1474 (56%) children were migrants; the proportion of migrants within each country ranged from 5% in Greece and Poland to 98% in Sweden (Table 1). Of 1161 migrant children with recorded country of birth, 980 (84%) were born in sub-Saharan Africa, 71 (6%) in Europe and 110 (9%) elsewhere. The median (interquartile range, IQR) durations of follow-up on ART among migrant and domestic-born children were 6.2 (3.4–9.2) and 7.8 (4.1–11.4) years, respectively ($p < 0.001$).

Migrant children were, on average, born in earlier calendar years than domestic-born children (77% vs. 56% born before 2003, $p < 0.001$), significantly older at HIV diagnosis [median (IQR) age, 6.1 (2.7–9.9) vs. 0.9 (0.2–3.3) years, $p < 0.001$], and at ART initiation [8.2 (4.0–12.0) vs. 1.8 (0.3–7.6) years, $p < 0.001$]. More migrant children had missing CD4 at ART initiation (26% vs. 17%); among those with data available, a larger proportion were severely immunocompromised compared with domestic-born children (48% vs. 40%, $p < 0.001$). A lower proportion of migrant children had an AIDS diagnosis by ART initiation (14% vs. 19%, $p = 0.003$), and active tuberculosis was rare in all children starting ART but was slightly more common in migrant children (2% vs. 1%, $p < 0.001$).

Non-suppressed VL and severe immunosuppression at 1 year after ART start

At 1 year on ART, lower proportions of migrant children had available VL and CD4 measurements compared with domestic-born children [74% and 85% had a VL available, respectively ($p < 0.001$), and 73% and 82% had a CD4 measurement ($p < 0.001$); Table 2].

TABLE 1 Demographics, characteristics at antiretroviral therapy (ART) initiation and follow-up status, by migrant status

	Domestic-born (*N* = 1146; 44%)	**Migrant (*N* = 1474; 56%)**	
	***n* (%) or median (IQR)**		***p***
Demographics			
Country of current residence			
Belgium	9 (11%)	72 (89%)	< 0.001
France	91 (71%)	37 (29%)	
Greece	18 (95%)	1 (5%)	
Italy	160 (55%)	130 (45%)	
The Netherlands	50 (24%)	162 (76%)	
Poland	54 (95%)	3 (5%)	
Portugal	24 (73%)	9 (27%)	
Spain	173 (60%)	117 (40%)	
Sweden	2 (2%)	84 (98%)	
Switzerland	27 (66%)	14 (34%)	
UK and Ireland	538 (39%)	845 (61%)	
Female sex	633 (55%)	752 (51%)	0.050
Ethnicity			
Black	440 (38%)	983 (67%)	< 0.001
Other	373 (33%)	144 (10%)	
Missing	333 (29%)	347 (24%)	
Mode of HIV acquisition			
Vertical	1108 (97%)	1258 (85%)	< 0.001
Other	8 (1%)	66 (4%)	
Missing	30 (3%)	150 (10%)	
Year of birth			
< 2003	638 (56%)	1131 (77%)	< 0.001
≥ 2003	508 (44%)	343 (23%)	
Place of birth			
Sub-Saharan Africa	–	980 (66%)	–
Europe	–	71 (6%)	
Other	–	110 (7%)	
Missing	–	313 (21%)	
Age at HIV diagnosis (years)			
N	916	1244	< 0.001
Median (IQR)	0.8 (0.2–3.2)	6.2 (2.8–10.0)	
Characteristics at ART initiation			
Calendar year			
Before 2004	371 (32%)	354 (24%)	< 0.001
2004–2007	360 (31%)	457 (31%)	
2008 or later	415 (36%)	663 (45%)	
Time between HIV diagnosis and ART initiation (months)			
N	916	1244	0.001
Median (IQR)	2.0 (0.6–22.0)	3.9 (0.9–26.4)	
Age (years)			
Median (IQR)	1.8 (0.3–7.6)	8.2 (4.0–12.0)	< 0.001

(Continues)

TABLE 1 (Continued)

