Clinical Infectious Diseases

MAJOR ARTICLE

Prevalence and Clinical Outcomes of Poor Immune Response Despite Virologically Suppressive Antiretroviral Therapy Among Children and Adolescents With Human Immunodeficiency Virus in Europe and Thailand: Cohort Study

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord[a]

Background. In human immunodeficiency virus (HIV)–positive adults, low CD4 cell counts despite fully suppressed HIV-1 RNA on antiretroviral therapy (ART) have been associated with increased risk of morbidity and mortality. We assessed the prevalence and outcomes of poor immune response (PIR) in children receiving suppressive ART.

Methods. Sixteen cohorts from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) contributed data. Children <18 years at ART initiation, with sustained viral suppression (VS) (≤400 copies/mL) for ≥1 year were included. The prevalence of PIR (defined as World Health Organization advanced/severe immunosuppression for age) at 1 year of VS was described. Factors associated with PIR were assessed using logistic regression. Rates of acquired immunodeficiency syndrome (AIDS) or death on suppressive ART were calculated by PIR status.

Results. Of 2318 children included, median age was 6.4 years and 68% had advanced/severe immunosuppression at ART initiation. At 1 year of VS, 12% had PIR. In multivariable analysis, PIR was associated with older age and worse immunological stage at ART start, hepatitis B coinfection, and residing in Thailand (all $P \leq .03$). Rates of AIDS/death (95% confidence interval) per 100 000 person-years were 1052 (547, 2022) among PIR versus 261 (166, 409) among immune responders; rate ratio of 4.04 (1.83, 8.92; $P < .001$).

Conclusions. One in eight children in our cohort experienced PIR despite sustained VS. While the overall rate of AIDS/death was low, children with PIR had a 4-fold increase in risk of event as compared with immune responders.

Keywords. HIV; children; antiretroviral therapy; poor immune response; viral suppression.

Antiretroviral therapy (ART) has led to a dramatic reduction in acquired immunodeficiency syndrome (AIDS) and mortality in children and adults living with human immunodeficiency virus (HIV) [1–3]. Adults receiving treatment who achieve immune recovery with CD4 counts over 500 cells/mm^3 have improved life expectancy, approaching that of the general population [4, 5]. However, some patients experience discordant treatment responses, with poor immune response (PIR) despite sustained viral suppression (VS).

A systematic review of 20 adult studies on discordant treatment response reported wide variations in the definitions of PIR; nonetheless, most studies were consistent in their findings of a 2–3-fold increase in risk of mortality among adults with PIR compared with immune responders [6]. The definitions of PIR ranged from a CD4 count increase of <50 cells/mm^3 at 6–12 months after start of suppressive ART to failure to reach absolute CD4 values of ≥200 to ≥500 cells/mm^3 at 6–60 months of suppressive ART (defined as a viral load [VL] of <50 to <1000 copies/mL) [6]. The prevalence of PIR ranged from 11% to 45%, and older age and lower CD4 values at ART start were commonly associated with PIR [7, 8]. Fewer studies assessed the risk of progression to AIDS or death as a composite outcome; some observed an elevated risk among adults with PIR [9], while others did not [6, 7].

There are scarce comparable data on PIR in children. Numerous studies have shown that most children achieve good immune response to ART, although those who initiate ART at older ages or with advanced immunosuppression were less likely to achieve immune recovery [10–13]. However, these studies included all children receiving ART irrespective of VS status, so it is unclear if the blunted immune recovery was partly due to nonsuppressive ART [14, 15] rather than intrinsic PIR.

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In this study, we assessed the prevalence of PIR among children who achieved sustained VS on ART, the associated factors, and clinical outcomes within the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

METHODS

Sixteen pediatric observational cohorts from 15 middle- and high-income countries across Europe and Thailand in EPPICC contributed data. Patient-level clinical data were pooled electronically using a modified HIV Cohorts Data Exchange Protocol (HICDEP) (www.hicdep.org), as described elsewhere [16].

Inclusion criteria for this analysis were as follows: (1) age less than 18 years at initiation of combination ART (defined as ≥3 drugs from ≥2 classes, excluding unboosted protease inhibitors [PIs], or a regimen of ≥3 nucleoside reverse transcriptase inhibitors [NRTIs] containing abacavir), (2) ≥1 CD4 and VL measurement on ART, and (3) achieved VS (defined as VL ≤400 copies/mL) within 1 year after ART start (or within 18 months for infants aged <12 months at ART start) and maintained VS for ≥1 year. Patients with documented sexual mode of transmission (n = 17) were excluded because they were much older at HIV diagnosis than children with perinatal HIV (median age at HIV diagnosis of 15.6 years; interquartile range [IQR]: 14.4, 16.7 years versus 6.0 years; IQR: 1.6, 10.6 years, respectively).

