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MAJOR ARTICLE

Time to Switch to Second-line Antiretroviral Therapy in Children With Human Immunodeficiency Virus in Europe and Thailand

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Background. Data on durability of first-line antiretroviral therapy (ART) in children with human immunodeficiency virus (HIV) are limited. We assessed time to switch to second-line therapy in 16 European countries and Thailand.

Methods. Children aged <18 years initiating combination ART (≥2 nucleoside reverse transcriptase inhibitors [NRTIs] plus nonnucleoside reverse transcriptase inhibitor [NNRTI] or boosted protease inhibitor [PI]) were included. Switch to second-line was defined as (*i*) change across drug class (PI to NNRTI or vice versa) or within PI class plus change of ≥1 NRTI; (*ii*) change from single to dual PI; or (*iii*) addition of a new drug class. Cumulative incidence of switch was calculated with death and loss to follow-up as competing risks.

Results. Of 3668 children included, median age at ART initiation was 6.1 (interquartile range (IQR), 1.7–10.5) years. Initial regimens were 32% PI based, 34% nevirapine (NVP) based, and 33% efavirenz based. Median duration of follow-up was 5.4 (IQR, 2.9–8.3) years. Cumulative incidence of switch at 5 years was 21% (95% confidence interval, 20%–23%), with significant regional variations. Median time to switch was 30 (IQR, 16–58) months; two-thirds of switches were related to treatment failure. In multivariable analysis, older age, severe immunosuppression and higher viral load (VL) at ART start, and NVP-based initial regimens were associated with increased risk of switch.

Conclusions. One in 5 children switched to a second-line regimen by 5 years of ART, with two-thirds failure related. Advanced HIV, older age, and NVP-based regimens were associated with increased risk of switch.

Keywords. HIV; children; antiretroviral therapy; second-line; switch.

Worldwide, an estimated 2.1 million children aged <15 years were living with human immunodeficiency virus (HIV) in 2016, of whom 43% were accessing antiretroviral therapy (ART), with coverage expected to increase further [1]. Sustaining long-term viral suppression on ART throughout childhood and adolescence is a challenge [2]. Observational cohorts in middle- and high-income countries with routine viral load (VL) monitoring have reported cumulative risk of virological failure in children ranging from 18% to 40% at 3–5 years after ART start [3–6]. As children currently require lifelong treatment, subsequent ART options will inevitably be required, and therefore program planning and forecasting demand for pediatric formulations are needed.

There remain limited and often conflicting estimates on the use of second-line ART in children, with wide variations in both clinical trials and observational cohorts, ranging from 2%–23% switching at 5 years after ART initiation [6–11]. This reflects variation in initial regimens, monitoring and switching strategies, availability of alternative regimens across studies and settings, and differences in the definitions of "switch" used. Some studies have restricted switch analyses to children with confirmed or unconfirmed virological failure [3, 12], which may underestimate the broader use of second-line treatment due to clinical and/or immunological failure, or major treatment limiting toxicities [6, 13].

In this study, we assessed time to switch to second-line ART for any cause and associated factors in the context of routine VL monitoring, within the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), composed of cohorts across 16 European countries and Thailand. These cohorts offer long-term follow-up data to assess incidence of switch in routine care settings across regions, which may inform other countries moving toward VL monitoring [14].

METHODS

Nineteen pediatric HIV observational cohorts across 17 countries contributed to an individual patient data meta-analysis carried out in December 2014. Routine demographic, clinical, laboratory, and treatment-related data were pooled electronically using a modified HIV Cohorts Data Exchange Protocol (HICDEP; www.hicdep.org). Children were included in this analysis if they were aged <18 years at start of a "standard" combination ART

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regimen, defined as ≥2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI). Children who participated in clinical trials of switching strategies or treatment interruption were excluded. All cohorts received local ethics approval to transfer anonymized data for this study.

