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

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.
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 infections were based on the US Centers for Disease Control and Prevention 2014 [17] definitions. 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/mm³ 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

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

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

<table>
<thead>
<tr>
<th></th>
<th>All Children With VS ≥1 year(^a) (N = 2318)</th>
<th>Immune Responders at 1 Year of VS (n = 1689)</th>
<th>Poor Immune Responders at 1 Year of VS (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>1084 (47)</td>
<td>783 (46)</td>
<td>121 (51)</td>
</tr>
<tr>
<td>Age at HIV diagnosis (n = 2090, 1546, 218), years</td>
<td>3.8 (1.0, 8.0)</td>
<td>4.0 (1.1, 7.9)</td>
<td>7.6 (3.3, 11.0)</td>
</tr>
<tr>
<td>Born abroad (n = 2248, 1641, 222)</td>
<td>810 (36)</td>
<td>614 (37)</td>
<td>80 (36)</td>
</tr>
<tr>
<td>Year of birth &lt;2000</td>
<td>1101 (48)</td>
<td>794 (47)</td>
<td>169 (71)</td>
</tr>
<tr>
<td><strong>Mode of HIV infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal</td>
<td>2119 (91)</td>
<td>1555 (92)</td>
<td>196 (82)</td>
</tr>
<tr>
<td>Blood products</td>
<td>88 (4)</td>
<td>58 (3)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (0.2)</td>
<td>3 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>106 (5)</td>
<td>73 (4)</td>
<td>20 (8)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom/Ireland</td>
<td>849 (37)</td>
<td>693 (41)</td>
<td>83 (35)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>332 (14)</td>
<td>183 (11)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Western/Central Europe</td>
<td>751 (32)</td>
<td>546 (32)</td>
<td>66 (26)</td>
</tr>
<tr>
<td>Thailand</td>
<td>386 (17)</td>
<td>267 (16)</td>
<td>76 (32)</td>
</tr>
<tr>
<td><strong>Characteristics at start of ART</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>6.4 (2.1, 10.4)</td>
<td>6.5 (2.4, 10.3)</td>
<td>9.7 (6.1, 13.5)</td>
</tr>
<tr>
<td>CD4% among those &lt;5 years (n = 740/970, 582/688, 36/46)</td>
<td>22 (14, 33)</td>
<td>22 (14, 33)</td>
<td>16 (8, 22)</td>
</tr>
<tr>
<td>CD4 count among those aged ≥5 years (n = 1180/1348, 887/1001, 173/191), cells/µL</td>
<td>256 (94, 417)</td>
<td>287 (130, 446)</td>
<td>112 (26, 220)</td>
</tr>
<tr>
<td>WHO immunological stage (n = 1931, 1473, 210)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>396 (21)</td>
<td>327 (22)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Mild</td>
<td>228 (12)</td>
<td>190 (13)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Advanced</td>
<td>305 (16)</td>
<td>238 (16)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Severe</td>
<td>1002 (52)</td>
<td>718 (49)</td>
<td>168 (80)</td>
</tr>
<tr>
<td>Viral load (n = 1862, 1390, 191), log(_{10}) copies/mL</td>
<td>5.0 (4.4, 5.5)</td>
<td>5.0 (4.4, 5.5)</td>
<td>4.9 (4.3, 5.3)</td>
</tr>
<tr>
<td>AIDS diagnosis (n = 2304, 1679, 236)</td>
<td>442 (19)</td>
<td>312 (19)</td>
<td>57 (24)</td>
</tr>
<tr>
<td>Hepatitis B coinfection (n = 2049, 1494, 216)</td>
<td>64 (3)</td>
<td>43 (3)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Hepatitis C coinfection (n = 1944, 1424, 203)</td>
<td>69 (4)</td>
<td>47 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Tuberculosis disease</td>
<td>56 (2)</td>
<td>38 (2)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>CMV coinfection</td>
<td>38 (2)</td>
<td>27 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>BMI-for-age z score &lt; –3 (n = 1509, 1152, 173)</td>
<td>74 (5)</td>
<td>45 (4)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Height-for-age z score &lt; –3 (n = 1511, 1153, 173)</td>
<td>195 (13)</td>
<td>135 (12)</td>
<td>31 (18)</td>
</tr>
<tr>
<td>Initial regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosted PI + NRTI</td>
<td>768 (33)</td>
<td>538 (32)</td>
<td>55 (23)</td>
</tr>
<tr>
<td>EFV + ≥2 NRTIs</td>
<td>833 (36)</td>
<td>626 (37)</td>
<td>108 (46)</td>
</tr>
<tr>
<td>NVP + ≥2 NRTIs</td>
<td>641 (28)</td>
<td>466 (28)</td>
<td>68 (29)</td>
</tr>
<tr>
<td>Other</td>
<td>76 (3)</td>
<td>59 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Calendar year at ART initiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2004</td>
<td>550 (24)</td>
<td>399 (24)</td>
<td>61 (26)</td>
</tr>
<tr>
<td>2004–2007</td>
<td>805 (35)</td>
<td>583 (35)</td>
<td>109 (46)</td>
</tr>
<tr>
<td>≥2008</td>
<td>963 (42)</td>
<td>707 (42)</td>
<td>67 (28)</td>
</tr>
</tbody>
</table>