Follow-up was from ART initiation until the earliest of death, loss to follow-up, 21st birthday, or last visit in pediatric care, with data through to 1 October 2016. All cohorts had routine CD4 and VL monitoring at least annually. AIDS-defining opportunistic infections and illnesses were based on the US Centers for Disease Control and Prevention 2014 [17] definition. All cohorts received local/national ethics approval.

Definitions of Viral Suppression and Poor Immune Response

The period of VS started at the midpoint between the first VL ≤400 copies/mL and the previous VL >400 copies/mL (or at ART initiation if later). Patients were censored at the end of VS (at last VL ≤400 copies/mL), defined as the earliest of the following: (1) viral rebound (2 consecutive VLs >400 copies/mL or a single unconfirmed VL >10 000 copies/mL), (2) gap between VL measurements of >15 months (censored at last VL before gap), (3) ART interruption (defined as stopping all drugs for >14 days), or (4) death or last follow-up in pediatric care. In sensitivity analyses, we censored patients at the start of a gap between VL measurements of >12 months.

PIR was defined as World Health Organization (WHO) advanced or severe immunological stage for age at 1 year of VS: CD4 <30% for age <12 months, CD4 <25% for 12–35 months, CD4 <20% for 35–59 months, or CD4 <15% or <350 cells/mm^3 for ≥5 years [18]. Children with CD4% or cell counts above these thresholds (WHO none or mild stage) were considered "immune responders."

Statistical Methods

Among patients with WHO advanced or severe immunosuppression at ART initiation, time to immune recovery was estimated using Kaplan-Meier survival functions.

Among patients with CD4 measurements available at 1, 2, and 3 years of sustained VS (±3-month window), the prevalence of PIR was assessed at each time point.

Factors associated with PIR at 1 year of VS were assessed using logistic regression. Potential risk factors were characteristics at ART initiation: sex, mode of HIV infection (perinatal vs other/unknown), born abroad (vs in country of cohort), year of birth (<2000 vs ≥2000), age, WHO immunological stage, viral load, AIDS diagnosis, body mass index (BMI)-for-age *z* score (based on WHO reference standards [19]), tuberculosis disease prior to or soon after ART start (±6 months), cytomegalovirus disease–related AIDS event prior to ART start, initial ART regimen, calendar year of ART initiation, ever diagnosed with hepatitis B (HBV) and C (HCV) coinfection, and geographic region (United Kingdom/Ireland, Eastern Europe [Russia/Ukraine], Western and Central Europe, and Thailand). All factors were considered in the multivariable model, and the final model was determined using backwards selection (exit probability = 0.05). The missing indicator method was used for variables with missing data. For HBV and HCV coinfection, cytomegalovirus, and tuberculosis disease, the odds ratios (ORs) of the missing groups were similar to those of the uninfected group and were combined. Interactions between variables included in the final model were considered. This analysis was repeated to explore factors associated with PIR at 2 years of VS.

AIDS and Death on Suppressive ART

We assessed the rate of clinical events (new/recurrent AIDS event or death) while on suppressive therapy by PIR status at 1 year of VS. Children entered at risk at 1 year of VS and were censored at first AIDS event or death or at the end of VS.

To explore the management of PIR, we assessed the rate of treatment changes (defined as a change in main drug class, from nonnucleoside reverse transcriptase inhibitors to PI-based regimen, or vice versa, or addition of a new drug class) during VS. We also described the median change in height and BMI-for-age *z* scores [19] between ART initiation and 1 year of VS by PIR status.

All statistical analyses were performed using Stata version 14.2 (StataCorp).

RESULTS

Of 3395 children with over 1 year of follow-up after ART start, 2318 (68%) had sustained VS for ≥1 year and were included in this analysis (Figure 1). The largest proportion were from the United Kingdom/Ireland (37%), followed by Western/Central Europe (32%), Thailand (17%), and Eastern Europe (14%) (Table 1). Half were female, and 91% had perinatal HIV. At ART

initiation, median (IQR) age was 6.4 years (2.1, 10.4 years), median CD4 was 22% (14%, 33%) among those aged <5 years and 256 cells/mm^3 (94, 417 cells/mm^3) among those aged ≥5 years. Overall, 68% were advanced or severely immunocompromised and 19% had a prior AIDS diagnosis at ART start. One-third were initiated on PI-based regimens (87% on lopinavir), 36% on efavirenz-based regimens, and 28% on nevirapine-based regimens. The median duration of follow-up after ART start was 6.8 years (4.0, 9.7 years), during which 23 (1%) children died, 271 (12%) were lost to follow-up, 660 (28%) transferred to other clinics/adult care, and 170 (7%) were censored at their 21st birthday.