Switch to second-line ART was defined as either (*i*) change across drug class (from NNRTI to PI or vice versa) or change within PI class, plus change of ≥1 NRTI; (*ii*) change from single to dual PI; or (*iii*) addition of a new drug class. Switches with documented reasons of simplification, tuberculosis prophylaxis, or pregnancy were ignored. This stringent definition of switch was used to reflect World Health Organization (WHO) and European guideline recommendations on the management of treatment failure in children [15–17]. In sensitivity analyses, we (*i*) ignored any switches during the first 6 months after ART initiation, as these were unlikely to be related to treatment failure, and (*ii*) relaxed our switch criteria by not requiring a change of ≥1 NRTI when switching across drug class or within PI class, if the reason for switch was reported as failure, as some settings may need to preserve NRTIs.

Among patients meeting our definition of switch, we described the reasons reported for switching and explored evidence for clinical failure in those with missing reason (defined as VL >1000 copies/mL; new Centers for Disease Control and Prevention [CDC] stage B/C event); or no CD4 gain from ART initiation, within the 6 months prior to switch). We describe the characteristics at time of switch and virological response (<400 copies/mL) at 12 and 24 months after switch.

Time to switch was summarized using cumulative incidence, accounting for competing risks of death and loss to follow-up. Children were at risk from ART start until the earliest of switch, death, last visit in pediatric care, or 21st birthday. Cohorts contributed follow-up data through to December 2013 except for Germany (until April 2012), Portugal (September 2013), and Romania (October 2013). Loss to follow-up was defined as children not known to have died or transferred to another clinic, whose last visit was >2 years before the cohort censoring date, or children reported as lost to follow-up by their cohort.

The associations between time to switch and characteristics at ART initiation were investigated using competing risks proportional hazards regression [18]. In univariable analysis, associations with the following factors at the start of ART were explored: age, sex, immunosuppression (WHO 2007 classification severe vs nonsevere for age [19]), VL, CDC stage (C vs N/A/B), initial ART regimen, calendar year (1997–2003, 2004–2007, ≥2008), region of cohort (United Kingdom [UK] and Ireland, Thailand, Russia and Ukraine [Eastern Europe], and remaining countries [Central and Western Europe]). The final multivariable model was selected using backwards elimination (exit probability $P = .05$), with baseline hazard stratified by region. Region was not included in the multivariable model as a covariate due to evidence of non-proportional hazards between regions. The functional form of continuous age was explored using regression splines. Differences in the effect of initial regimen on switch by age and year at ART start were explored. A subgroup analysis in children aged <3 years in the UK/Ireland compared nevirapine (NVP) plus 3 NRTIs (rarely used in other regions) to other initial regimens. *P* values are 2-sided, and analyses were carried out using Stata version 14.1 software (StataCorp, College Station, Texas).

RESULTS

Of 3953 children who initiated ART, 3668 (93%) met the study inclusion criteria (88 were excluded due to participation in clinical trials; 197 were initiated on nonstandard regimens). Half of the children were male; 90% were perinatally infected (Table 1).

The 3 largest cohorts were from the UK/Ireland (29% of children), Thailand (19%), and Ukraine (13%). Earliest year of ART initiation ranged from 1997 in UK/Ireland to 2002 in Thailand. Approximately one-third of children started ART on efavirenz (EFV)–, NVP-, or PI-based regimens (93% lopinavir/ritonavir). Median age at the start of ART was 6.1 (interquartile range (IQR), 1.7–10.5) years, and lower in children who initiated on PI- and NVP-based regimens than EFV-based regimens (Table 1). A larger proportion of children initiating on PI-based regimens started treatment in later calendar years (2008 and beyond) compared to other regimens. Children in the UK/Ireland and Thailand were more likely to initiate on NNRTI-based regimens compared with other regions where more children started on PI-based regimens. The median duration of follow-up after start of ART was 5.4 (IQR, 2.9–8.3) years. The median gap between VL measurements after ART start varied across regions: 36, 26, and 13–14 weeks in Eastern Europe, Thailand, and the rest of Europe, respectively.

Switch to Second-line ART

Overall, 820 (22%) children met the definition of switch, while 71 (2%) died and 374 (10%) were lost to follow-up before switching. There were significantly fewer patients lost to follow-up in the UK/Ireland, more deaths in Thailand, and fewer patients switching in Eastern Europe ($P < .001$) (Supplementary Figure 1). Among those who switched, the median time from ART start to switch was 30 (IQR, 16–58) months, the majority (72%) switching from an NNRTI- to a PI-based second-line regimen.