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.
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/mm³) 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 status at ART start (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.
### Table 2. Predictors of Poor Immune Response at 1 Year of Viral Suppression

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Univariable</th>
<th>Multivariable</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number (%) With PIR (N = 1926)</td>
<td>OR</td>
</tr>
<tr>
<td>Demographic Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>116/1022 (11)</td>
<td>0.83</td>
</tr>
<tr>
<td>Male</td>
<td>121/904 (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country of cohort</td>
<td>142/1169 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abroad</td>
<td>80/694 (12)</td>
<td>0.94</td>
</tr>
<tr>
<td>Unknown</td>
<td>15/83 (24)</td>
<td>2.26</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2000</td>
<td>169/963 (18)</td>
<td>1.00</td>
</tr>
<tr>
<td>≥2000</td>
<td>86/963 (7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mode of HIV infection</td>
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<td></td>
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<tr>
<td>Perinatal</td>
<td>195/1750 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other/ unknown</td>
<td>42/176 (24)</td>
<td>2.50</td>
</tr>
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<td>Region of cohort</td>
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<tr>
<td>United Kingdom/Ireland</td>
<td>83/776 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>12/195 (6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Western/Central Europe</td>
<td>68/812 (11)</td>
<td>1.01</td>
</tr>
<tr>
<td>Thailand</td>
<td>76/343 (22)</td>
<td>2.38</td>
</tr>
<tr>
<td>Characteristics at start of ART</td>
<td></td>
<td></td>
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<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>46/734 (6)</td>
<td>1.00</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>79/824 (13)</td>
<td>2.17</td>
</tr>
<tr>
<td>10 to &lt;15</td>
<td>78/483 (16)</td>
<td>2.88</td>
</tr>
<tr>
<td>≥15</td>
<td>34/85 (41)</td>
<td>9.97</td>
</tr>
<tr>
<td>WHO immune stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4/321 (1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mild</td>
<td>5/256 (3)</td>
<td>2.15</td>
</tr>
<tr>
<td>Advanced</td>
<td>33/271 (12)</td>
<td>11.34</td>
</tr>
<tr>
<td>Severe</td>
<td>168/886 (19)</td>
<td>19.12</td>
</tr>
<tr>
<td>Unknown</td>
<td>27/243 (11)</td>
<td>10.22</td>
</tr>
<tr>
<td>Viral load, copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 000</td>
<td>79/753 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>≤100 000</td>
<td>112/828 (14)</td>
<td>1.33</td>
</tr>
<tr>
<td>Unknown</td>
<td>46/345 (13)</td>
<td>1.31</td>
</tr>
<tr>
<td>AIDS diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57/369 (15)</td>
<td>1.40</td>
</tr>
<tr>
<td>No</td>
<td>180/1557 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatitis B coinfection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14/57 (25)</td>
<td>2.40</td>
</tr>
<tr>
<td>No/unknown</td>
<td>223/1869 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatitis C coinfection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5/52 (10)</td>
<td>0.75</td>
</tr>
<tr>
<td>No/unknown</td>
<td>232/1874 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tuberculosis disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11/49 (22)</td>
<td>2.11</td>
</tr>
<tr>
<td>No</td>
<td>226/1877 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>CMV coinfection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>229 (7)</td>
<td>0.52</td>
</tr>
<tr>
<td>No</td>
<td>235/1897 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI-for-age z score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0</td>
<td>68/634 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>≤-3 to 0</td>
<td>86/629 (14)</td>
<td>1.35</td>
</tr>
<tr>
<td>&lt; -3</td>
<td>17/82 (27)</td>
<td>3.14</td>
</tr>
</tbody>
</table>
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/mm³), 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

