

Supplemental Digital Content 1

Technical appendix

Multiple imputation

The multiple imputation was carried out using the *mi* suite of Stata 12 (Stata Corporation, College Station, Texas, USA) under the assumption that observations were missing at random. We imputed the logarithms of CD4 counts and CD4% simultaneously using predictive mean matching and chained equations with a burn in period of 10. Diagnostic plots showed that this burn in period was sufficient. To allow for interaction terms in the analyses, we stratified the multiple imputation by age, gender and income groups. We included the variables country, year, continent, income group and coverage group. We coded the variable year and all the other variables as categorical variables. To minimize variability, we created 50 imputed datasets.

Computation of smoothers

We used the R package *gamm4* in R 2.12 (R Core Team, Vienna, Austria)¹ to fit generalized additive mixed models. Basis representations were constructed using tensor products. Basis construction was done for year and age group as well as for year, age group and income group. Collinear terms in the latter basis were removed. We included a random intercept for every country. More complex random effects structures – such as a random slope – did not improve the model fit. We fitted the model separately for each imputed dataset and combined predicted values and standard errors in a point wise manner. To get estimates of the median CD4 counts and CD4%, we aggregated the data for each combination of year, gender, country and age group (the predictors) taking the median for each combination. We used the aggregated data in all the generalized additive model analyses. To account for the varying number of observations available for each combination of the predictors, we used weights in all the analyses where the aggregated data was used. The weights were set equal to the number of observations on which a particular value is based on normalized by the average number of observations in each combination of the predictors.

¹Wood, S. and Scheipl, F. (2013). *gamm4*: Generalized additive mixed models using mgcv and lme4. R package version 0.2-1. Available at: <http://CRAN.R-project.org/package=gamm4>

Figure S1: Flow chart of patients included and excluded from analyses.