The overall cumulative incidence of switch was 14% (95% confidence interval [CI], 13%–15%) at 3 years, 21% (95% CI, 20%–23%) at 5 years, and 27% (95% CI, 26%–29%) at 7 years after ART start. The cumulative incidence varied across regions, and these regional differences changed over time (Figure 1). At 1 year after ART start, Thailand and Eastern Europe had lowest cumulative incidence of switch at 2% (95% CI, 1%–3%), but it rapidly increased in Thailand to 16% (95% CI, 13%–19%) by 3 years, a similar level to Western and Central Europe and the

Table 1. Characteristics of Children at Antiretroviral Therapy (ART) Initiation, by Initial ART Regimen

Characteristic	bPI (n = 1191)	EFV (n = 1214)	NVP (n = 1263)	Total (N = 3668)
Male sex	559 (47)	589 (49)	599 (47)	1747 (48)
Perinatal infection[a]	1110 (93)	973 (80)	1208 (96)	3291 (90)
Age, y, median (IQR)	3.2 (0.7–8.4)	9.5 (6.1–12.6)	3.9 (0.9–8.5)	6.1 (1.7–10.5)
<1	357 (30)	4 (0)	340 (27)	701 (19)
1–2	224 (19)	67 (6)	226 (18)	517 (14)
3–5	182 (15)	220 (18)	202 (16)	604 (16)
6–10	233 (20)	474 (39)	347 (27)	1054 (29)
≥11	195 (16)	449 (37)	148 (12)	792 (22)
CDC stage C	146 (12)	155 (13)	129 (10)	430 (12)
CD4% in those aged <5 y (n = 1183/1614), median (IQR)	23 (16–32)	16 (11–22)	22 (14–34)	21 (14–32)
CD4 count in those aged ≥5 y (n = 1614/2054), median (IQR)	281 (134–462)	202 (55–360)	170 (43–358)	220 (63–388)
WHO severely immunocompromised (n = 2808)	436 (48)	634 (63)	508 (57)	1578 (56)
HIV RNA, $\log_{10}$ copies/mL (n = 2518), median (IQR)	5.2 (4.5–5.3)	5 (4.4–5.4)	5.1 (4.4–5.7)	5 (4.4–5.6)
Calendar year of ART initiation				
1997–2003	127 (11)	356 (29)	516 (41)	999 (27)
2004–2007	357 (30)	477 (39)	498 (39)	1332 (36)
≥2008	707 (59)	381 (31)	249 (20)	1337 (36)
Region				
UK/Ireland	201 (17)	438 (36)	436 (35)	1075 (29)
Eastern Europe	402 (34)	122 (10)	108 (9)	632 (17)
Central and Western Europe	541 (45)	407 (34)	321 (25)	1269 (35)
Thailand	47 (4)	247 (20)	398 (32)	692 (19)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; bPI, boosted protease inhibitor; CDC, Centers for Disease Control and Prevention; EFV, efavirenz; HIV, human immunodeficiency virus; IQR, interquartile range; NVP, nevirapine; WHO, World Health Organization.

[a]Nonperinatal route of infection reported as parenteral (noninjected drug use) (5%), blood products/transfusion (2%), other (1%), or unknown (3%).

UK/Ireland, and plateaued thereafter. At 5 years after ART initiation, the cumulative incidence of switch was lowest in Eastern Europe at 12% (95% CI, 9%–16%), and ranged from 20% to 25% in the other regions.

Reasons for Switch

Among those switched to second-line ART, 652 (80%) had a documented reason for switch available, of which 63% were "treatment failure," 11% "toxicity," and the remainder for "other reasons" including noncompliance. Clinicians were more likely to report toxicity as the reason for switching from a PI-based regimen, whereas NVP-based regimens were more likely to be for failure ($P < .001$) (Figure 2). Among the 168 (20%) children with missing reason for switch, 56% were likely to be due to treatment failure based on their clinical, immunological, and virological data in the 6 months prior to switch. There was no

