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## **Predictors of faster virological suppression in early treated infants with perinatal HIV from Europe and Thailand**

**Short title:** Predictors of viral suppression in infants with perinatal HIV

**Group authorship<sup>#</sup>:** The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) and Early-treated Perinatally HIV-infected Individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies (EPIICAL)

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## Abstract

**Objective:** To identify predictors of faster time to virological suppression among infants starting combination antiretroviral therapy (cART) early in infancy.

**Design:** Cohort study of infants from Europe and Thailand included in studies participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

**Methods:** Infants with perinatal HIV starting cART aged <6 months with  $\geq 1$  viral load (VL) measurement within 15 months of cART initiation were included. Multivariable interval-censored flexible parametric proportional hazards models were used to assess predictors of faster virological suppression, with timing of suppression assumed to lie in the interval between last VL $\geq 400$  and first VL $< 400$  copies/ml.

**Results:** Of 420 infants, 59% were female and 56% from Central/Western Europe, 26% UK/Ireland, 15% Eastern Europe and 3% Thailand; 46% and 54% started a boosted protease inhibitor- or non-nucleoside reverse transcriptase inhibitor- based regimen, respectively. At cART initiation, the median age, CD4% and VL were 2.9 (IQR:1.4-4.1) months, 34 (IQR:24-45)% and 5.5 (IQR:4.5-6.0) log<sub>10</sub>copies/ml, respectively. Overall, an estimated 89% (95%CI:86-92%) achieved virological suppression within 12 months of cART start. In multivariable analysis, younger age (aHR:0.84 per month older; P<0.001), higher CD4% (aHR:1.11 per 10% higher; P=0.010) and lower log<sub>10</sub> VL (aHR:0.85 per log<sub>10</sub> higher; P<0.001) at cART initiation independently predicted faster virological suppression.

**Conclusion:** We observed a significant independent effect of age at cART initiation, even within a narrow 6 months window from birth. These findings support the earliest feasible cART initiation in infants and suggest that early therapy influences key virological and immunological parameters that could have important consequences for long term health.

**Keywords:** Predictors; virological suppression; early cART; perinatal HIV; infants

## **Introduction**

The clinical benefits of starting combination antiretroviral therapy (cART) early in HIV-infected infants have been demonstrated in several observational studies and trials. The Children with HIV Early Antiretroviral Therapy (CHER) trial showed that starting cART before 12 weeks of age markedly reduces mortality and morbidity in HIV-infected infants [1, 2]. These findings were confirmed in the European Infant Collaboration (EIC) observational study [3] and the French perinatal cohort [4]. Several other studies have shown that early cART initiation controls proviral replication [5], limits establishment of latent HIV reservoirs [6-8], preserves immune function [9] and contributes to long-term viral suppression [10, 11]. Rare case reports have further highlighted the beneficial effect of early cART in sustaining HIV remission in children who subsequently discontinue cART [12-15].

Several studies investigating virological outcomes have also demonstrated that early cART improves initial viral control in infants, although results have been variable. For instance, an Italian study reported that infants starting cART at <6 months of age had better virological responses compared to those starting after 6 months of age over all follow-up time-points [16]. A subgroup analysis of data from the EIC cohort showed that early therapy within 3 months of life was associated with a faster control of viral replication [11]. Similarly, a trial evaluating safety and tolerability of three cART regimens in the United States and Puerto Rico showed that early therapy in the first 3 months of life was associated with improved long-term viral suppression [17]. However, in contrast, a recent South African study reported inconsistent benefits of early cART on timing of virological suppression in infants starting cART <6 months of age [18]. In addition, few studies have examined factors associated with time to virological suppression in infants starting cART before 6 months of age; most studies have evaluated children initiating cART during the first year of life [19-21] or at older ages [22] and results have been variable.

