Duration of first line antiretroviral therapy (ART) in children in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

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on behalf of the EPPICC study group in EuroCoord

Background

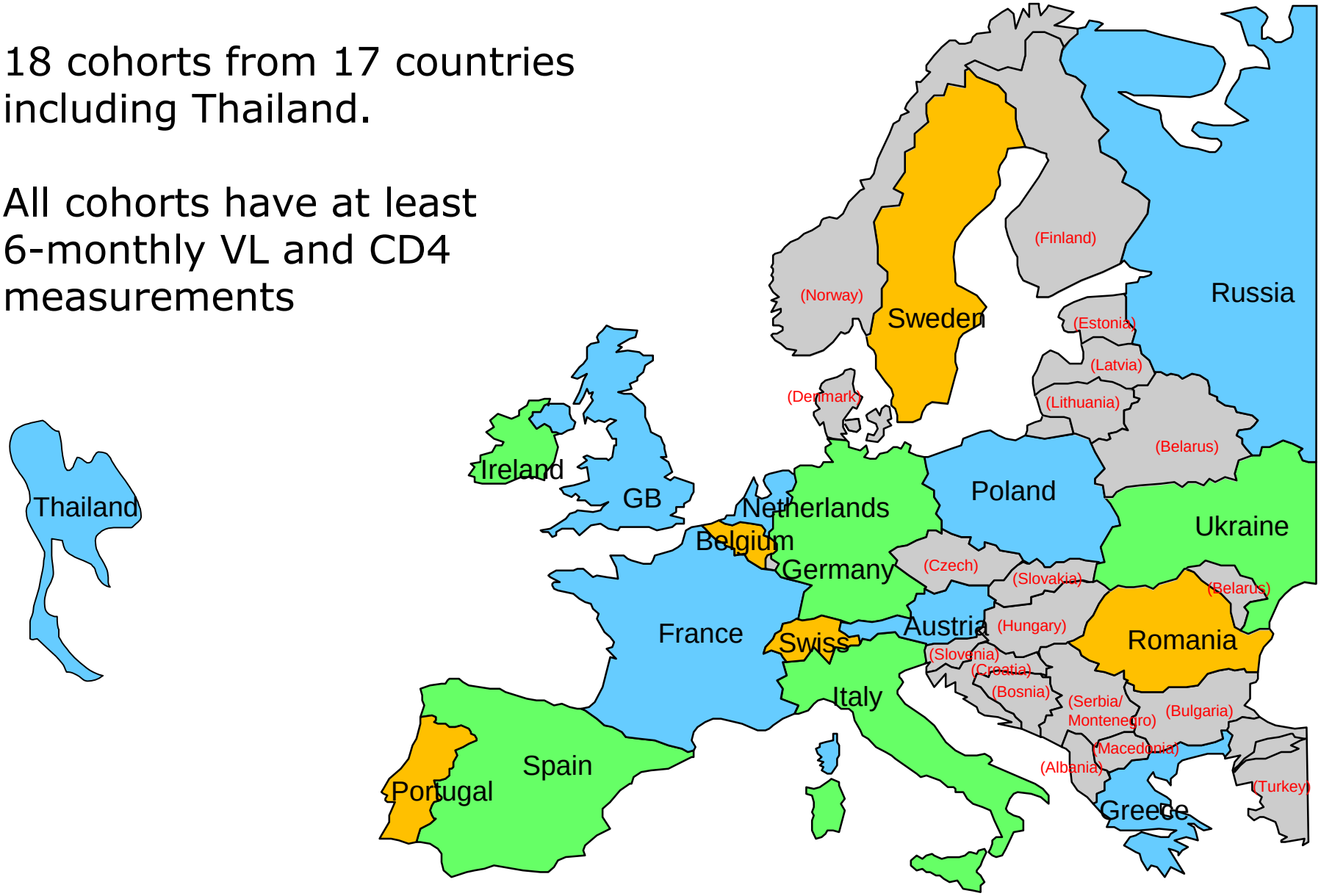
- Limited data on durability of first line ART in children in routine care settings across regions
- Estimated rates of switch vary
  - Clinical trials: 23% in PENPACT-1[1], ~5% in ARROW[2] and 2% in CHER[3] at 5 years of ART
  - Observational cohorts: 17% in EPPICC[4] infants, 21% in Thailand[5] at 5 years and 6.2% at 3 years in South Africa[6].
- Studies used different definitions of 'switch' and regimens varied
- Need data to inform:
  - programme planning & forecasts for paediatric formulations
  - treatment guidelines

1. PENPACT-1. Lancet ID 2011; 2. Arrow Trial; Lancet 2013;381(9875):1391-403; 3. CHER: Cotton et al.; Lancet 2013;382(9904):1555-563; 4 Judd, EPPICC: AIDS 2011; 5. Collins et al. JAIDS 2013; 6. Davies et al. JAIDS 2011

EPPICC

18 cohorts from 17 countries including Thailand.