Immune Response

At 1 year of VS, 83% of children (n = 1926 of 2318) had a CD4 measurement available, of whom 88% had good immune status, an increase from 32% at ART start. Among patients with advanced/severe immune suppression at ART start, the time to immune recovery was rapid for the vast majority: 72% (95% confidence interval [CI], 70, 74) reached WHO none/mild stage by 1 year after ART start (Figure 2).

Overall, 12% (237 of 1926) of children had PIR at 1 year of VS; they were more likely to be from Thailand, older, with poorer immune status, and with a higher proportion being severely stunted and wasted at ART start as compared with immune responders (Table 2; all $P < .001$). However, one-fifth of children with PIR were not severely immunocompromised at ART start. The median CD4 at 1 year of VS was 21% (16%, 23%) among those aged <5 years and 299 cells/mm^3 (246, 336 cells/mm^3) in those aged ≥5 years among children with PIR compared with 36% (31%, 42%) and 690 cells/mm^3 (537, 915 cells/mm^3) among immune responders, respectively. Among children aged ≥5 years, the median increase in CD4 from ART start to 1 year of VS was 150 (66, 243) versus 357 (212, 566) cells/mm^3, respectively ($P < .001$).

Children with missing CD4 at 1 year of VS (n = 392) were more likely to be from Eastern European cohorts (41% missing among children from Eastern Europe versus 13% in other regions, $P < .001$), initiated ART at younger ages (median, 3.3 [0.8, 8.5] years versus 6.9 [2.6, 10.6] years, $P < .001$) with better immune status (16% WHO stage none/mild versus 11%, $P = .009$) compared with children with CD4 measurements (data not shown).

The number of children with sustained VS for 2 (n = 1873) and 3 (n = 1509) years after ART start declined over time. Among those with CD4 measurements available, the prevalence of PIR fell to 7% (n = 104 of 1594) and 3% (n = 46 of 1332), respectively.

Factors Associated With PIR

In multivariable analyses, factors associated with PIR at 1 year of VS were as follows: older age and worse immune stage at ART start, HBV coinfection, and being in the Thai cohort (Table 2). Children aged 5–10 years at ART start had 1.8 times higher odds of PIR compared with those aged <5 years, with the odds increasing with each older age group ($P < .001$). The odds of PIR increased with worse levels of immunodeficiency at ART start and in those with missing baseline CD4 values ($P < .001$), Children in the Thai cohort had a 2-fold increased odds of PIR (adjusted OR [aOR], 2.16; 95% CI, 1.49, 3.13) compared with

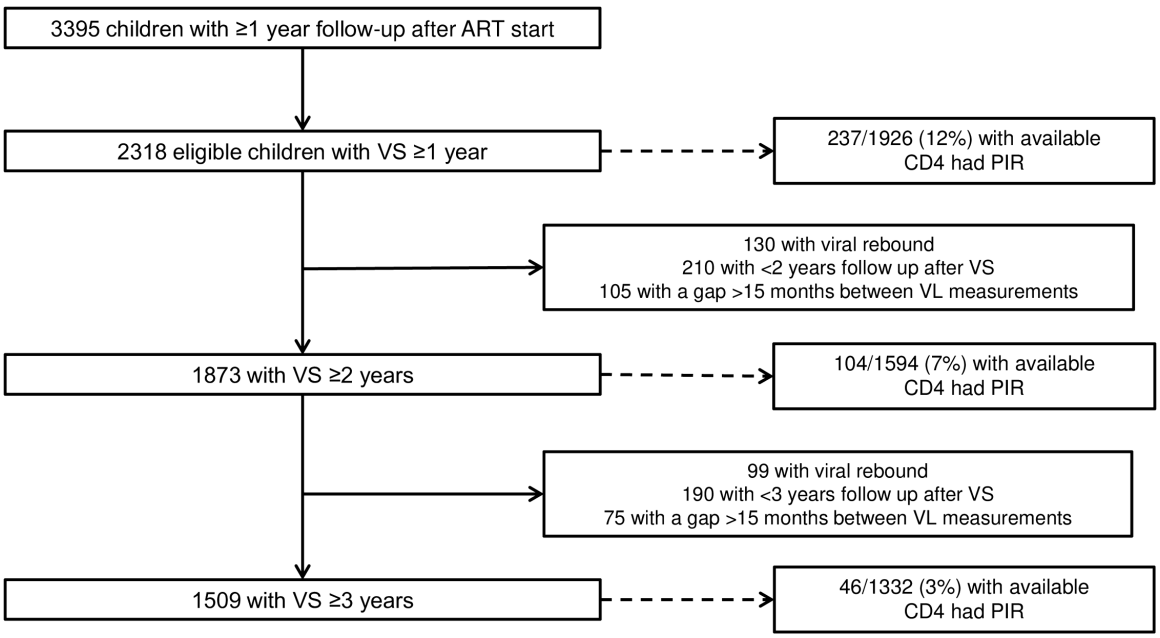

Figure 1. Flowchart of children included in the analysis. Abbreviations: ART, antiretroviral therapy; PIR, poor immune response; VS, viral suppression.

