Long-term Non-progression in Children With Perinatally Acquired HIV

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On behalf of The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study group

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Background

- Long-term non-progression (LTNP) of HIV refers to long-term survival without disease progression in the absence of antiretroviral treatment (ART).
- There is no consensus on the definition of LTNP in children. Understanding characteristics of LTNP may inform the HIV cure agenda.
- Previous estimates of the prevalence of LTNP in children range from 2-42%[1,2], using a wide variety of definitions of LTNP, e.g. using different age (5, 8, 10 years) and CD4 (500 cells/μL or 25%) thresholds[3].
- Previous studies have often been limited by small sample sizes and unclear denominators.
- **Aim:** To assess the prevalence of LTNP and the associated factors in children living with in Europe and Thailand.

Methods

Study population

- Children enrolled in observational cohorts in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC).

Definitions

- LTNP: absence of disease progression by age i) 5 years or ii) 8 years.
- Disease progression: any of the following: AIDS diagnosis, death, ART initiation (proxy for clinical progression) or ever meeting an immunodeficiency criterion.
- Different immunodeficiency criteria produced four different definitions of LTNP:
  - i. Age-specific CD4 z-score < -2.0 (relative to HIV-exposed uninfected children)
  - ii. Age-specific CD4 z-score < -3.0
  - iii. CD4 count < 500 cells/μL
  - iv. WHO advanced or severe immunodeficiency for age[4]*
- Children with "confirmed" LTNP had none of the above events before age 5 (or 8) years. Children were considered to have "possible" LTNP if they had no clinical events but the timing of CD4 depletion relative to age and ART initiation was unclear.

Inclusion criteria for analysis

- Children with perinatally acquired HIV or unknown mode of transmission and first seen in HIV care aged <10 years.
- ≥1 CD4 measurement available.
- Potential for follow-up to age 5 or 8 by time of data closure in 2016 (born in 2011 / 2008 or earlier).
- Not lost to follow-up before age 5 / 8 years.

Statistical analysis

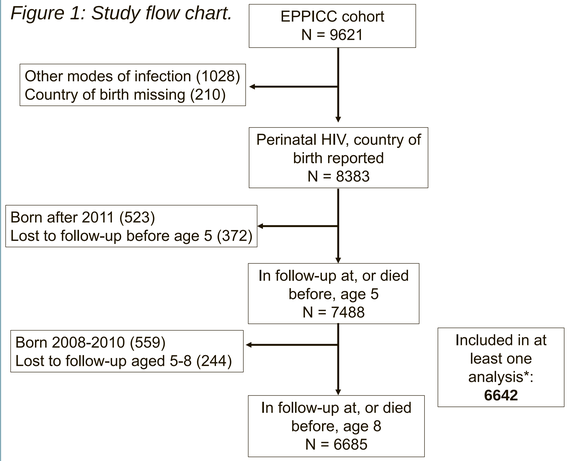
- Factors potentially associated with confirmed LTNP status (sex**, region of cohort and birth year) were explored using multivariable logistic regression for criterion i. All analyses were stratified by country of birth (domestic versus abroad).

* CD4% <30, <25, <20, <15 at age <11m, 12-35m, 36-59m, >5y, or CD4 count <350/μL at >5y
** Data on gender were not available

Results

- Of 9621 children followed in EPPICC, 6642 (69%) met the inclusion criteria in 16 cohorts from 12 European countries and Thailand (Figure 1).

Figure 1: Study flow chart.



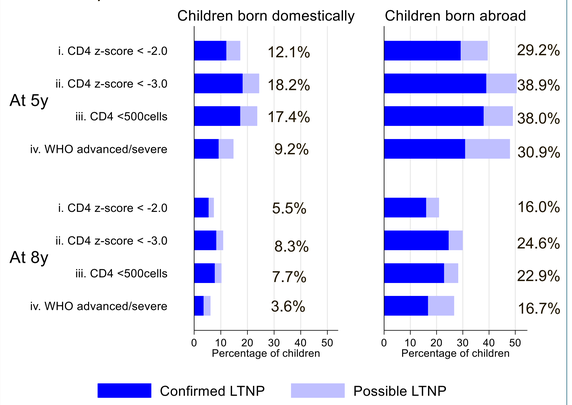
* Denominator varies by definition depending on availability of CD4 data

- Participant characteristics are shown in Table 1. 1468/6642 children (22.1%) were born abroad.