Therefore the aim of our study was to investigate predictors of faster virological suppression, focusing on infants with perinatal HIV initiating standard cART within the first 6 months of life living in Europe and Thailand and included in studies participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

## **Methods**

### **Study inclusion criteria**

Data from the EPPICC Paediatric merger 2014 (n=3953) were used, as described previously [23, 24]. In brief, the EPPICC merged individual patient data on routine demographic, clinical, laboratory, and treatment-related variables from 19 observational cohorts across 17 countries prepared according to a standardised data specification. The inclusion criteria for this analysis were infants with perinatal HIV and aged <6 months at start of standard cART, defined as boosted protease inhibitor (bPI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) plus 2 or more nucleoside reverse transcriptase inhibitors (NRTI), with a baseline viral load (VL) measure at cART initiation plus at least 1 VL within the 15 months following initiation.

### **Statistical analysis**

The endpoint for this analysis was virological suppression. The exact time of viral suppression could not be observed and it was only known to have occurred at some point in an interval of time. Therefore, interval-censored methods for analysing survival data were required to accurately estimate the distribution of time of the event (i.e. virological suppression). Owing to the nature of our observational cohort study, there were natural differences in follow-up visit schedules across regions resulting in subsequent differences in gap between consecutive VL measurements by region. As a result, interval-censored methods were also required to estimate an unbiased effect of region. In our main analysis, the time of virological suppression was assumed to have occurred in the interval between last  $VL \geq 400$  and first  $VL < 400$  copies/ml (referred as “virological suppression [Interval]” thereafter). Time

from cART initiation to virological suppression was analysed using time-to-event methods, censoring follow-up at the earliest of last VL measurement before >15 month gap in measurements or last VL measurement. The cumulative probability of infants achieving virological suppression over time from cART initiation was estimated using interval-censored flexible parametric survival models. In sensitivity analyses, cumulative probabilities were also estimated using Kaplan-Meier methods and non-parametric maximum likelihood estimate (MLE) for interval-censored data, as implemented in the R package *interval* [25].

Univariable and multivariable interval-censored flexible parametric proportional hazards (PH) survival models were used to identify predictors of faster virological suppression. These models were chosen as the main analysis to allow for analysis of interval censored data, where virological suppression was assumed to occur in the interval between last VL $\geq$ 400 and first VL $<$ 400copies/ml. These models further extend standard parametric models using restricted cubic splines rather than linear functions for the underlying log cumulative hazard, as implemented in Stata *stpm* function [26]. Akaike Information Criteria (AIC) was used to identify the best-fitting model (lowest AIC), testing 1–6 degrees of freedom of the underlying spline for the log cumulative hazard. Predictors identified from univariable models with  $P < 0.10$  met criteria for inclusion into multivariable model, along with those identified *a priori* (geographical region and initial cART regimen). Backward stepwise elimination (exit probability  $P = 0.05$ ) was applied to reach the final multivariable model. The functional form of significant predictors was explored using regression splines.

We evaluated the following factors: age at cART initiation, baseline VL, CD4% and count, gender, ethnicity, initial cART regimen [bPI or NNRTI plus 2 or more NRTI], infant antiretroviral prevention of mother-to-child transmission (PMTCT) prophylaxis regimen given within 4 weeks of birth, maternal antiretroviral PMTCT regimen used in the prenatal and delivery period, birth abroad (whether infants were born in the same country in which

they were enrolled for HIV care), year of birth, year of cART initiation, CDC C event by cART initiation and geographical region. Geographical region of cohort was categorised *a priori*, as described previously [24]: Eastern Europe [Russia and Ukraine], Central and Western Europe [Belgium, Germany, Italy, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland, France and Greece], United Kingdom [UK]/Ireland and Thailand. Missing values for baseline VL (18%) and CD4% (22%) were multiply imputed by chained equations (MICE) (20 cycles), on the complete EPPICC dataset to avoid imputation bias. Imputation diagnostics was performed by adjusting number of imputations to minimise proportion of total sampling variance that is due to missing data.

Sensitivity analyses were carried out using both multiply imputed and non-imputed data (complete case analysis) and by considering two additional definitions of time of virological suppression: (1) Midpoint between last VL $\geq$ 400 and first VL<400copies/ml (referred as “virological suppression [Midpoint]”); (2) date VL<400copies/ml (referred as “virological suppression [Observed]”). The proportional hazards assumption for each predictor was tested and accounted for by including predictor\*time (\_t) interaction term in the multivariable model, where applicable. To further confirm results, Cox PH models and interval-censored parametric survival models with Weibull distribution were also fitted. Stata version 15.1 (Stata Corporation, College Station, Texas, USA) was used for all analyses, unless otherwise stated.