All cohorts have at least 6-monthly VL and CD4 measurements



Methods

- Inclusion criteria: age<18 years at initiation of a 'standard' ART regimen: NNRTI or boosted PI + ≥2NRTI.
- Switch to second line defined as:
  - (i) change across drug class (PI to NNRTI or vice versa) and ≥1 NRTI;
  - (ii) change within PI-class plus ≥1 NRTI;
  - (iii) single to dual PI; or
  - (iv) an addition of a new drug class (eg. PI to an NNRTI-based regimen)
- Ignored switches with reason due to simplification, TB or pregnancy
- Competing risk model with death as competing risk to switch

Results

- 3,696 children included : 48% male, 90% perinatally infected. Median duration of follow up: 5.6 years [2.9-8.7].

Characteristics at ART initiation	
Age in years, median [IQR]	6.0 [1.7-10.4]
CD4% if <5 yrs ; CD4 cell count if ≥5 yrs	20% [14-31%]; 215 cells [60-376]
Viral load, log_{10} copies/mL	5.0 [4.4-5.6]
CDC stage C	431 (12%)
Initial regimen: EFV-based	1193 (32%)
NVP based	1123 (30%)
PI-based	1214 (33%)
NNRTI+3NRTI	166 (4)
Region: UK/Ireland	1077 (29%)
Thailand	695 (19%)
Ukraine	510 (14%)
Russia	137 (4%)
Rest of Europe	1277 (35%)