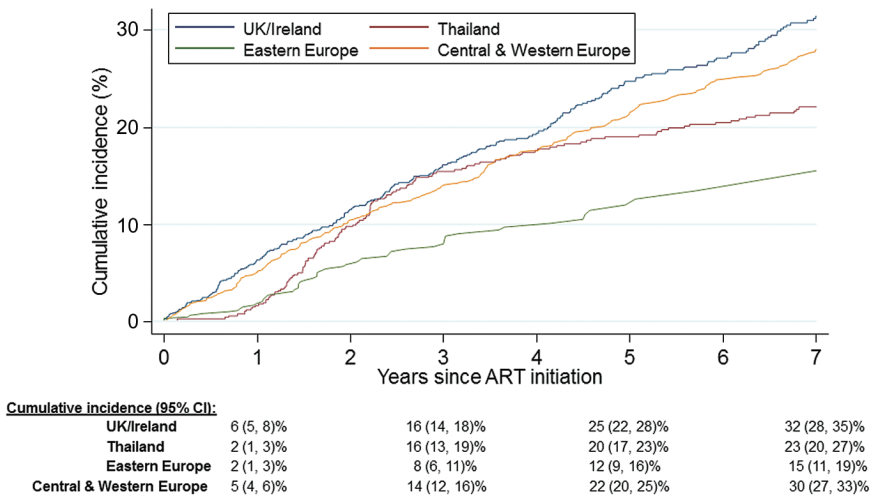

Figure 1. Cumulative incidence of switch to second-line antiretroviral therapy, by region. Abbreviations: ART, antiretroviral therapy; CI, confidence interval.

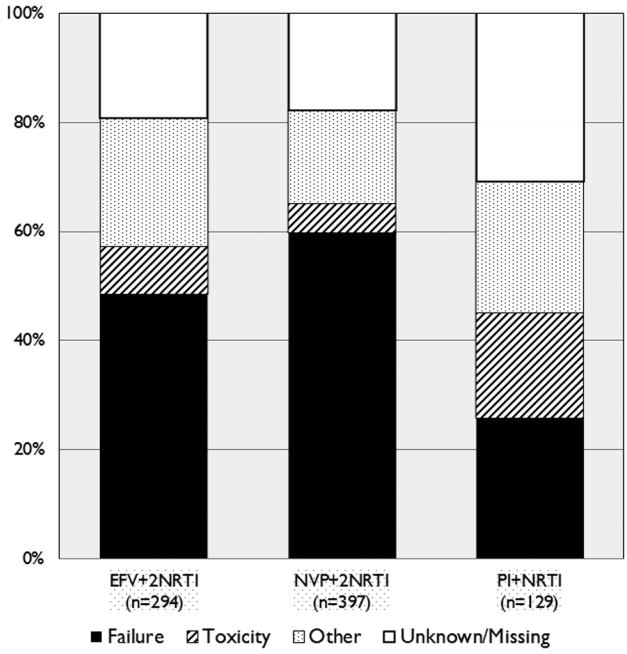

Figure 2. Reasons reported for switch to second-line antiretroviral therapy (ART), by initial ART regimen. Abbreviations: EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor.

significant difference in time to switch between those with and without a reason for switch reported ($P = .5$).

Factors at ART Initiation Associated With Switch

Children who initiated on NVP-based regimens had >2-fold increased risk of switch compared with children starting on PI-based regimens (adjusted subhazard ratio [sHR], 2.47 [95% CI, 1.86–3.27]; $P = .001$), whereas those starting EFV-based regimens had a smaller increased risk (sHR, 1.53 [95% CI, 1.16–2.02]; $P = .002$) (Table 2). In a subgroup analysis of UK/Ireland children aged <3 years, there was no difference in risk of switch between children taking NVP with a 3-NRTI (n = 40) vs 2-NRTI (n = 41) backbone (sHR, 0.99 [95% CI, .51–1.91]; $P = .97$), with both groups at increased risk of switch compared with those starting a PI-based regimen. The effect of age on hazard rate of switch was linear, with a 5% increase in risk of switch per year increase in age at start of ART (sHR, 1.06 [95% CI, 1.03–1.08]; $P < .0001$) (Figure 3). Severe immunosuppression and higher VL at ART start were associated with increased risk of switch. After adjusting for these factors, sex, CDC stage, and calendar year at ART initiation were not associated with risk of switch. There was no evidence of an interaction between age at ART start and initial regimen ($P = .3$).