## **Results**

### **Patient characteristics**

Of the 3953 children included in the dataset, 420 (11%) infants met the study inclusion criteria of being perinatally HIV-infected, aged <6 months at cART initiation with  $\geq$ 1 VL measurement within 15 months of cART start (1998-2013) (Figure 1). Of these, 59% were



female, 35% were white and 29% were of black ethnicity (Table 1). Most (90%) were born in the same country in which they were enrolled for HIV care and the vast majority (94%) were born after the year 2000. In total, 56% were from Central/Western Europe, 26% from UK/Ireland, 15% from Eastern Europe and 3% from Thailand. Among infants that had PMTCT prophylaxis data available, over half (59%) received PMTCT and 44% received maternal PMTCT, and 16% had a CDC C event by the time of cART initiation.

Median age at cART initiation was 2.9 [interquartile range (IQR): 1.4-4.1] months, with 43% initiating cART after the year 2008. Forty-six percent of infants started on a bPI [lopinavir (LPV)] based regimen, and 54% on a NNRTI [nevirapine (NVP)] based regimen. Median CD4%, CD4 count and VL at cART initiation were 34 [24-45]%, 1781 [995-2644] cells/mm<sup>3</sup> and 5.5 [4.5-6.0] log<sub>10</sub> copies/ml, respectively (Table 1). Of the 420 infants included, 17 (4%) had 1 viral load after cART start. The remaining 403 (96%) had  $\geq 2$  viral loads. The median and mean number of viral load measurements after cART start was 15 and 19 per infant, respectively. Median duration of follow-up after cART initiation was 5.2 [2.1-8.8] years. Median gap between consecutive VL measurements was 9 [5-13] weeks and this varied by geographical region, ranging from 7 weeks in the UK/Ireland, 9 weeks in Central/Western Europe, 17 weeks in Thailand to 18 weeks in Eastern Europe. Baseline VL was missing in 76 infants (18%). These missing values were multiply imputed for analysis. The numbers missing baseline VL by age at cART start bracket were similar. The proportions missing versus non-missing baseline VL were also not significantly different by age bracket (P=0.795) (Supplementary Appendix 1, <http://links.lww.com/QAD/B452>).

### **Cumulative probability of virological suppression**

Overall, the cumulative probability of achieving virological suppression [Interval] by 12 months after cART initiation was estimated at 89% [95% confidence interval (CI): 86-92]%,

using the interval-censored flexible parametric survival model (Supplementary Figure 1, <http://links.lww.com/QAD/B452>). In sensitivity analyses, the cumulative probabilities estimated by the non-parametric MLE method were very similar to those obtained using the parametric survival model. The probabilities of virological suppression [Midpoint] and [Observed] by 12 months were estimated (Kaplan–Meier) at 84% [80-87]% and 77% [73-81]%, respectively (Supplementary Figure 1, <http://links.lww.com/QAD/B452>).

### **Baseline predictors of virological suppression**

Results of interval-censored univariable and multivariable analyses using multiply imputed data are shown in Table 2. In multivariable analysis, independent predictors of faster virological suppression [Interval] were younger age at cART initiation [adjusted hazard ratio (aHR): 0.84 (95%CI: 0.78-0.91) per month older;  $P < 0.001$ ], higher baseline CD4% [aHR: 1.11 (95%CI: 1.03-1.20) per 10% higher;  $P = 0.010$ ] and lower baseline  $\log_{10}$  VL [aHR: 0.85 (95%CI: 0.78-0.93) per  $\log_{10}$  higher;  $P < 0.001$ ], adjusting for initial cART regimen and geographical region. Figure 2 illustrates the significant effect of age at cART initiation on time to virological suppression. Of note, in univariable analysis, higher CD4 count also predicted faster virological suppression. However, due to multicollinearity with CD4%, CD4 count was not included in the final multivariable model. CD4% was included as it is a more stable measurement in children aged  $< 5$  years [21, 27]. There was no significant effect of any of the remaining factors examined on time to virological suppression (Table 2).