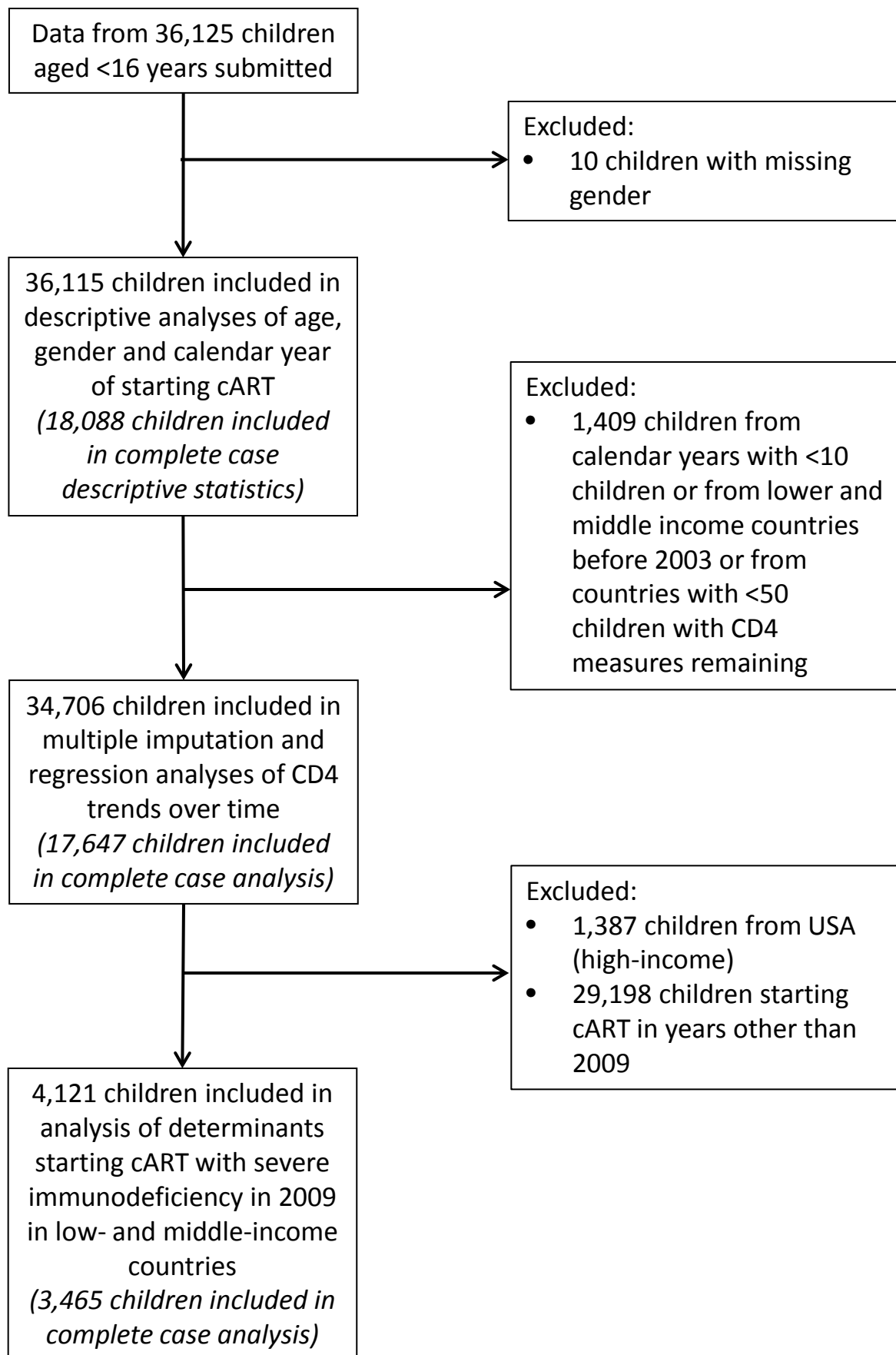


Table S1. Comparison of children starting cART with and without CD4 cell count or CD4%.
Analysis of 34,706 children included in multiple imputation and regression analyses.

Variable	CD4 cell count or percentage at start of cART available (n = 28,178)	Both CD4 cell count and percentage at start of cART missing (n = 6,528)
Median age (years)	5.3 (IQR 2.1 - 9.1)	4.4 (IQR 1.5 - 8.7)
Gender		
Female	13,962 (50%)	3,232 (50%)
Male	14,216 (50%)	3,296 (50%)
Clinical stage		
WHO Stage I/II or CDC Stage A/B	10,000 (35%)	1,456 (22%)
WHO Stage III/IV or CDC Stage C	13,173 (47%)	3,037 (47%)
Missing	5,005 (18%)	2,035 (31%)
Country income level		
Low	6,910 (25%)	2,332 (36%)
Lower middle	11,542 (41%)	2,483 (38%)
Upper middle	8,339 (30%)	1,713 (26%)
High	1,387 (5%)	0 (0%)
Median year of starting cART	2007 (IQR 2005 - 2008)	2007 (IQR 2005 - 2008)