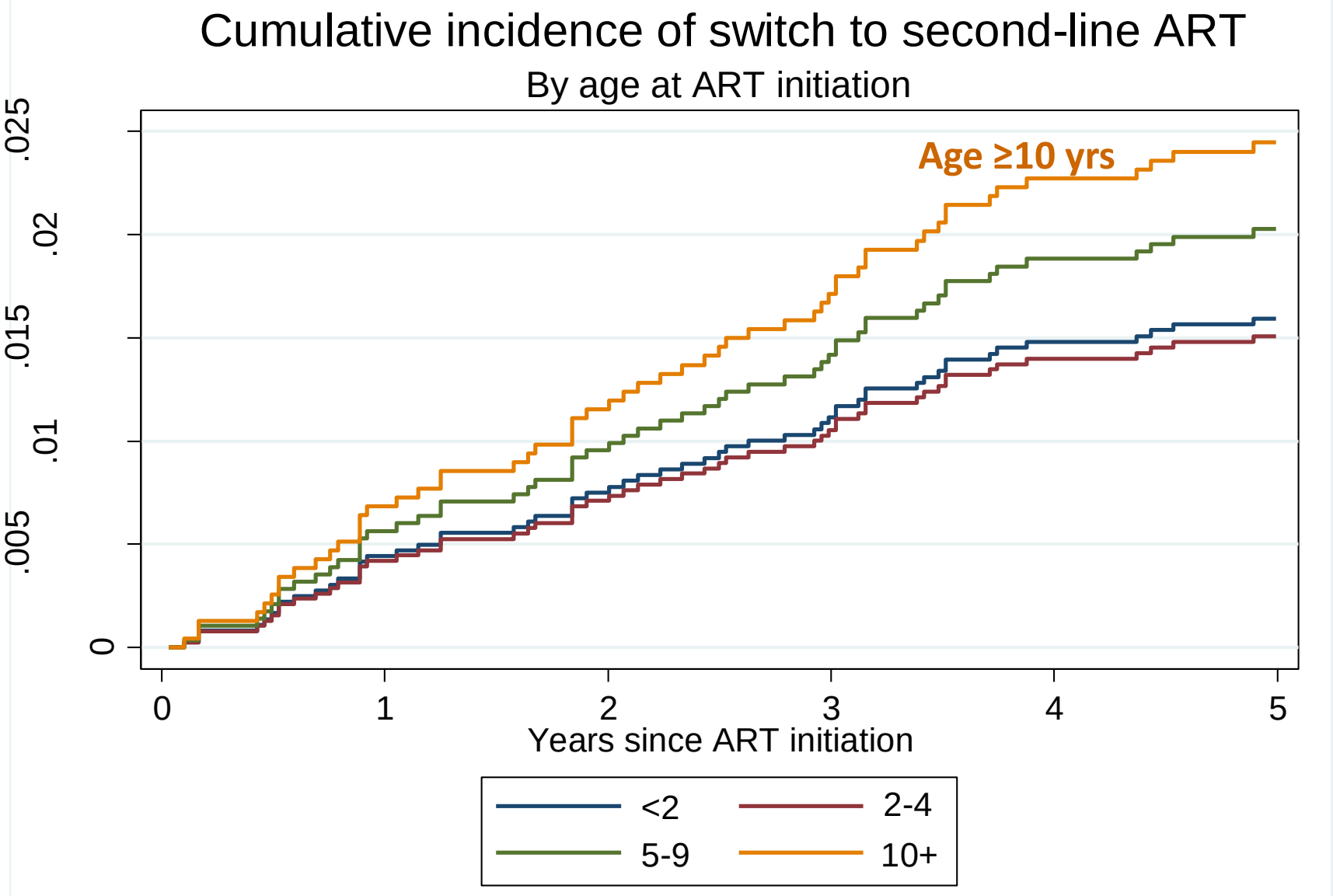
Results

- Overall, 107 (3%) children died, 514 (14%) lost to follow up and 829 (22%) met the definition of switch.
- Cumulative proportion of switch:
  - **14% (95% CI, 13-15) at 3 years**
  - **21% (95% CI, 20-23) at 5 years**
- Median time to switch: 30 months [IQR, 15-58]
- Reasons for switch were reported in 654/829 (79%):
  - **63% were for failure**
  - 12% toxicity
  - 25% other reasons.
- Assessing failure in the 6 months prior to switch:
  - 587/829 **(71%)** had VL>1000 copies *or* a new/recurrent CDC B/C event *or* no CD4 gain from baseline.
- Time to switch was similar in those with/without reason for switch