### **Sensitivity analyses of predictors of virological suppression**

Restricted to the complete case analysis, the same factors (age at cART initiation, baseline CD4% and VL) remained significantly associated with faster virological suppression [Interval] (Supplementary Table 1, <http://links.lww.com/QAD/B452>). Regression spline analysis further revealed a linear relationship of significant predictors with the outcome

(Supplementary Figure 2, <http://links.lww.com/QAD/B452>). Results from multivariable analyses of time to virological suppression [Midpoint] and [Observed] were similar, both with and without multiple imputation (Supplementary Tables 1 and 2, <http://links.lww.com/QAD/B452>). In some sensitivity analyses, initial cART regimen and/or geographical region were found to violate the PH assumption (i.e. interact with analysis time) hence, corresponding interaction terms were included in the relevant final multivariable models to account for this effect. Additional univariable and multivariable analyses using Cox PH models and interval-censored parametric survival models with Weibull distribution further confirmed the main findings (data not shown).

## **Discussion**

To our knowledge, this is the largest study reported to date exploring predictors of faster virological response in infants with perinatal HIV initiating cART within 6 months of life. Most infants achieved virological suppression within 12 months of starting cART. This is the first study to show that even amongst infants initiating therapy within 6 months of life, earlier cART initiation predicted faster virological suppression. Higher baseline CD4% and lower  $\log_{10}$  VL were also independent predictors of faster virological suppression.

Our findings are consistent with the general conclusions from smaller studies that have identified early treatment as a determinant of faster virological suppression. The European EIC study reported faster suppression in infants starting cART earlier (<3 months of age) compared to later treated infants [11]. In another study (n=128) investigating older ART naïve African children aged 1.7–13.5 years, children younger than 8 years had increased probability of attaining virological suppression compared to older children [28]. Other studies conducted in the United States/Puerto Rico (n=52), Italy (n=133) and South Africa (n=1748; total of 5 cohorts), revealed that early therapy was a significant predictor of long-term viral suppression in children starting cART at <3 months (versus  $\geq 3$  months of age) [17] and <6

months (versus  $\geq 6$  months of age) [16, 18]. While determining the onset of infection in adults is problematic, recent studies specifically designed to capture this information, have also identified early ART during primary infection as a key factor for faster viral suppression in adults [29].

The estimated cumulative probability of achieving virological suppression [Interval], [Midpoint] and [Observed] was 89%, 84% and 77%, respectively. This is consistent with previous findings despite the variability in definitions of suppression. In the CHER trial (n=377) conducted in South Africa, the proportion of infants with VL<400copies/ml by 12 months post-cART initiation was 77% [30]. Similar findings were reported by the EIC study among 139 infants starting cART before 3 months of age [11]. In two studies conducted in Kenya (n=121) and Mozambique (n=119), the proportion of children suppressed to <1000copies/ml was 75% [31] and 77% [32], respectively, by 12 months after cART start. Similarly, in a Ugandan study (n=91), the probability of suppression to <400copies/ml was 83.1% in infants starting cART <12 months of age [33]. Further evidence that with early intervention high levels of suppression can be achieved comes from a pilot trial of infants randomised to receive immediate or deferred four-drug (three-class) antiretroviral therapy (n=63) [19] at a median age of 28 days (intrauterine-infected) and 55 days (intrapartum-infected). The proportions attaining virological suppression to <400copies/ml and <50copies/ml were higher at 100% and 94%, respectively, 12 months post-cART.

The reasons for the critical timing of cART initiation on virological suppression are unclear. The relationship with lower baseline VL has been observed before in various settings and at different ages [17, 19, 21, 22, 34]. There are sound virological and immunological reasons why an individual with lower levels of circulating virus would suppress more rapidly. The viral decay following initiation of ART occurs in phases. Firstly, the initial decline signifies early loss of short-lived virally productive cells. This is followed by the slower loss of longer-

lived but productive cells. Finally, there is the much slower loss of latently infected cells [35]. In the context of our findings, the implication would be that earlier treatment may target the short-lived cells, which could have important implications for limiting viral reservoirs. This in turn may also provide optimal opportunities for adjunctive therapies as part of the cure agenda [36].