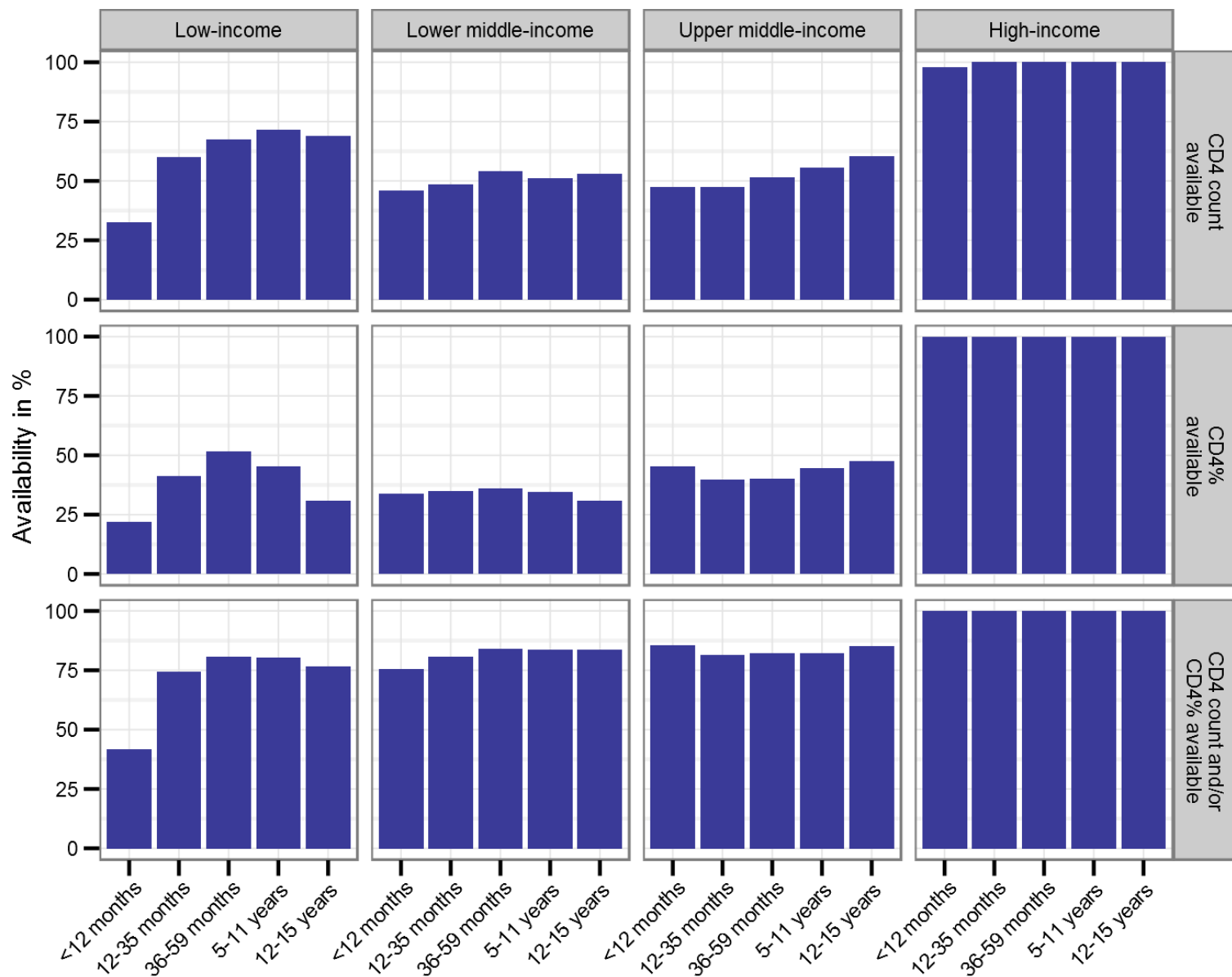


Figure S2. Availability of measurements of CD4 counts, CD4% or either by income groups and age groups.

Analysis based on 34,706 children.