	Domestic-born ($N = 1146$; 44%)	Migrant ($N = 1474$; 56%)	
	n (%) or median (IQR)		*p*
≤ 2	658 (57%)	285 (19%)	< 0.001
3–10	290 (25%)	620 (42%)	
≥ 11	198 (18%)	569 (39%)	
Severe immunosuppression			
Yes	379 (33%)	519 (35%)	< 0.001
No	573 (50%)	567 (38%)	
Missing	194 (17%)	388 (26%)	
Severe wasting (weight for age *z*-score < −2)			
Yes	131 (11%)	119 (8%)	0.001
No	602 (53%)	735 (50%)	
Missing	413 (36%)	620 (42%)	
Tuberculosis disease	7 (1%)	36 (2%)	< 0.001
AIDS diagnosis	219 (19%)	210 (14%)	0.003
Initial ART regimen			
Boosted PI-based	407 (36%)	494 (34%)	0.016
NNRTI-based	658 (57%)	911 (62%)	
NRTI only	42 (4%)	30 (2%)	
Other	39 (3%)	39 (3%)	
Follow-up status			
Duration of follow-up (years)			
Median (IQR)	7.8 (4.1–11.4)	6.2 (3.4–9.2)	< 0.001
Follow-up status			
Still in paediatric care	635 (55%)	724 (49%)	< 0.001
Transferred to adult care	207 (18%)	455 (31%)	
Censored at 21st birthday	86 (8%)	72 (5%)	
Dropped out	60 (5%)	89 (6%)	
Lost to follow-up	141 (12%)	111 (8%)	
Died	17 (1%)	23 (2%)	

Abbreviations: IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor.

Among those with a VL measurement at 1 year, 18% of migrant children versus 24% of domestic-born children had VL ≥ 400 copies/mL (Table 2) [odds ratio (OR) = 0.70 for migrant children vs. domestic-born, 95% confidence interval (CI): 0.56–0.88, $p = 0.002$]. However, this difference did not remain in multivariable analysis [adjusted OR (aOR) = 0.95, 95% CI: 0.71–1.26, $p = 0.702$], with adjustment for age and calendar year of ART initiation being the biggest confounders. Results were similar in sensitivity analyses using VL ≥ 50 copies/mL (aOR = 1.02, 95% CI: 0.81–1.28) (data not shown).

Among those with a CD4 measurement available at 1 year, similar proportions of migrant and domestic-born children had severe immunosuppression (8% and 6%, respectively; $p > 0.1$ in univariable and multivariable analyses).

In multivariable analysis there was no evidence of an interaction between migrant status and year of birth on either outcome (both $p > 0.4$).

Results when considering only migrants born in sub-Saharan Africa were similar (Table S1).

AIDS-free survival after ART start

Of the 2620 children initiating ART, 423 (16%) were excluded from the main analysis of AIDS-free survival as they already had an AIDS diagnosis when beginning ART, and a further 24 children (13 domestic-born and 11 migrant) were excluded due to unknown date of an AIDS-defining event. Among the remaining 2173 children who were AIDS-free at ART initiation, 120 (6%; 47 domestic-born

TABLE 2 Effect of migrant status on non-suppressed viral load, severe immunosuppression and first AIDS event/death at 1 year after antiretroviral therapy (ART) initiation

	Number with outcome available	Number meeting outcome	Univariable			Multivariable[a]		
			OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Non-suppressed viral load (≥ 400 copies/mL) at 1 year after ART initiation								
Domestic-born	906/1065 (85%)	216/906 (24%)	1	–	0.002	1	–	0.702
Migrant	1016/1367 (74%)	183/1016 (18%)	0.70	0.56–0.88		0.95	0.71–1.26	
Severe immunosuppression at 1 year after ART initiation								
Domestic-born	869/1065 (82%)	53/869 (6%)	1	–	0.174	1	–	0.409
Migrant	999/1367 (73%)	77/999 (8%)	1.29	0.90–1.85		0.82	0.52–1.30	
			HR	**95% CI**	***p*-value**	**aHR**	**95% CI**	***P*-value**
First AIDS event/death								
Domestic-born	–	49/918 (5%)	1	–	0.206	1	–	0.072
Migrant	–	81/1255 (6%)	1.26	0.88–1.79		1.51	0.96–2.38	

Abbreviations: (a)HR, (adjusted) hazard ratio; (a)OR, (adjusted) odds ratio; CI, confidence interval.

[a]Adjusted for: sex; grouped year of birth; mode of HIV acquisition; initial ART regimen; region; and grouped year of cART initiation, age group, weight-for-age z-score and severe immunosuppression at ART initiation.

and 73 migrants) had an AIDS event and 15 died (1%; three domestic-born and 12 migrant – of whom five also had an AIDS event). Overall, 5% of domestic-born and 6% of migrant children experienced the composite outcome of AIDS/death by the end of follow-up. The most common AIDS events were encephalopathy (40%) and tuberculosis (21%) among domestic-born and migrant children respectively (Table S2). Of the 15 deaths, six (40%) were caused by an HIV-related infection, four (27%) had another HIV-related cause, three (20%) were not directly HIV-related and the cause was unknown for the remaining two (13%), with no difference in cause by migrant status ($p = 0.577$) (Table S3).

