Long-term trends in mortality and AIDS-defining events among perinatally HIV-infected children across Europe and Thailand

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Background: There are limited data on the prognostic effects of time-updated covariates on long-term mortality rates of perinatally HIV-infected children after starting ART. We analysed individual patient data from 19 cohorts in 16 European countries and Thailand in EPPICC.

Methods: Perinatally HIV-infected children aged <18yrs starting cART were followed until death, loss to follow-up (LTFU), transfer to adult care, their 21st birthday or last visit to 31/12/2013. Crude rates of death and first AIDS-defining events were calculated. Baseline and time-updated risk factors for death ≤/>6 months of cART and progression to AIDS were assessed using inverse-probability-censoring-weighted Cox models to account for informative censoring of LTFU.

Results: Of 3527 children, 32%, 20%, 18% and 30% were from the UK/Ireland, Thailand, Russia/Ukraine, and the rest of Europe respectively. At cART initiation, median (IQR) age was 5.2(1.4-9.3) years and 42% had severe WHO immunological stage. Median follow-up was 5.6(2.9-8.7) years. There were 94 deaths and 174 first AIDS-defining events, of which 43(46%) and 79(45%) occurred within 6 months of cART initiation. The crude mortality rate was 2.50[95%CI 1.86-3.38]/100 person-years (PY) in the ≤6 month period, and 0.27[0.21-0.36] thereafter. 59(63%) {31≤6 months} deaths were from HIV-related infections, 19(20%) {9} HIV-related non-infectious conditions, 12(13%) {1} HIV-unrelated, and 4(4%) {2} unknown. The rate of first AIDS-defining event was 0.88[0.76-1.02]/100PY, including 31(18%) HIV encephalopathy, 29(17%) tuberculosis and 25(14%) HIV wasting syndrome. Table 1 shows multivariable predictors of increased risk of death >6 months of cART. Predictors for death ≤6 months (baseline only) and progression to AIDS (baseline and time-updated) were broadly similar.

Conclusion: Almost half of deaths occurred ≤6 months of cART, after which current severe WHO immune stage, low BMI-for-age z-score, and fewer VL copy-years suppressed were the strongest predictors for mortality. The raised mortality risk in those age≥14 and in middle-income countries raises concern.

Table: Predictors of death >6 months of cART

Variable		Adjusted HR (95% CI)	P
Country type	Middle-income (Russia, Ukraine, Thailand)	ref	0.028
	High-income	0.5(0.2–0.9)	
Calendar year at cART start	1997–<2004	Ref	0.035
	2004–<2008	0.4(0.2–0.8)	
	≥2008	0.5(0.1–1.5)	
BMI-for-age z-score at cART start	>0	0.2(0.1–0.6)	0.045
	-3 to 0	Ref	
	<-3	0.5(0.2–1.6)	
VL copy-years suppressed (≤400c/ml) since cART initiation (per year increase)		0.7(0.6–0.9)	0.001
Current (time updated) age (years)	<2	4.2(1.4–12.7)	0.002
	2–<5	0.2(0.1–1.8)	
	5–<14	Ref	
	≥14	2.1(1.0–4.2)	
Current (time updated) WHO immune stage severe	No	0.1(0.1–0.2)	<0.001
	Yes	Ref	
Current (time updated) BMI-for-age z-score	>0	1.1(0.4–2.8)	<0.001
	-3 to 0	Ref	
	<-3	19.5(7.2–52.8)	