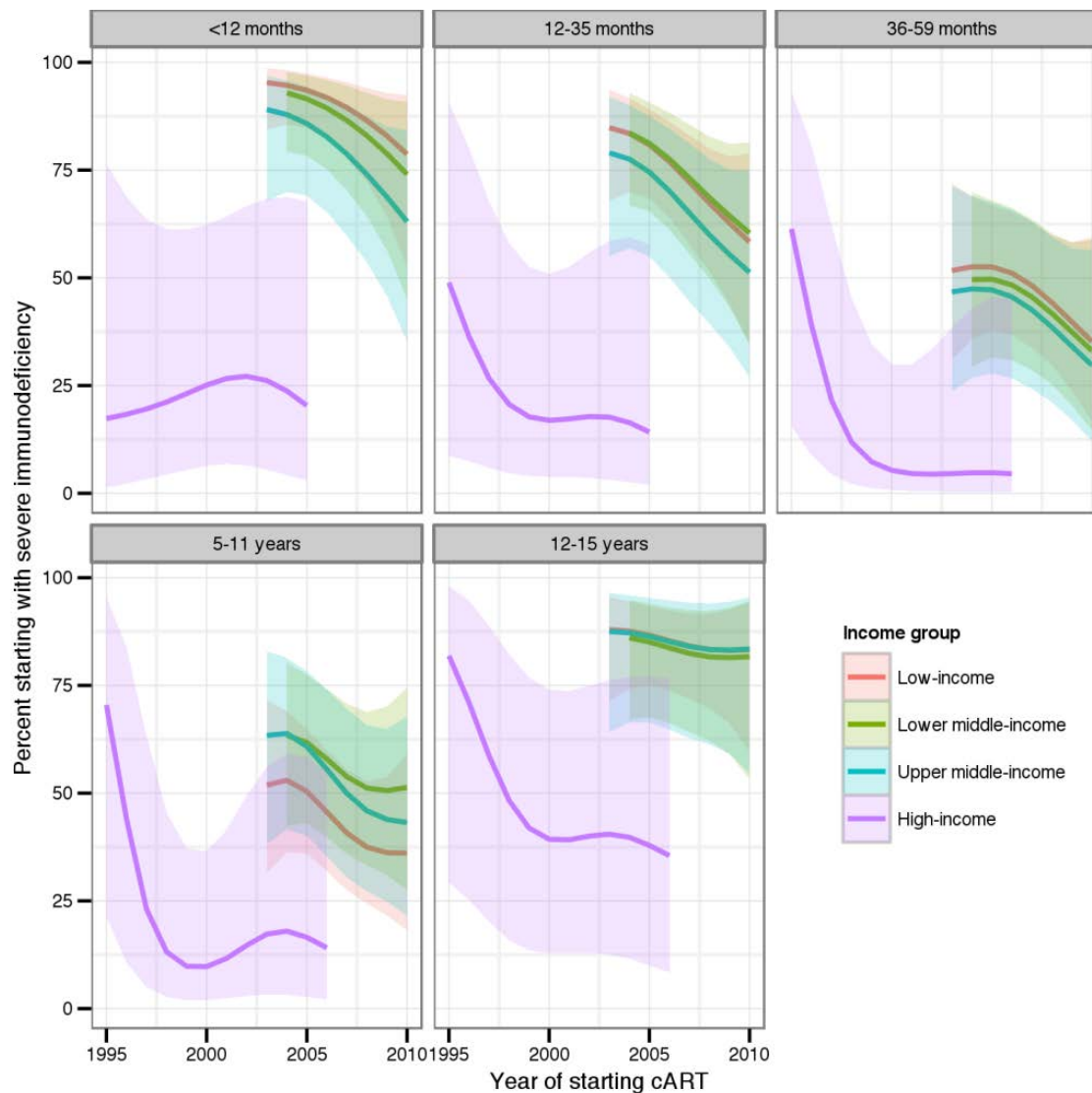


Figure S3. Severe immunodeficiency at start of combination antiretroviral therapy by age and country income group (complete case analysis).

Results from generalized additive mixed effects model based on 6,818 children aged below 5 years with CD4% and 10,829 children 5 years and older with CD4 count data. 95% confidence intervals are shown as shaded areas.