Table 2. Cumulative Incidence of Switch at 5 Years After Antiretroviral Therapy (ART) Initiation and Factors Associated With Switch to Second-line ART

		Univariable Model		Multivariable Model[a]	
Factor	Cumulative Incidence at 5 y, % (95% CI)	SHR (95% CI)	*P* Value	aSHR (95% CI)	*P* Value
First-line ART regimen					
Boosted PI + NRTI	12 (10–15)	1	<.0001	1	<.0001
EFV + 2 NRTIs	23 (20–26)	1.94 (1.58–2.39)		1.53 (1.16–2.02)	
NVP + 2 NRTIs	27 (24–29)	2.23 (1.83–2.73)		2.47 (1.86–3.27)	
Age at ART initiation, y					
Per 1-y increase	…	1.04 (1.03–1.06)	<.0001	1.06 (1.03–1.08)	<.001
<1	19 (16–22)	0.85 (.69–1.05)	<.0001	…	
1–2	18 (16–22)	0.79 (.62–.99)			
3–5	15 (12–19)	0.79 (.64–.99)			
6–10	21 (18–24)	1			
≥11	32 (28–36)	1.45 (1.21–1.74)			
HIV RNA at ART initiation, copies/mL					
<100 000	17 (14–20)	0.83 (.69–.98)	.03	0.74 (.61–.90)	.003
≥100 000	21 (19–24)	1		1	
WHO severely immunocompromised					
No	16 (14–19)	1	.01	1	.04
Yes	23 (21–25)	1.26 (1.06–1.49)		1.23 (1.01–1.50)	
CDC stage C diagnosis					
No	20 (19–22)	1	.01	…	
Yes	28 (24–33)	1.27 (1.05–1.54)			
Calendar year of ART initiation					
1991–2003	27 (24–29)	1.53 (1.31–1.78)	<.0001	…	
2004–2007	20 (18–22)	1			
≥2008	16 (13–20)	0.79 (.64–.98)			

Proportional hazards regression model accounting for competing risks of death and loss to follow-up.

Abbreviations: ART, antiretroviral therapy; aSHR, adjusted subhazard ratio; CDC, Centers for Disease Control and Prevention; CI, confidence interval; EFV, efavirenz; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor, NVP, nevirapine; PI, protease inhibitor; SHR, subhazard ratio; WHO, World Health Organization.

[a]Multivariable regression model stratified by region.

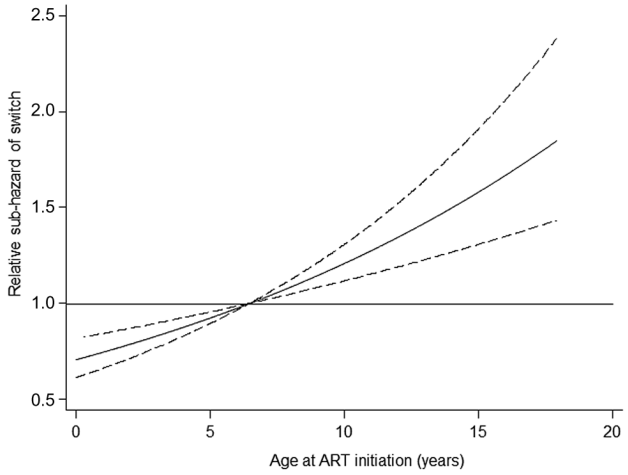

Figure 3. Relative hazard of switch by age at antiretroviral therapy (ART) initiation. Relative hazard for age predicted from a proportional hazard regression model including ART regimen, World Health Organization immunosuppression status, and viral load at ART initiation. Hazard rate is plotted relative to a child of age 6.7 y (the median age of the cohort); dashed lines represent the 95% confidence interval.