Table 1. Characteristics of Children With Sustained Viral Suppression for ≥1 Year, by Immune Response Status

	All Children With VS ≥1 year[a] (N = 2318)	Immune Responders at 1 Year of VS (n = 1689)	Poor Immune Responders at 1 Year of VS (n = 237)
Demographic characteristics			
Sex, male	1084 (47)	783 (46)	121 (51)
Age at HIV diagnosis (n = 2090, 1546, 218), years	3.8 (1.0, 8.0)	4.0 (1.1, 7.9)	7.6 (3.3, 11.0)
Born abroad (n = 2248, 1641, 222)	810 (36)	614 (37)	80 (36)
Year of birth <2000	1101 (48)	794 (47)	169 (71)
Mode of HIV infection			
Perinatal	2119 (91)	1555 (92)	195 (82)
Blood products	88 (4)	58 (3)	22 (9)
Other	5 (0.2)	3 (0.2)	0
Unknown	106 (5)	73 (4)	20 (8)
Region			
United Kingdom/Ireland	849 (37)	693 (41)	83 (35)
Eastern Europe	332 (14)	183 (11)	12 (5)
Western/Central Europe	751 (32)	546 (32)	66 (28)
Thailand	386 (17)	267 (16)	76 (32)
Characteristics at start of ART			
Age, years	6.4 (2.1, 10.4)	6.5 (2.4, 10.3)	9.7 (6.1, 13.5)
CD4% among those <5 years (n = 740/970, 582/688, 36/46)	22 (14, 33)	22 (14, 33)	16 (8, 22)
CD4 count among those aged ≥5 years (n = 1180/1348, 887/1001, 173/191), cells/μL	256 (94, 417)	287 (130, 446)	112 (26, 220)
WHO immunological stage (n = 1931, 1473, 210)			
None	396 (21)	327 (22)	4 (2)
Mild	228 (12)	190 (13)	5 (2)
Advanced	305 (16)	238 (16)	33 (16)
Severe	1002 (52)	718 (49)	168 (80)
Viral load (n = 1862, 1390, 191), $\log_{10}$ copies/mL	5.0 (4.4, 5.5)	5.0 (4.4, 5.5)	4.9 (4.3, 5.3)
AIDS diagnosis (n = 2304, 1679, 236)	442 (19)	312 (19)	57 (24)
Hepatitis B coinfection (n = 2049, 1494, 216)	64 (3)	43 (3)	14 (6)
Hepatitis C coinfection (n = 1944, 1424, 203)	69 (4)	47 (3)	5 (2)
Tuberculosis disease	56 (2)	38 (2)	11 (5)
CMV coinfection	38 (2)	27 (2)	2 (1)
BMI-for-age *z* score < –3 (n = 1509, 1152, 173)	74 (5)	45 (4)	17 (10)
Height-for-age *z* score < –3 (n = 1511, 1153, 173)	195 (13)	135 (12)	31 (18)
Initial regimen			
Boosted PI + NRTI	768 (33)	538 (32)	55 (23)
EFV + ≥2 NRTIs	833 (36)	626 (37)	108 (46)
NVP + ≥2 NRTIs	641 (28)	466 (28)	68 (29)
Other	76 (3)	59 (3)	6 (3)
Calendar year at ART initiation			
<2004	550 (24)	399 (24)	61 (26)
2004–2007	805 (35)	583 (35)	109 (46)
≥2008	963 (42)	707 (42)	67 (28)

Data are no. (%) or median (interquartile range). n in row header refers to the number with available data.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CMV, cytomegalovirus; EFV, efavirenz; HIV, human immunodeficiency syndrome; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; VS, viral suppression; WHO, World Health Organization.

[a]Includes 392 children with missing CD4 at 1 year of viral suppression.

the United Kingdom/Ireland, whereas there was no significant difference within the European regions. HBV coinfection was also associated with an increase in risk of PIR (aOR, 2.14; 95% CI, 1.08, 4.25; $P = .029$). After adjustment for these factors, no other factors were associated and no significant interactions were found.