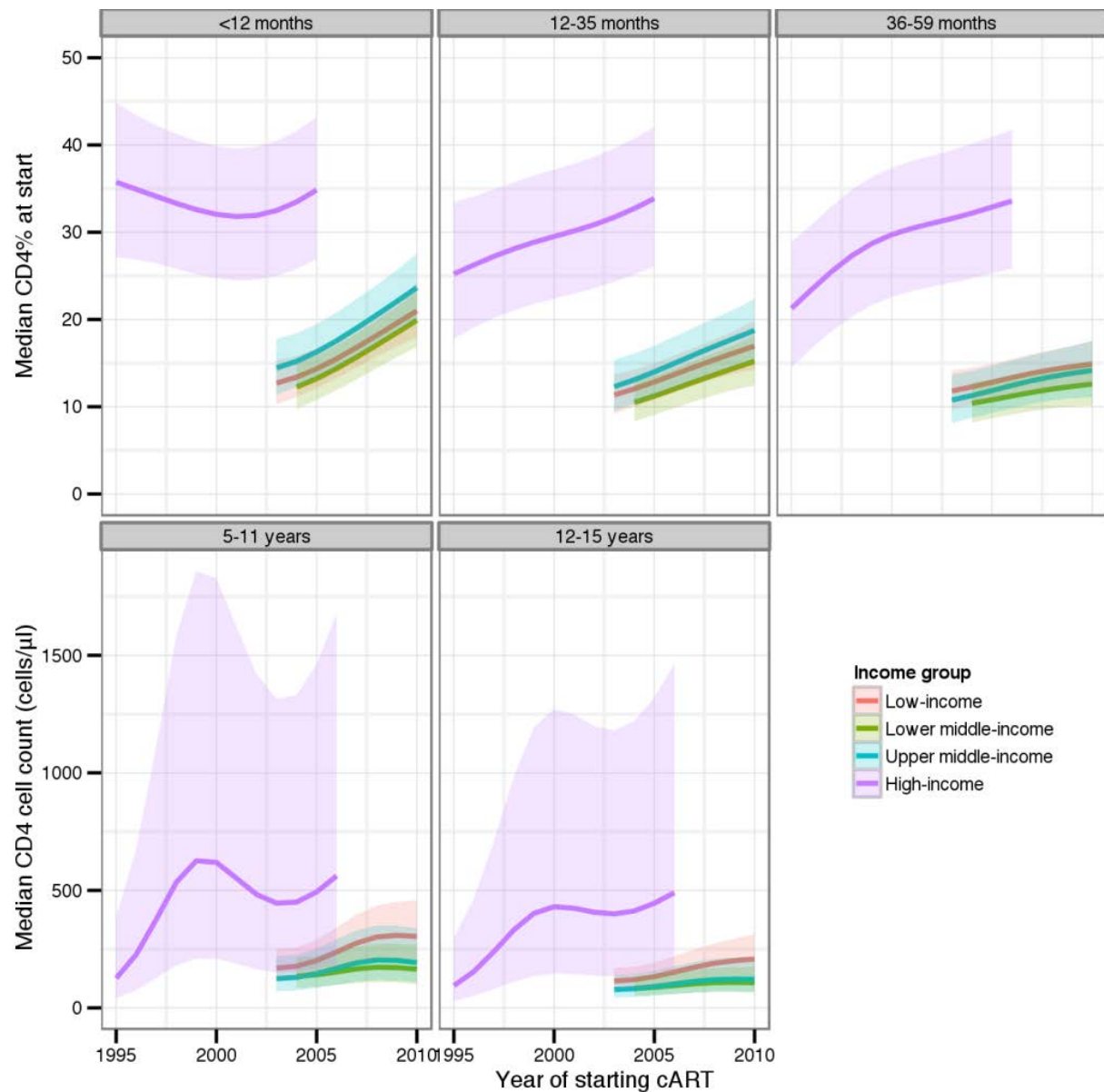


Figure S4. Median CD4 cell count in children aged 5 years or older and median CD4% in children below 5 years of age at start of combination antiretroviral therapy by age and country income group (complete case analysis).

Results from generalized additive mixed effects model based on 6,818 children aged below 5 years with CD4% and 10,829 children 5 years and older with CD4 count data. 95% confidence intervals are shown as shaded areas.