<table>
<thead>
<tr>
<th>Country and Patient Number</th>
<th>Initial Regimen</th>
<th>At 1 Year After Start of VS</th>
<th>At Onset of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age, years</td>
<td>CD4 Count, Cells/µL</td>
<td>Event</td>
</tr>
<tr>
<td></td>
<td>Art Start Age, years</td>
<td>CD4 Count, Cells/µL</td>
<td>Age, years</td>
</tr>
<tr>
<td>United Kingdom/Ireland</td>
<td>EFV + 2 NRTIs</td>
<td>7.9</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>EFV + 2 NRTIs</td>
<td>10.0</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>EFV + 2 NRTIs</td>
<td>9.4</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td>EFV + 2 NRTIs</td>
<td>15.0</td>
<td>218</td>
</tr>
<tr>
<td>Italy</td>
<td>Boosted PI + NRTI</td>
<td>13.6</td>
<td>28</td>
</tr>
<tr>
<td>Romania</td>
<td>NVP + 2 NRTIs</td>
<td>1.2</td>
<td>217</td>
</tr>
<tr>
<td>Thailand</td>
<td>NVP + 2 NRTIs</td>
<td>12.3</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>EFV + 2 NRTIs</td>
<td>9.6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>NVP + 2 NRTIs</td>
<td>13.6</td>
<td>70</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PIR, poor immune response; WHO, World Health Organization.
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

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

<table>
<thead>
<tr>
<th>Country and No.</th>
<th>Initial Regimen</th>
<th>ART Start</th>
<th>At 1 Year After Start of VS</th>
<th>At Onset of Event</th>
<th>Cause of Death/Description of AIDS Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>Boosted PI + NRTI</td>
<td>5.6</td>
<td>6.9</td>
<td>10.0</td>
<td>CDC C Mycobacterium avium complex or Kanasii, extrapulmonary</td>
</tr>
<tr>
<td>2</td>
<td>NNRTI + 3 NRTIs</td>
<td>9.5</td>
<td>10.6</td>
<td>176</td>
<td>CDC C Candidiasis, esophageal, bronchial, trachea, or lungs</td>
</tr>
<tr>
<td>United Kingdom/ Ireland</td>
<td>Boosted PI + NRTI</td>
<td>0.3</td>
<td>1.9</td>
<td>3.3</td>
<td>CDC C HIV wasting syndrome</td>
</tr>
<tr>
<td>4</td>
<td>Boosted PI + NRTI</td>
<td>8.4</td>
<td>9.5</td>
<td>13.8</td>
<td>Death Cause of death: accidental drowning</td>
</tr>
<tr>
<td>5</td>
<td>EFV + 2 NRTIs</td>
<td>7.1</td>
<td>8.1</td>
<td>9.8</td>
<td>Death Cause of death: Mycobacterium tuberculosis, meningitis</td>
</tr>
<tr>
<td>6</td>
<td>NVP + 2 NRTIs</td>
<td>7.7</td>
<td>9.3</td>
<td>13.2</td>
<td>AIDS Mycobacterium tuberculosis, pulmonary</td>
</tr>
<tr>
<td>7</td>
<td>NVP + 2 NRTIs</td>
<td>2.4</td>
<td>3.5</td>
<td>8.3</td>
<td>AIDS Encephalopathy</td>
</tr>
<tr>
<td>Spain</td>
<td>EFV + 2 NRTIs</td>
<td>4.2</td>
<td>5.5</td>
<td>5.9</td>
<td>AIDS Candidiasis, esophageal, bronchial, tracheal, or lungs</td>
</tr>
<tr>
<td>9</td>
<td>Boosted PI + NRTI</td>
<td>3.1</td>
<td>4.1</td>
<td>4.2</td>
<td>AIDS Serious recurrent/multiple bacterial infections</td>
</tr>
<tr>
<td>10</td>
<td>NVP + 2 NRTIs</td>
<td>0.0</td>
<td>1.2</td>
<td>5.0</td>
<td>AIDS Encephalopathy</td>
</tr>
<tr>
<td>Thailand</td>
<td>EFV + 2 NRTIs</td>
<td>10.5</td>
<td>11.7</td>
<td>17.6</td>
<td>AIDS Mycobacterium tuberculosis, extrapulmonary or disseminated</td>
</tr>
<tr>
<td>12</td>
<td>NVP + 2 NRTIs</td>
<td>10.8</td>
<td>11.8</td>
<td>12.3</td>
<td>AIDS Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td>13</td>
<td>EFV + 2 NRTIs</td>
<td>7.9</td>
<td>8.9</td>
<td>9.1</td>
<td>AIDS Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Poland</td>
<td>NNRTI + 3 NRTIs</td>
<td>0.1</td>
<td>1.2</td>
<td>3.5</td>
<td>AIDS Encephalopathy</td>
</tr>
<tr>
<td>Romania</td>
<td>EFV + 2 NRTIs</td>
<td>12.0</td>
<td>13.1</td>
<td>13.1</td>
<td>AIDS Mycobacterium tuberculosis, pulmonary</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Boosted PI + NRTI</td>
<td>12.7</td>
<td>13.9</td>
<td>13.9</td>
<td>AIDS Mycobacterium tuberculosis, pulmonary</td>
</tr>
<tr>
<td>17</td>
<td>EFV + 2 NRTIs</td>
<td>10.6</td>
<td>12.0</td>
<td>12.7</td>
<td>AIDS Mycobacterium tuberculosis, extrapulmonary or disseminated</td>
</tr>
<tr>
<td>18</td>
<td>EFV + 2 NRTIs</td>
<td>8.4</td>
<td>9.6</td>
<td>11.4</td>
<td>Death Cause of death: unknown</td>
</tr>
<tr>
<td>19</td>
<td>EFV + 2 NRTIs</td>
<td>4.0</td>
<td>5.4</td>
<td>6.3</td>
<td>AIDS Mycobacterium tuberculosis, extrapulmonary or disseminated</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CDC C, US Centers for Disease Control and Prevention 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.
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.