Factors associated with PIR at 2 years of VS were broadly similar, with older age and worse immune stage at ART start being the strongest predictors, whereas the association with HBV coinfection weakened ($P = .068$) and the effect of the Thai cohort was no longer present (Supplementary Table S1)

Risk of AIDS/Death, Treatment Change, and Growth by Immune Response

Overall, there were 7 deaths and 21 new AIDS events on suppressive therapy, of which 4 (57%) deaths and 5 (23%) AIDS events were among children with PIR at 1 year of VS, corresponding

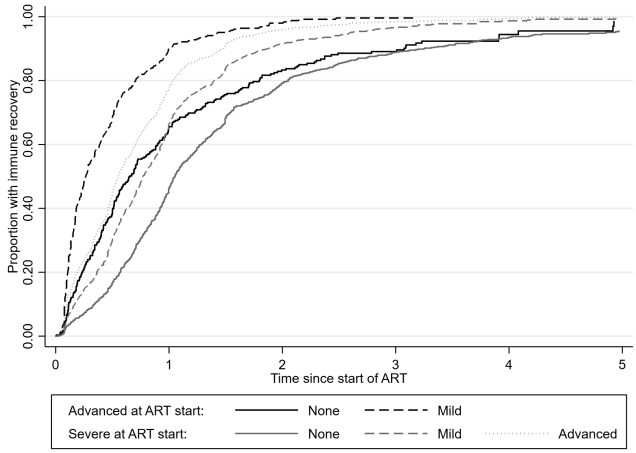

Figure 2. Time to immune recovery among children with advance or severe immunosuppression at ART start (n = 1307). Abbreviation: ART, antiretroviral therapy.

to 3.8% (9 of 237) of children with PIR versus 1.1% (19 of 1689) of immune responders. The majority of events were infection related (Tables 3 and 4). The median time from ART start to first event was 1.4 years (IQR, 1.3, 1.7) among children with PIR versus 3.0 years (IQR, 1.6, 5.4) in immune responders (P = .121). The rate of AIDS or death (95% CI) during VS was 1052 (547, 2022) per 100 000 person-years among those with PIR versus 261 (166, 409) among immune responders, a rate ratio of 4.04 (1.83, 8.92; P < .001) (Supplementary Table S2).

There was no difference in the proportion or rate of switching to alternative treatment regimens by immune response status (8.4% in those with PIR versus 9.1% in immune responders, P = .733; 1.88 per 100 person-years [1.21, 2.92] versus 1.78 [1.52, 2.09], respectively; P = .821). The median increase in BMI-for-age z score from ART start to 1 year of VS among those with PIR was comparable at 0.3 (IQR, −0.3, 1.1) versus 0.2 (IQR, −0.3, 0.9), respectively (P = .120), whereas the median increase in height-for-age z score was lower among those with PIR at 0.1 (IQR, −0.2, 0.4) versus 0.2 (IQR, −0.1, 0.6), respectively (P < .001) (Supplementary Table S3).

In sensitivity analyses where we censored patients with a >12-month gap in VL measurements, the findings were consistent with the main analyses, with a 12% prevalence of PIR at 1 year of VS, similar associated factors, and elevated risk of AIDS/death among those with PIR (data not shown).

DISCUSSION

To our knowledge, this is one of the first studies to estimate the prevalence and clinical outcomes of PIR among children on suppressive ART in settings with routine CD4 and VL monitoring. In our cohort, 12% of children had PIR at 1 year of VS and these children had a 4-fold increased risk of progression to AIDS or death on suppressive therapy as compared with immune responders.

Our prevalence of PIR was relatively low compared with that in adult studies, which may be partly due to the differences in inclusion criteria and definitions of PIR [6]. One large study in adults in Europe reported 15% with PIR at 3 years of VS, where PIR was defined as severe immunosuppression (CD4 <200 cells/ mm^3) and was restricted to patients severely immunocompromised at the start of the VS period [20]. In contrast, we focused on PIR at 1 year of VS, defined as advanced or severe immunosuppression for age, and included all children irrespective of their baseline immune status, and one-fifth of children with PIR were not severely immunocompromised at ART start. Encouragingly, the 12% prevalence of PIR at 1 year of VS declined to 3% among those who were virologically suppressed for 3 years. This probably reflects the increased thymic output and capacity for immune reconstitution in children as compared with adults [21, 22].

The overall rate of AIDS or death in children receiving suppressive ART in our cohort was low, including among children with PIR, which highlights the significant benefit of treatment for these children. However, children with PIR had a disproportionately high burden of events, accounting for over half of the deaths and one-quarter of AIDS events.