Sensitivity Analyses

When 63 switches in the first 6 months of ART were excluded, the cumulative proportion of switch was lower, at 19% (95% CI, 18%–21%) at 5 years after ART start. Including switches across class or within PI class without a simultaneous change in ≥1 NRTI, if the reported reason for switch was failure, increased the number of children switching to second-line ART by 95 and the cumulative proportion of switch at 5 years to 24% (95% CI, 22%–25%). Additional switches were predominately from Thailand (51%), and from an NNRTI- to a PI-based regimen (82%). The median time to switch was comparable to that observed in the main analysis. In multivariable analyses, the same factors remained associated with switch, with limited change to the point estimates, apart from the risk of switch for NVP-based regimens being reduced to 2.13 and 2.16, respectively. In addition, risk of switch was increased for children starting ART before 2004 when ignoring switches <6 months (data not shown).

Characteristics at Time of Switch and Response to Second-line ART

Among those switched to second-line ART, median age at switch was 11 (IQR, 6–15) years, VL (n = 671) was 4.1 (IQR, 3.0–4.9) $\log_{10}$ copies/mL, and CD4 percentage (n = 682) was 20% (IQR, 11%–29%). The majority of children (72%) received a PI-based second-line regimen (lopinavir/ritonavir, 57%; atazanavir, 11%; darunavir, 5%), and <1% (n = 7) received an integrase inhibitor (INSTI)–based regimen. The median duration of follow-up after start of the second-line regimen was 3.8 (IQR, 1.8–6.5) years; among those with a VL measurement at 12 (n = 561) and 24 (n = 480) months after start of second-line ART, 65% and 69%, respectively, were suppressed at <400 copies/mL.

DISCUSSION

This study of time to switch to second-line ART for any cause in children with routine VL monitoring is the largest to date. It includes many national cohorts across Europe [5, 20] and benefits from long duration of follow-up (>5 years) and low levels of mortality and loss to follow-up. There are 4 key findings from our study. First, approximately 80% of children remained on their first-line regimen at 5 years after ART initiation (allowing for minor drug modifications and treatment simplifications). One in 5 children met our definition of switch at 5 years, although there were significant regional variations in the proportion switching, with lowest estimates of 12% in Eastern Europe and highest of 25% in the UK and Ireland.

Second, older age at start of ART was associated with increased risk of switch, with no evidence that this effect varied by initial regimen. Previous studies have reported increased risk of virological failure among children starting ART at older ages [21]. While our outcome was switch for all-causes, more than two-thirds of the switches were failure related. The higher risk of switch in older children may reflect increased risk of failure as well as greater treatment options and/or willingness to switch adolescents experiencing failure compared with younger children. A recent global meta-analysis (including EPPICC) of approximately 100 000 children on ART, the large majority from sub-Saharan Africa, also reported increased risk of switch to second-line ART with older age at ART start [22]. This highlights the need to consider novel adherence or support interventions for children initiating treatment at older ages, particularly adolescents [23]. This may include treatment simplification strategies such as the "weekends off" short-cycle therapy. The breaks in adolescent and child therapy using efavirenz and two NRTIs (BREATHER) trial randomized adolescents virologically suppressed on EFV-based regimens to continuous treatment vs short treatment cycle of 5 days on and 2 days (weekends) off ART. The latter group reported high acceptability [24], maintained high levels of viral suppression, with low rates of switch at 48 and 144 weeks of follow-up, and reported no difference in inflammation markers [25, 26].

Third, children initiating an NVP-based regimen had increased risk of switch, as did those starting EFV (although to a lesser degree), compared with those starting PI-based regimens. This is consistent with findings from previous studies showing increased risk of switch to second-line ART in NVP- vs PI-based regimens [3, 5, 27]. This could partly reflect the reluctance of clinicians to switch children failing a PI-based regimen due to the difficulty in deciding what to switch to, and recommendations to first address adherence issues due to the high resistance barrier [17]. However, studies have also shown increased risk of virological failure for NVP- vs PI-based regimens [5, 27], and a higher proportion of the switches from NVP-based regimens in our cohort were reported as failure related. These findings support Paediatric European Network for the Treatment of AIDS (PENTA) and US guideline recommendations to consider PI-based first-line regimens in all

children (aged >14 days) and adolescents [17, 28]. Nonetheless, NVP remains a widely used, low-cost, essential drug option for children in resource-limited settings with poor access to PIs [22, 29]. It is important to note that the majority of children who initiated NVP in our cohort remained on it at 5 years (73%), suggesting that those who tolerated and responded to NVP did achieve long durability on this first-line regimen.