**Notes**

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Acknowledgments. The authors thank all the patients for their participation in these cohorts, and the staff members who cared for them.

Financial support. This work was supported by funding from the European Union Seventh Framework Programme for Research, Technological Development, and Demonstration under EuroCoord grant agreement 260694. The MRC Clinical Trials Unit at University College London is supported by the Medical Research Council (program number MC_UU_12023/26). C. S. reports grants from Dutch Ministry of Health, Welfare and Sport, during the conduct of the study. This work has been partially funded by the Fundación para la Investigación y Prevención de SIDA en España (FIPSE) 366029/09, FIPSE 248080/09, FIPSE 361910/10, Red Temática de Investigación en SIDA (RED RIS) supported by Instituto de Salud Carlos III (ISCIII) (R12/0017/0035 and RD12/0017/0037) project as part of the Plan R+D+I and cofinanced by the ISCIII-Subdirección General de Evaluación and Fondo Europeo de Desarrollo Regional (FEDER), Mutua Madrileña 2012/007, Gilead Fellowship 2013/0071, FIS PI15/00694, and CoRISpe (RED RIS RD06/0006/0035 y RD06/0006/0021).

Potential conflicts of interest. A. J. reports grants from Gilead Sciences, Inc, Janssen Pharmaceuticals, PENTA Foundation, and the Collaborative Initiative for Paediatric HIV Education and Research, outside the submitted work. C. T. reports grants from Abbvie and ViV, outside the submitted work; C. T. also serves on the Advisory Board of ViV. I. J. C. reports grants from Gilead Sciences, Inc, Janssen Pharmaceuticals, and the Collaborative Initiative for Paediatric HIV Education and Research, outside the submitted work. L. G. reports personal fees from ViV Healthcare, outside the submitted work. R. G. reports grants from Janssen Pharmaceuticals and the Collaborative Initiative for Paediatric HIV Education and Research, outside the submitted work. J. W. reports grants from INSERM-ANRS (Agence Nationale de Recherche sur le Sida et les Hépatites Virales, Agence autonome INSERM) and SFCE (Société Française des Cancers de l’Enfant), outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