It is difficult to directly compare our findings with previous pediatric studies on PIR as they were not restricted to children receiving suppressive ART. However, the main factors associated with PIR were consistent with our study: older age and poorer immune stage at ART start [10, 12, 13]. This highlights the critical importance of early HIV diagnosis and initiation of ART in infancy and prior to disease progression to minimize the risk of poor immune recovery [23]. In our analysis, being in the Thai cohort was associated with increased odds of PIR as compared with the United Kingdom/Ireland. Children in Thailand were more likely to be at advanced disease stage at ART start, and there may be unmeasured confounding and/or higher background risk of infectious diseases [24]. HBV coinfection was also associated with increased risk of PIR. Poor immune recovery among HIV-HBV coinfected patients has been reported in adult studies, which may be due to systemic inflammation related to HBV chronic infection [25–27]. However, it should be noted that factors associated with PIR at 2 years of VS found a weakened association with HBV coinfection and the Thai cohort effect was no longer present, although this was based on a smaller sample size.

Our findings highlight 3 key issues. First, timely ART initiation in early life, prior to immunosuppression as per WHO recommendations, was highly protective of PIR [23]. However, on the global level, only half of children living with HIV have access to ART [1], and the majority of children in sub-Saharan Africa still start ART with advanced or severe immunosuppression and therefore are at increased risk of PIR [28]. The expansion of targeted services for early HIV diagnosis, including testing at birth in high-prevalence settings, has resulted in earlier initiation of ART in infancy [29].

Table 2. Predictors of Poor Immune Response at 1 Year of Viral Suppression

		Univariable			Multivariable		
	Number (%) With PIR (N = 1926)	OR	95% CI	*P*	aOR	95% CI	*P*
Demographic Characteristics							
Sex							
Female	116/1022 (11)	0.83	.63, 1.09	.175	…		
Male	121/904 (13)	1.00	…				
Place of birth							
Country of cohort	142/1169 (12)	1.00	…	.021	…		
Abroad	80/694 (12)	0.94	.70, 1.26				
Unknown	15/63 (24)	2.26	1.23, 4.14				
Year of birth							
<2000	169/963 (18)	1.00	…	<.001	…		
≥2000	68/963 (7)	0.36	.27, .48				
Mode of HIV infection							
Perinatal	195/1750 (11)	1.00	…	<.001	…		
Other/ unknown	42/176 (24)	2.50	1.71, 3.64				
Region of cohort							
United Kingdom/Ireland	83/776 (11)	1.00	…	<.001	1.00	…	<.001
Eastern Europe	12/195 (6)	0.55	.29, 1.02		0.92	.48, 1.78	
Western/Central Europe	66/612 (11)	1.01	.72, 1.42		1.19	.82, 1.72	
Thailand	76/343 (22)	2.38	1.69, 3.34		2.16	1.49, 3.13	
Characteristics at start of ART							
Age, years							
<5	46/734 (6)	1.00	…	<.001	1.00	…	<.001
5 to <10	79/624 (13)	2.17	1.48, 3.17		1.82	1.22, 2.71	
10 to <15	78/483 (16)	2.88	1.96, 4.23		2.39	1.60, 3.55	
≥15	34/85 (41)	9.97	5.89, 16.88		9.49	5.42, 16.62	
WHO immune stage							
None	4/321 (1)	1.00	…	<.001	1.00	…	<.001
Mild	5/256 (3)	2.15	.57, 8.11		1.98	.52, 7.51	
Advanced	33/271 (12)	11.34	3.96, 32.43		9.35	3.23, 27.06	
Severe	168/886 (19)	19.12	7.04, 52.00		13.96	5.08, 38.37	
Unknown	27/243 (11)	10.22	3.53, 29.61		9.23	3.15, 27.01	
Viral load, copies/mL							
>100 000	79/753 (11)	1.00	…	.153	…		
≤100 000	112/828 (14)	1.33	.98, 1.81				
Unknown	46/345 (13)	1.31	.89, 1.94				
AIDS diagnosis							
Yes	57/369 (15)	1.40	1.01, 1.93	.042	…		
No	180/1557 (12)	1.00	…				
Hepatitis B coinfection							
Yes	14/57 (25)	2.40	1.29, 4.46	.006	2.14	1.08, 4.25	.029
No/unknown	223/1869 (12)	1.00	…		1.00	…	
Hepatitis C coinfection							
Yes	5/52 (10)	0.75	.30, 1.91	.551	…		
No/unknown	232/1874 (12)	1.00	…				
Tuberculosis disease							
Yes	11/49 (22)	2.11	1.07, 4.20	.032	…		
No	226/1877 (12)	1.00	…				
CMV coinfection							
Yes	2/29 (7)	0.52	.12, 2.22	.380	…		
No	235/1897 (12)	1.00	…				
BMI-for-age *z* score							
>0	68/634 (11)	1.00	…	.001	…		
–3 to 0	86/629 (14)	1.35	.97, 1.90				
< –3	17/62 (27)	3.14	1.71, 5.80				