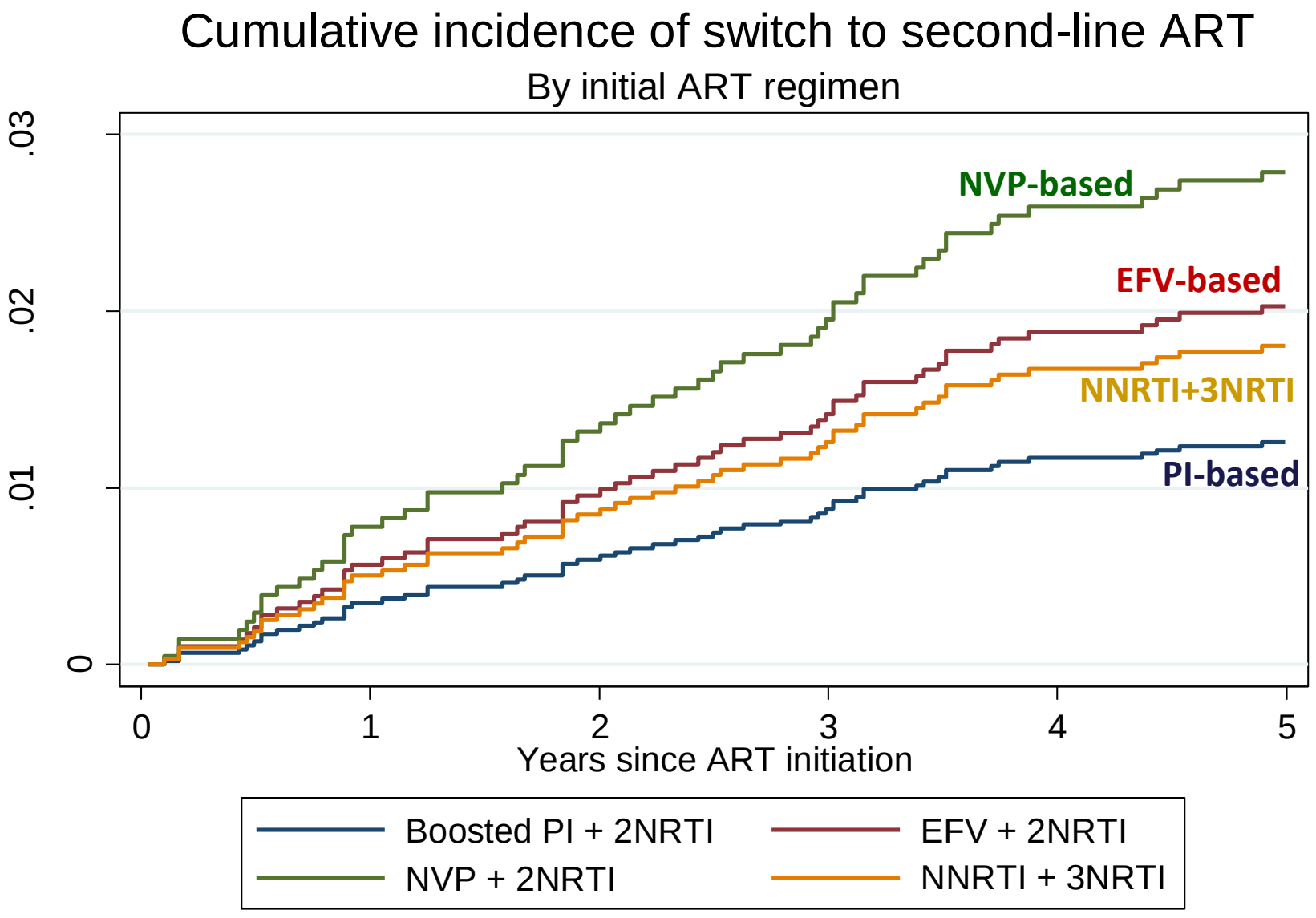
Predictors of switch

		Multivariable model		
		SHR	95% CI	p
Region	UK/Ireland	1		<0.0001
	Rest of Europe	0.90	(0.76-1.07)	
	Russia/Ukraine	0.65	(0.47-0.88)	
	Thailand	0.52	(0.42-0.64)	
Age at ART initiation, years	<2	1		<0.0001
	2-4	0.95	(0.75-1.20)	
	5-9	1.27	(1.03-1.58)	
	10+	1.54	(1.24-1.92)	
First-line regimen	EFV + 2NRTI	1		<0.0001
	NVP + 2NRTI	1.38	(1.16-1.65)	
	NNRTI+3NRTI	0.89	(0.62-1.27)	
	bPI + 2 NRTI	0.62	(0.49-0.78)	
VL at ART initiation, c/ml	<100,000	1		0.0001
	≥100,000	1.37	(1.14-1.64)	