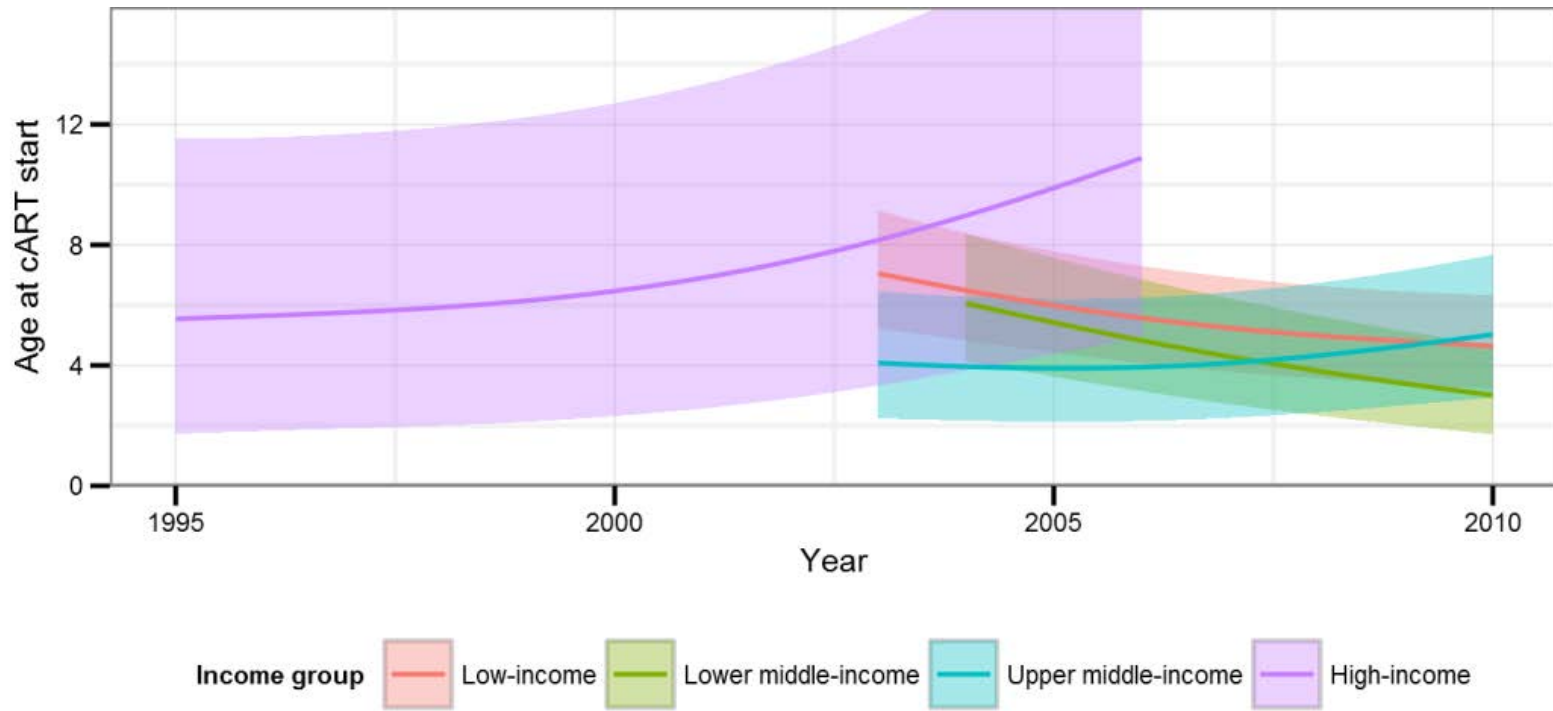


Figure S5. Median age in years at start of combination antiretroviral therapy by income group.

Analysis based on 34,706 children.

Table S2. Individual level and country level predictors for starting cART with severe immunodeficiency in 2009.

Results from generalized linear mixed model based on 3,465 patients from the countries Brazil, Cambodia, Indonesia, Malawi, Malaysia, Rwanda, South Africa, Thailand, Vietnam, Zambia and Zimbabwe. Complete case analysis.

Variable	Odds ratios	95% confidence intervals
Gender		
Female	1.00	
Male	1.11	(0.96 - 1.28)
Age group (years)		
< 1	1.00	
1 - <3	0.58	(0.45 - 0.74)
3 - <5	0.20	(0.15 - 0.26)
5 - <12	0.33	(0.26 - 0.42)
12 - <16	1.75	(1.29 - 2.38)
Country income level		
Low	1.00	
Lower middle	1.98	(0.97 - 4.03)
Upper middle	1.05	(0.54 - 2.07)
National cART coverage (%)*		
< 40	1.00	
40 - <60	1.69	(0.61 - 4.7)
60 - <80	1.37	(0.56 - 3.33)
>= 80	1.19	(0.44 - 3.19)

* Based on a separate analysis that included national cART coverage instead of country income level.