Table 2. Continued

		Univariable			Multivariable		
	Number (%) With PIR (N = 1926)	OR	95% CI	*P*	aOR	95% CI	*P*
Unknown	64/601 (11)	0.99	.69, 1.42				
Initial regimen							
Boosted PI + NRTI	55/593 (9)	1.00	…	.023	…		
EFV + ≥2 NRTIs	108/734 (15)	1.68	1.20, 2.38				
NVP + ≥2 NRTIs	68/534 (13)	1.43	1.98, 2.08				
Other	6/165 (9)	0.99	.41, 2.41				
Calendar year							
<2004	61/460 (13)	1.00	…	<.001	…		
2004 to <2008	109/692 (16)	1.22	.87, 1.72				
≥2008	67/774 (9)	0.62	.43, .90				

Abbreviations: aOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; EFV, efavirenz; HIV, human immunodeficiency syndrome; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OR, odds ratio; PI, protease inhibitor; PIR, poor immune response; WHO, World Health Organization.

Second, after adjusting for patient characteristics, children in Thailand were at increased risk of PIR at 1 year of VS compared with those in the United Kingdom/Ireland. The clinical outcomes of PIR among children in low- and middle-income countries are largely unknown; they may face a similar or higher burden of disease progression and death than that observed in our cohorts. Currently, there are no clear recommendations to reduce the excess morbidity and mortality associated with PIR [6]. The recent Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy in sub-Saharan Africa reported a significant reduction in early deaths among children and adults initiating ART with very severe immunodeficiency (CD4 <100 cells/mm^3), when provided with an enhanced antimicrobial prophylaxis package compared with standard prophylaxis to prevent opportunistic infections [30]. We did not have data on the use of antimicrobial prophylaxis in this cohort and could not explore this question further.

Third, our findings highlight the potential importance of CD4 monitoring alongside the global scale-up of VL monitoring [31] in the assessment of baseline immune status and early response to ART to identify patients with PIR who may require closer follow-up and to inform decisions on starting/stopping prophylaxis [23]. While there is growing consensus that CD4 monitoring in stable patients receiving suppressive therapy with no or mild

Table 3. Listing of AIDS events and Deaths While on Virally Suppressed Antiretroviral Therapy Among Children With Poor Immune Response

		ART Start		At 1 Year After Start of VS		At Onset of Event			
Country and Patient Number	Initial Regimen	Age, years	CD4 Count, Cells/µL	Age, years	CD4 Count, Cells/µL	Age, years	CD4 Count, Cells/µL	Event	Cause of Death/Description of AIDS event
United Kingdom/ Ireland									
1	EFV + 2 NRTIs	7.9	14	9.1	186	9.3	292	Death	Cause of death: respiratory infection
2	EFV + 2 NRTIs	10.0	96	11.0	26	11.7	16	AIDS event	Kaposi sarcoma
3	EFV + 2 NRTIs	9.4	159	10.5	343	15.8	465	AIDS event	Mycobacterium, other
4	EFV + 2 NRTIs	15.0	218	16.0	339	16.1	339	AIDS event	*Mycobacterium tuberculosis*, extrapulmonary or disseminated
Italy									
5	Boosted PI + NRTI	13.6	28	14.6	253	14.8	…	Death	Cause of death: unknown
Romania									
6	NVP + 2 NRTIs	1.2	217	2.8	1219	2.9	1219	AIDS event	Encephalopathy
Thailand									
7	NVP + 2 NRTIs	12.3	70	13.5	11	13.7	…	Death	Cause of death: fungal pneumonia
8	EFV + 2 NRTIs	9.6	4	10.8	273	12.8	…	Death	Cause of death: atrioventricular block
9	NVP + 2 NRTIs	13.6	70	14.8	183	14.9	…	AIDS event	*Mycobacterium tuberculosis*, extrapulmonary or disseminated

Abbreviations: ART, antiretroviral therapy; EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; VS, viral suppression

Table 4. Listing of Death/AIDS Events While on Virally Suppressed Antiretroviral Therapy Among Children With Good Immune Response