Outside of Eastern Europe, our estimates of switch at 5 years were remarkably similar across regions, despite wide variations in the initial regimens used and age and immune status at start of ART. As severe immunosuppression at ART initiation was confirmed as a risk factor for switch in our study [11], one may have expected higher switch rates in Thailand, which had the highest proportions of children starting NNRTI-based regimens (93%) and of those who were severely immunocompromised. The lower levels of switch observed in Thailand most likely reflect differences in frequency of VL testing, as well as availability/readiness to switch to second-line regimens.

Comparison of unadjusted cumulative incidence estimates of switch across studies and contexts is challenging, as the distribution of risk factors in heterogeneous populations is not taken into account. Notwithstanding this limitation, our overall estimate of switch to second-line ART of 21% at 5 years is comparable to recent findings from the Asia Pacific cohort, which reported 23% switch at 5 years among children with routine VL monitoring [11]. Importantly the authors report that children without VL monitoring had a 53% lower incidence of switch compared to children with VL monitoring. As more countries shift toward routine or targeted VL monitoring [29], the use of second-line ART, which is currently very low (≤3%) in settings without VL monitoring [22], is expected to increase following improved detection of treatment failure and efforts to improve availability of PI-based and INSTI-based regimens in pediatric formulations [30]. The global use of second-line ART may then reach similar levels to that observed in our cohort.

The clinical implication of the shift to routine VL testing remains unclear. The PENPACT-1 (PENTA 9/PACTG 390) trial reported no difference in clinical outcomes when switching children early or late, at high (30 000 copies/mL) or low (1000 copies/mL) VL levels, although the trial was conducted mainly in high-income countries. However, earlier switch did minimize the accumulation of drug resistance mutations in those initiating on NNRTI-based regimens [7, 31]. Similarly, recent studies of adult patients in sub-Saharan African (the large majority initiated on NNRTI-based regimens) have reported that delayed switch to second-line ART after prolonged virological failure was associated with accumulation of resistance mutations, which limited the NRTI options for second-line ART [32], as well as increased risk of failure, morbidity, and mortality on second-line ART [12, 33, 34]. These findings are likely to be generalizable to children in such settings. More information on accumulation of drug resistance mutations while on failing PI-based regimens is needed.

Fourth, more than two-thirds of children in our cohort achieved viral suppression at 12 and 24 months after switch to second-line ART. This is broadly consistent with the prevalence of suppression at 1 year after switch reported in other pediatric cohorts [35–37]. However, one-third of patients experienced viremia. It is unclear if this is due to poor adherence or resistant virus. Further studies on the clinical outcomes on second- and third-line ART in children and adolescents are warranted.

There are some important limitations to this study. First, 20% of children switched to second-line ART had no reported reason for switch. Although for these children we used data on clinical status, CD4 count, and VL in the 6 months before switch to assess likelihood of the switch being failure related, this may not reflect the true reason for switch. Second, there are unmeasured potential confounders including exposure to maternal/infant antiretroviral prophylaxis, adherence, resistance profile, and availability of alternative regimens, all of which may influence the probability of switch.

In summary, in our cohort of children with routine VL monitoring, a fifth had switched to second-line ART whereas the large majority remained on their first-line regimen at 5 years of ART. These estimates provide an insight on the expected use of second-line regimens as the global pediatric HIV population matures and access to VL monitoring expands. A commitment to the availability of affordable pediatric drugs with high resistance barriers [38, 39] and low pill burden will be essential to ensure these needs are met [30].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. All members of the project team participated in discussions about the study design, choice of statistical analyses, and interpretation of the findings and were involved in the preparation and review of the final manuscript. Additionally, J. C. and R. G. drafted the manuscript and R. G. performed all statistical analyses. All members of the writing group were involved in the collection of data and interpretation of the findings.

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APPENDIX: COLLABORATING COHORTS

Belgium: Hospital St Pierre Cohort, Brussels: Tessa Goetghebuer, MD, PhD; Marc Hainaut, MD, PhD; Evelyne Van der Kelen, Research nurse; Marc Delforge, data manager.

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Greece: Greek cohort. Vana Spoulou.

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