As well as baseline VL, faster virological suppression was also associated with a higher baseline CD4% (also CD4 count). This association has been seen in multiple studies [19, 20, 34] in infants, children, pregnant women and adults. Whilst it is tempting to link the lower VL with the higher CD4%, they were actually independent predictors of viral suppression, indicating an immunological basis for this finding. Our previous work has shown how critical early treatment is for preserving CD4 counts [37]. In the CHER study, even though early treatment arrested CD4 decline, it did not fully restore levels to those seen in HIV uninfected children [37]. When therapy was stopped as part of planned treatment interruption, there was a rapid decline in CD4 T-cells, which on retreatment returned to levels observed before interruption. This indicates that baseline CD4 levels provides insight into CD4 cell homeostasis, with individuals with higher CD4 having a greater proportion of recent thymic emigrants, which are relatively resistant to HIV infection [37]. The combination of early treatment, low VL and high baseline CD4 cells is therefore desirable for many reasons including faster immune reconstitution [31], limiting viral reservoir seeding, preserving age appropriate CD4 cell homeostasis and providing opportunities for 'HIV cure' [38]. Infants with these characteristics may represent the target population in which to investigate therapeutic vaccines, with the ultimate goal of achieving ART-free HIV remission. Therapeutic vaccines are an integral part of the HIV cure agenda and an increasing global health priority [38].

Apart from age at cART initiation, baseline CD4% and VL, none of the remaining factors examined predicted faster virological suppression in our final multivariable analysis. A few other studies in Europe have, however, reported significant associations with initial cART regimen [21] and calendar year [22] in older children starting cART <18 years of age. On the other hand, in an Ugandan study, none of the baseline factors investigated (age, gender, CD4%, WHO stage, cART regimen, weight-for-age or height-for-age z-scores) were found to predict virological suppression to VL<400copies/ml [33]. Although there was no significant effect of infant and maternal PMTCT prophylaxis on time to virological suppression, the potential effect of PMTCT on suppression has recently been demonstrated [39].

Our study had limitations. It was a sub-group analysis of pooled observational cohort data, hence potential effects of selection bias and unmeasured confounders cannot be ruled out. Data on exact timing of HIV infection and antiviral treatment adherence were not available and could not be investigated. Although year of cART initiation was not associated with time to virological suppression, our data date back to 1998. Given the changes in treatment guidelines over time across countries, all analyses were adjusted for initial cART regimen and geographical region despite their lack of association with the outcome. Longitudinal investigation of long-term viral suppression in early treated infants is also of interest, but was outside the scope of this manuscript. Finally, although our study supports the earliest feasible cART initiation in infants, there are still challenges that need to be addressed before infants can indeed benefit from very early therapy. These challenges relate to difficulties in scaling up birth testing in low and middle income countries with the highest burden [40-42].

In conclusion, we showed that effective treatment response was achieved in the majority of infants initiating cART within 6 months of life across Europe and Thailand. We identified the conditions needed to attain faster virological suppression in these infants. We demonstrated that even amongst early treated infants, earlier cART initiation, higher baseline CD4% and

lower baseline VL independently predicted faster virological suppression. These results provide additional support for earlier cART initiation in infants with perinatal HIV and indicate that early treatment influences key virological and immunological parameters that could have important consequences for long term health.

### **Author contributions**

MC and RG performed the statistical analyses and drafted the manuscript. AB, AJ, DG and PR conceptualised and designed the study and, were involved in the preparation and review of the final manuscript. All co-authors participated in discussions about interpretation of findings, were involved in the preparation and critical review of the final manuscript. All participating cohorts within EPPICC were involved in the collection of data and interpretation of the findings.

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### **Potential conflicts of interest**

No conflicts of interest.