		ART Start		At 1 Year After Start of VS		At Onset of Event			
Country and No.	Initial Regimen	Age, years	CD4 Count, Cells/μL	Age, years	CD4 Count, Cells/μL	Age, years	CD4 Count, Cells/μL	Event	Cause of Death/Description of AIDS Event
Netherlands									
1	Boosted PI + NRTI	5.6	20	6.9	690	10.0	…	CDC C	*Mycobaterium avium* complex or *Kanasii*, extrapulmonary
2	NNRTI + 3 NRTIs	9.5	540	10.6	2030	17.6	…	CDC C	Candidiasis, esophageal, bronchi, trachea, or lungs
United Kingdom/ Ireland									
3	Boosted PI + NRTI	0.3	1704	1.9	1096	3.3	…	CDC C	HIV wasting syndrome
4	Boosted PI + NRTI	8.4	1953	9.5	788	13.8	1047	Death	Cause of death: accidental drowning
5	EFV + 2 NRTIs	7.1		8.1	764	9.8	…	Death	Cause of death: *Mycobacterium tuberculosis*, meningitits
6	NVP + 2 NRTIs	7.7	220	9.3	530	13.2	627	AIDS	*Mycobacterium tuberculosis*, pulmonary
7	NVP + 2 NRTIs	2.4	670	3.5	1290	8.3	921	AIDS	Encephalopathy
Spain									
8	EFV + 2 NRTIs	4.2	369	5.5	658	5.9	1225	AIDS	Candidiasis, esophageal, bronchi, trachea, or lungs
9	Boosted PI + NRTI	3.1	2358	4.1	1899	4.2	1899	AIDS	Serious recurrent/multiple bacterial infections
10	NVP + 2 NRTIs	0.0	2328	1.2	1977	5.0	304	AIDS	Encephalopathy
Thailand									
11	EFV + 2 NRTIs	10.5	22	11.7	767	17.6	…	AIDS	*Mycobacterium tuberculosis*, extrapulmonary or disseminated
12	NVP + 2 NRTIs	10.8	26	11.8	487	12.3	…	AIDS	Cryptococcosis, extrapulmonary
						12.6	…	AIDS	Progressive multifocal leukoencephalopathy
13	EFV + 2 NRTIs	7.9	3	8.9	530	9.1	…	AIDS	*Pneumocystis carinii* pneumonia
Poland									
14	NNRTI + 3 NRTIs	0.1	1343	1.2	1983	3.5	…	AIDS	Encephalopathy
Romania									
15	EFV + 2 NRTIs	12.0	15	13.1	456	13.1	456	AIDS	*Mycobacterium tuberculosis*, pulmonary
Ukraine									
16	Boosted PI + NRTI	12.7	283	13.9	440	13.9	440	AIDS	*Mycobacterium tuberculosis*, pulmonary
17	EFV + 2 NRTIs	10.6	585	12.0	835	12.7	750	AIDS	*Mycobacterium tuberculosis*, extrapulmonary or disseminated
18	EFV + 2 NRTIs	8.4	3	9.6	620	11.4	212	Death	Cause of death: unknown
19	EFV + 2 NRTIs	4.0	824	5.4	471	6.3	456	AIDS	*Mycobacterium tuberculosis*, extrapulmonary or disseminated

Abbreviations: ART, antiretroviral therapy; CDC C, US Centers for Disease Control disease C stage (AIDS); EFV, efavirenz; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; VS, viral suppression.

immunosuppression offers limited benefits in settings with routine VL monitoring due to the low risk of CD4 decline in this population, these recommendations do not extend to patients with PIR, despite VS [32]. Furthermore, there is limited evidence on when to reduce or stop CD4 monitoring in children; this is identified as a key area for research needed to inform future policies [33]. Similarly, the optimal clinical management of PIR in children in both resource-rich and resource-limited settings remains unclear and is a research gap in pediatric HIV infection.

Although our study benefits from a large sample size of children with a long duration of follow-up of over 6 years, there are important study limitations. First, 392 (17%) children had missing CD4 values at 1 year of VS, which may have led to under- or overestimation of PIR. This includes 16 children aged ≥5 years with CD4% >15% but with no CD4 cell count measurements to confirm their immune status for age. Second, our clinical outcome was limited to AIDS or death; we did not have complete reporting of Centers for Disease Control and Prevention B events or serious non-AIDS events, which have been associated with PIR in some adult studies [34].

Conclusions

One in eight children receiving suppressive ART had PIR. While the overall rate of AIDS and death in this cohort was low, children with PIR had a disproportionately high risk of disease

progression and death. Optimal management of PIR remains unclear but should include continuation of antimicrobial prophylaxis and investigation of subclinical opportunistic and chronic infections. The key finding is that treatment at a young age and prior to severe immunosuppression will likely minimize the risk of PIR.

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.

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