Table 1: Characteristics of children included in at least one analysis (n=6642). Data are n (%) or median [IQR].

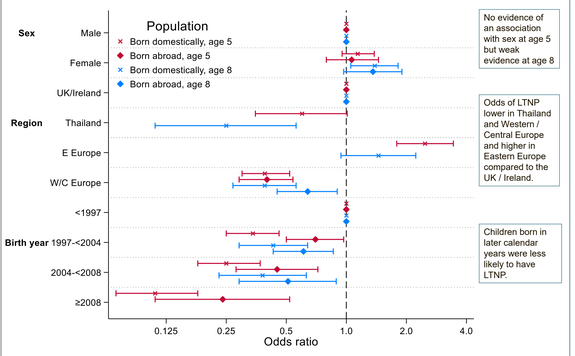
		Born domestically (n=5174)	Born abroad (n=1468)
Sex	Female	2715 (52.5)	774 (52.8)
Year of birth		1998 [1993-2004]	1998 [1994-2002]
Age first seen in cohort (y)		1.0 [0.1-2.8]	4.8 [2.2-7.6]
Year first seen in cohort		2001 [1994-2006]	2004 [2000-2007]
Region	UK / Ireland	775 (15.0)	840 (57.2)
	Western / Central Europe	2385 (46.1)	614 (41.8)
	Eastern Europe	1549 (29.9)	5 (0.3)
	Thailand	465 (9.0)	9 (0.6)
Mode of HIV acquisition	Perinatal	5070 (98.0)	1387 (94.5)
	Unknown	104 (2.0)	81 (5.5)
Ever on ART		4596 (88.9)	1299 (88.5)
Age at ART initiation (y)		2.8 [0.8-5.9]	5.9 [3.0-9.7]
Year of ART initiation	<1997	1147 (25.0)	111 (8.6)
	1997 - <2004	1402 (30.5)	408 (31.4)
	2004 - <2008	920 (20.0)	333 (25.6)
	≥2008	1127 (24.5)	447 (34.4)
Duration of follow-up (y)		10.8 [6.8-15.9]	9.5 [6.1-13.1]

Figure 2: Prevalence of confirmed and possible LTNP in children by age 5 and 8 years, according to different immunological criteria and by country of birth. Percentages show the prevalence of confirmed LTNP.



- Prevalence of LTNP varied markedly depending on the definition (Figure 2):
  - e.g. in children born domestically at age 5 years the prevalence of confirmed LTNP ranged from 9.2% (criterion iv) to 18.2% (criterion ii)
  - at age 8 years, prevalence of confirmed LTNP was lower across all definitions.
- Prevalence of confirmed LTNP was approximately 2-3 times higher in children born abroad versus those born domestically.
- Associations between sex, region and birth year and LTNP (criterion 1) are summarised in Figure 3.

Figure 3: Factors associated with LTNP status (definition i) at age 5 and 8 years for children born domestically and abroad.



Odds ratios (95% CIs) from four different multivariable logistic regression models (one per population) including sex, region and birth year. [No estimates for children born abroad for Thailand or Eastern Europe because numbers of children born abroad were small in these regions and none met the definition of LTNP.]

Conclusions

- The prevalence of LTNP is highly dependent on the age threshold and immunodeficiency criteria used in the definition.
- Key limitations are:
  - Selection bias of healthy children born abroad surviving long enough to migrate (reflected in higher prevalence of LTNP in children born abroad).
  - Lack of data (including CD4) before migration.
  - We assumed that children had not experienced progression events (including ART initiation) before presenting to care.
  - We used ART initiation as a proxy for clinical progression; the validity of this assumption changes over time with the shift towards immediate ART for all children, irrespective of immune/clinical status – accounting for the lower prevalence of LTNP with later calendar year of birth.
- Estimates for domestic born children are likely to be subject to less bias, with LTNP prevalence at age 8 ranging from ~4% to ~9%, broadly similar to estimates for adults (~2-9%)[5-7].
- Age 5 is likely too early to define LTNP as many more children had progressed by age 8.
- This work is ongoing. Future analysis will further refine the definition of LTNP (e.g. requiring multiple CD4 measurements below the threshold or including viral load measurements) and assess subsequent outcomes.

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Acknowledgements

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