At 5 years after ART initiation, the probability of AIDS-free survival was 94% (95% CI: 93–95%), with no difference by migrant status (log-rank test $p = 0.206$) (Figure S1). The rates of AIDS/death after starting ART were 7.4 (95% CI: 5.6–9.8) per 1000 patient-years of follow up among domestic-born, and 10.6 (8.5–13.1) among migrant children ($p = 0.052$). In multivariable analysis, there was some evidence of an independent effect of migrant status on risk of AIDS/death [adjusted hazard ratio (aHR) = 1.51, 95% CI: 0.96–2.38, $p = 0.072$; Table 2]. There was no evidence of non-proportional hazards. In sensitivity analysis including children with an AIDS diagnosis prior to ART initiation, the trend was weaker (aHR = 1.24, 95% CI: 0.86–1.78, $p = 0.251$; data not shown). In sensitivity analysis restricted to migrants born in sub-Saharan Africa there was evidence of an increased risk of AIDS/death (aHR = 1.84, 95% CI: 1.12–3.01, $p = 0.017$) (Table S1).

DISCUSSION

This study is one of the largest to date to explore the effect of migrant status on clinical outcomes on ART in children living with HIV across Europe, with data on over 2600 children from 12 countries. Migrants in this study were predominantly from sub-Saharan Africa, and were older at treatment initiation with a slightly higher proportion with poor immunological status at ART start compared with domestic-born children, comparable to findings reported in other paediatric studies [16]. However, the clinical outcomes in terms of immune and virological response at 1 year after ART initiation were similar between migrant and domestic-born children, after adjustment for key characteristics, in particular age and calendar year of ART initiation. These findings are consistent with a stand-alone analysis from the Dutch paediatric HIV cohort (patients from which were included here), which reported no difference by migrant status in long-term immune and viral response by 5 years on ART [11]. However, in our cohort, in the adjusted analysis there was some evidence of a trend towards increased risk of AIDS or death among migrant children who were AIDS-free at ART initiation, indicating a possible difference in longer-term clinical outcomes on ART in this larger multi-country cohort. This difference was greater when analysis was restricted to migrants born in sub-Saharan Africa. Further monitoring is required, in particular as children and adolescents move into young adulthood and transition to adult HIV care [17]. In addition, tuberculosis represented a higher proportion of the reported AIDS events among migrants, highlighting the need for screening and treatment of latent tuberculosis infection in this population.

Many adult HIV studies in western Europe have reported that migrants are at higher risk of late diagnosis and ART initiation (as observed in our cohort), although this does not always translate to poorer outcomes on treatment. One large study reported no difference in mortality by migrant status among men who have sex with men and heterosexual men, but higher risk of death was observed among migrant women with heterosexual mode of HIV acquisition from some geographical regions, and increased risk among migrant people who inject drugs [5]. This probably reflects important differences in health access and health-seeking behaviour across different adult populations. A study of pregnant women with HIV in Europe also reported a higher risk of late HIV diagnosis and low CD4 among migrant women as compared with domestic-born populations; however, there was no difference in detectable VL at delivery once on ART [18]. This may suggest equity in continuing access to care once initially linked.

This study has several limitations. First, there may be survivor bias of migrant children who survived the high mortality period of early infancy without ART [19], and were well enough to migrate. This may contribute to the lack of observed difference in the clinical outcomes in our study [20]. Further, we have not considered differences in access to ART. Second, migrant children were less likely to have CD4 and VL data available at ART initiation; if these data were not missing in a random way, this may have biased our multivariable model results, in either direction. Similarly, there may have been missing AIDS events and incomplete ART history, particularly in the migrant population, for whom ART use in their country of origin may not have been reported. Third, children classified as a migrant here represent a heterogeneous population from a range of countries/regions with no data on socioeconomic, orphan/adoption status available. Further, we have not considered second-generation migrants. Finally, the analyses did not explore longer-term immune and virological response, or differences in non-HIV-related conditions.

In conclusion, despite generally poorer characteristics at initiation, early immunological and virological response to treatment were similar between migrant and domestic-born children living with HIV in Europe after adjustment for key characteristics. However, there was some evidence of an increased risk of AIDS with longer duration on ART among migrant children, which warrants further monitoring.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

MVK, RLG, IJC, LCR conceived the project. AJ, IJC, RLG, SC, EC, LG, TG, ANJ, HS, CS, AB, MLN, JTR, JW, VS, EC, EV, FP, CK, MM, LM, LN and CT contributed to the collection of the data. The statistical analysis was conducted by MVK and EC. All authors are members of the EPPICC Migrant Project Team or Writing Committee, critically appraised the manuscript, and approved its submission.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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