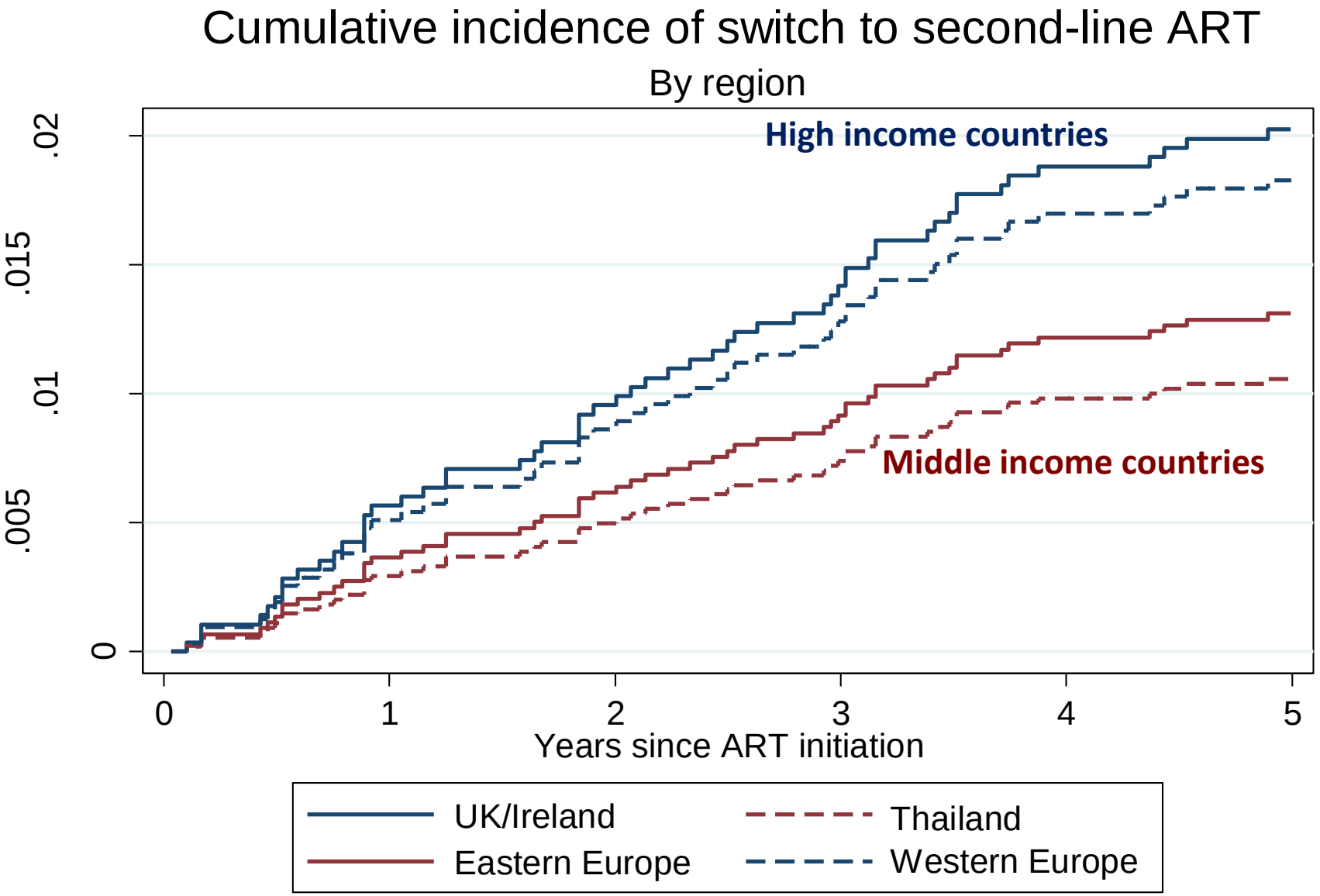
Age at Initiation of ART



Initial regimen



Cohort Region



Sensitivity Analyses

- Including switches across class or within PI class with no change in NRTI
  - 112 additional people switched
  - 91% NNRTI -> PI with **no change to NRTI**; 46% Thailand, 26% UK/Ireland
  - Cumulative proportion of switch: **23% (95% CI, 22-25) at 5 years**
  - Thailand becomes more similar to Russia/Ukraine; other risk factors unchanged.
- Ignoring switches in first 6 months:
  - 67 switches: 19% bPI, 33% EFV, 36% NVP, 12% 3NNRTI
  - Cumulative proportion of switch: **19% (95% CI, 17-21) at 5 years**
  - No change in factors associated with switch
- Treating LTFU as a competing risk: No change in risk factors

Conclusion

- 21% of children in EPPICC, with access to VL and CD4 monitoring, switched to second line ART by 5 years of therapy
- two-thirds of switches were failure related
- older age, higher viral load at ART initiation, and NVP based regimen associated with more rapid time to switch
- children in Thailand, Russia and Ukraine switched later compared to those in Western Europe, possibly due to lack of available second-line regimen

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- **Belgium:** Hospital St Pierre Cohort, Brussels (Dr Tessa Goetghebuer)
- **France:** French Perinatal Cohort Study / Enquête Périnatale Français (Dr Josiane Warszawski)
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- **Greece:** Greek cohort (Dr Vana Spoulou)
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- **Portugal:** Centro Hospitalar do Porto (Laura Marques)
- **Portugal:** Lisbon paediatric cohort (Filipa Prata)
- **Romania:** "Victor Babes" Hospital Cohort, Bucharest (Dr Luminita Ene)
- **Russia:** Republican Hospital of Infectious Diseases, St Petersburg (Prof E Voronin, Dr Inga Latysheva)
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- **Sweden:** Swedish Cohort Study (Lars Naver)
- **Switzerland:** Swiss Mother and Child HIV Cohort Study (Dr Christoph Rudin)
- **Thailand:** Perinatal HIV Prevention Trials cohort (Dr Gonzague Jourdain)
- **Ukraine:** Paediatric HIV Cohort (Dr Ruslan Malyuta, Dr Galena Kiseleva)
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