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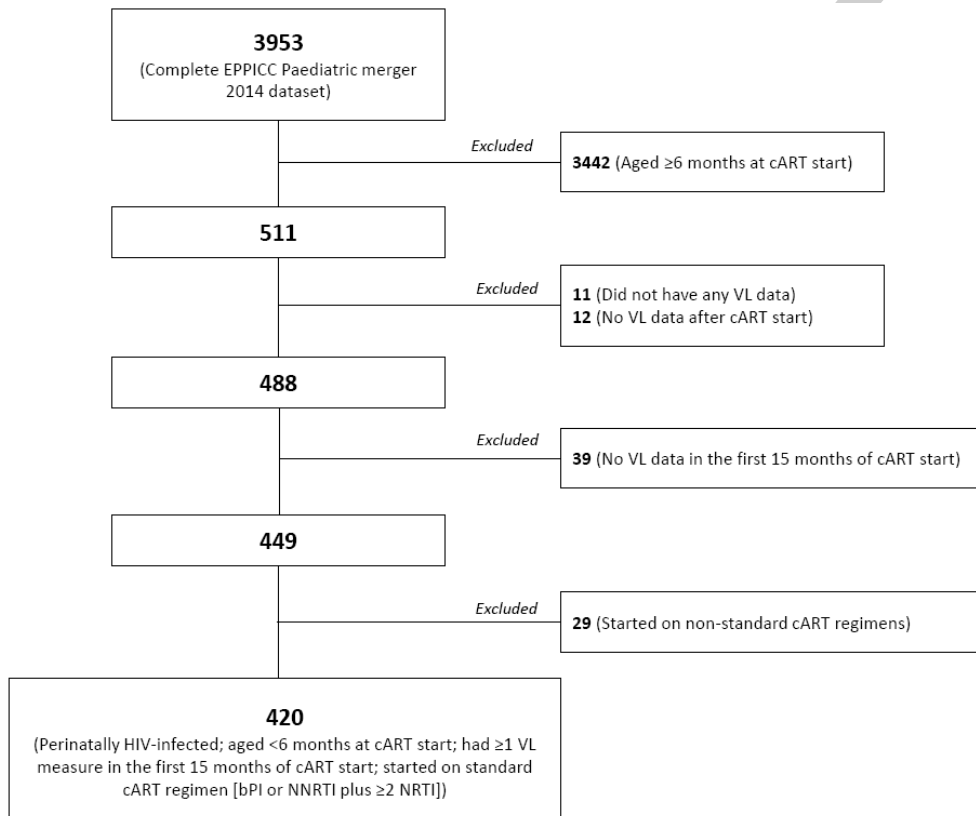
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## Figures

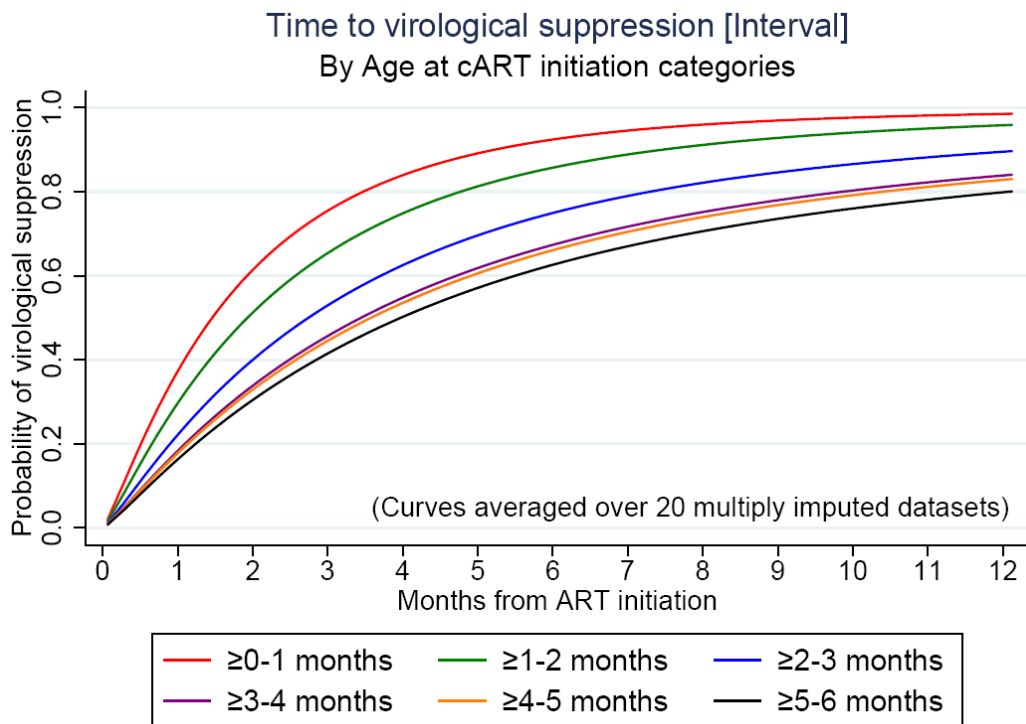
**Figure 1. Patient inclusion flowchart**

This figure shows patient inclusion selection from the complete EPPICC Paediatric merger 2014 dataset.



## Figure 2. Effect of age at cART initiation on time to virological suppression [Interval]

This figure shows the estimated cumulative probabilities of achieving virological suppression [Interval] by age at cART initiation during the first 12 months of antiretroviral therapy. Probabilities were estimated from the flexible parametric survival model using multiply imputed data. Curves were averaged over 20 multiply imputed datasets.



## Tables

**Table 1. Baseline characteristics**

N=420	Median (IQR) or N (%)
<b>Sociodemographic characteristics [N<sup>##</sup>]</b>	
<b>Gender</b>	
Male	173 (41%)
Female	247 (59%)
<b>Ethnicity<sup>†</sup></b>	
White	146 (35%)
Black	121 (29%)
Other	19 (5%)
Unknown	134 (32%)
<b>Geographical region</b>	
UK/Ireland	109 (26%)
Thailand	14 (3%)
Eastern Europe	61 (15%)
Central and Western Europe	236 (56%)
<b>Birth abroad [N=415]</b>	
No	374 (90%)
Yes	41 (10%)
<b>Year of birth</b>	
<2000	24 (6%)
≥2000	396 (94%)
<b>HIV related parameters</b>	
<b>Baseline</b>	
CD4% [N=329]	34 (24-45)
CD4 (cells/mm <sup>3</sup> ) [N=340]	1781 (995-2644)
Viral load (copies/ml) [N=344]	314116 (34324-1000000)
Log <sub>10</sub> Viral load (copies/ml) [N=344]	5.5 (4.5-6.0)
<b>CDC C event by cART initiation</b>	
No	353 (84%)
Yes	67 (16%)
<b>ART related characteristics</b>	
<b>Age at cART initiation (months)</b>	2.9 (1.4-4.1)
<b>Year of cART initiation</b>	
1998 -<2004	105 (25%)
2004 -<2008	133 (32%)
≥2008	182 (43%)
<b>Initial cART regimen</b>	
bPI+≥2NRTI	194 (46%)
NNRTI+2NRTI	150 (36%)
NNRTI+3NRTI	76 (18%)
<b>Maternal PMTCT<sup>#</sup> [N=326]</b>	
No	181 (56%)
Yes	145 (44%)
<b>If yes, the most potent PMTCT regimen used in the prenatal and delivery period [N=145]</b>	
PMTCT given but regimen unknown	10 (7%)
Mono or dual therapy including an NNRTI	20 (14%)
Triple therapy including an NNRTI	15 (10%)
Triple therapy not including an NNRTI	70 (48%)
Other	30 (21%)
<b>Infant PMTCT* [N=332]</b>	
No	135 (41%)

Yes	197 (59%)
<b>If yes, the most potent PMTCT regimen given within 4 weeks of birth [N=197]</b>	
PMTCT given but regimen unknown	15 (7.6%)
Mono or dual therapy including an NNRTI	56 (28%)
Triple therapy including an NNRTI	41 (21%)
Triple therapy not including an NNRTI	7 (3.6%)
Other	78 (40%)

<sup>##</sup>Numbers shown if data were available in <420 infants; <sup>†</sup>Ethnicity listed as a separate category if >20 per category, otherwise these are combined into the “Other” category; <sup>#</sup>Maternal PMTCT regimen used in the prenatal and delivery period; <sup>\*</sup>Infant PMTCT regimen given within 4 weeks of birth; **bPI**, boosted protease inhibitor – Lopinavir (LPV); **NRTI**, nucleoside reverse transcriptase inhibitors; **NNRTI**, non-nucleoside reverse transcriptase inhibitor – Nevirapine (NVP).

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**Table 2. Univariable and multivariable predictors of virological suppression [Interval]**

Predictors	Univariable model			Multivariable model*		
	HR	[95% CI]	P-value	aHR	[95% CI]	P-value
<b>At cART initiation</b>						
Age (per month older)	0.83	[0.77-0.88]	<0.001	0.84	[0.78-0.91]	<0.001
CD4% (per 10% higher)	1.16	[1.08-1.24]	<0.001	1.11	[1.03-1.20]	<b>0.010</b>
CD4 count (per 500 cell higher)	1.13	[1.07-1.18]	<0.001	---	---	---
Viral load (per log <sub>10</sub> higher)	0.80	[0.74-0.87]	<0.001	0.85	[0.78-0.93]	<0.001
Gender (Ref: Male)						
Female	1.03	[0.83-1.27]	0.810			
Infant PMTCT (Ref: No)						
Yes	1.16	[0.91-1.47]	0.221			
Maternal PMTCT (Ref: No)						
Yes	1.19	[0.94-1.51]	0.145			
Birth abroad (Ref: No)						
Yes	0.99	[0.70-1.40]	0.968			
Year of birth (Ref: <2000)						
≥2000	1.44	[0.93-2.24]	0.106	---	---	---
CDC C event by cART initiation (Ref: No)						
Yes	0.81	[0.61-1.08]	0.151			
Year of cART initiation (Ref: 1998-<2004)						
2004-<2008	0.95	[0.73-1.24]	0.695	---	---	---
≥2008	1.27	[0.98-1.65]	0.073	---	---	---
Initial cART regimen <sup>#</sup> (Ref: bPI+NRTI)						
NNRTI+2NRTI	0.95	[0.75-1.21]	0.696	0.83	[0.64-1.07]	0.156
NNRTI+3NRTI	1.04	[0.78-1.39]	0.780	0.93	[0.63-1.39]	0.740
Ethnicity (Ref: Black)						
White	0.86	[0.66-1.11]	0.246			
Other	1.11	[0.66-1.87]	0.700			
Unknown	0.94	[0.72-1.22]	0.645			
Geographical region <sup>#</sup> (Ref: Central/Western Europe)						
UK/Ireland	1.08	[0.85-1.37]	0.540	1.29	[0.93-1.80]	0.131
Thailand	0.97	[0.54-1.75]	0.921	1.77	[0.92-3.39]	0.085
Eastern Europe	0.88	[0.64-1.21]	0.434	1.13	[0.79-1.62]	0.505

HR, Hazard ratio; aHR, Hazard ratio adjusted for the other factors included the multivariable model; 95% CI, 95% confidence interval; \*Criteria for inclusion into the multivariable model: univariable model P<0.10, along with those identified *a priori*<sup>#</sup> (geographical region and initial cART regimen); **in bold**, P<0.05; **bPI**, boosted protease inhibitor – Lopinavir (LPV); **NRTI**, nucleoside reverse transcriptase inhibitors; **NNRTI**, non-nucleoside reverse transcriptase inhibitor – Nevirapine (NVP); **baseline VL** was defined as closest measurement within 6 months before and 1 week after cART initiation and was expressed in copies/ml (copies/ml); **baseline CD4% and count** were defined as closest measurements within 6 months before and 1 month after cART initiation. In all cases, the closest pre-cART measurement was taken, if available. **Note:** In univariable analysis, higher CD4 count also predicted faster virological suppression. However, due to multicollinearity with CD4%, CD4 count was not included in the final multivariable model. CD4% was included as it is a more stable measurement in children aged <5 years than CD4 count [21, 27].