Effectiveness of Pediatric Antiretroviral Therapy in Resource-limited Settings: A Systematic Review and Meta-analysis

Andrea L. Ciaranello, MD, MPH1, Yuchiao Chang, PhD2, Andrea V. Margulis, MD, MS3, Adam Bernstein, MD4, Ingrid V. Bassett, MD, MPH1,2, Elena Losina, PhD2,5,7, and Rochelle P. Walensky, MD, MPH1,2,6,8

1Division of Infectious Disease, Massachusetts General Hospital, Boston, MA, USA
2Division of General Medicine, Massachusetts General Hospital, Boston, MA, USA
3Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
4Department of Nutrition, Harvard School of Public Health, Boston, MA, USA
5Department of Orthopedic Surgery, Brigham and Women’s Hospital, Boston, MA, USA
6Division of Infectious Disease, Brigham and Women’s Hospital, Boston, MA, USA
7Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA
8the Center for AIDS Research, Harvard Medical School, Boston, MA, USA

Abstract

Background—Responses to ART among HIV-infected children in resource-limited settings have recently been reported, but outcomes vary. We sought to derive pooled estimates of the 12-month rate of virologic suppression (HIV RNA<400 copies/ml) and gain in CD4 cell percentage (ΔCD4%) for children initiating ART in resource-limited settings.

Methods—We conducted a systematic review and meta-analysis of published reports of HIV RNA and CD4 outcomes for treatment-naïve children (0–17 years) using the Medline, EMBASE, and LILACS electronic databases and the Cochrane Clinical Trials Register. Pooled estimates of the reported proportion with RNA<400/ml and ΔCD4% after 12 months of ART were derived using patient-level estimates and fixed- and random-effects models. To approximate “intention-to-treat” analyses, in sensitivity analyses, children with missing 12-month data were assumed to have RNA>400/ml or ΔCD4% of zero.

Results—Using patient-level estimates after 12-months of ART, the pooled proportion with virologic suppression was 70% (95%CI: 67–73); the pooled ΔCD4% was 13.7% (95%CI: 11.8–15.7). Results from the fixed- and random-effects models were similar. In approximated “intention-to-treat” analyses, the pooled estimates fell to 53% with virologic suppression (95%CI: 50–55) and to a ΔCD4% of 8.5% (95%CI: 5.5–11.4).

Corresponding Author: Andrea L. Ciaranello, MD, MPH, Division of Infectious Disease, Massachusetts General Hospital, 50 Staniford Street, 9th Floor, Boston, Massachusetts 02114, Phone: (617) 724-3470, Fax: (617) 726-2691, aciaranello@partners.org.

This paper describes a systematic review and meta-analysis of treatment outcomes for treatment-naïve, HIV-infected children in resource-limited settings after 12 months of antiretroviral therapy. The pooled proportion with HIV RNA <400 copies/ml was 70%; pooled gain in CD4% was 13.7%.

This work has not been previously presented or published. An abstract describing this analysis will be presented at the 2009 International AIDS Society Meeting (Cape Town, South Africa, July 2009).

The authors have no conflicts of interest to report.
Conclusions—Pooled estimates of reported virologic and immunologic benefits after 12 months of ART among HIV-infected children in resource-limited settings are comparable to those observed among children in developed settings. Consistency in reporting on reasons for missing data will aid in the evaluation of ART outcomes in resource-limited settings.

Keywords
HIV; pediatric; antiretroviral therapy; resource-limited settings; meta-analysis

INTRODUCTION
Combination antiretroviral therapy (ART) is effective in preventing morbidity and mortality in HIV-infected children living in developed settings.\(^1\textendash}\(^5\) Ninety percent of the 2.1 million HIV-infected children worldwide live in resource-limited settings, where lack of access to ART for children remains a substantial problem.\(^6\) Recently, government- and donor-funded programs have expanded access to ART for HIV-infected children in resource-limited settings.\(^7\) Clinical, virologic, and immunologic responses to ART among HIV-infected children have now been described by programs in Africa, Asia, and the Caribbean, but reported outcomes vary.\(^8\textendash}\(^13\)

Single combined estimates of virologic and immunologic responses to ART for children in a wide range of resource-limited settings will serve two primary functions. First, in the absence of multiple randomized trials, pooled estimates will comprise useful comparators for outcomes from individual programs and new treatment strategies. Second, these estimates will allow comparison with published ART outcomes for children in developed countries. We therefore performed a systematic review and meta-analysis to aggregate virologic suppression rates and CD4 cell responses at 12 months after ART initiation among ART-naïve, HIV-infected children in resource-limited settings.

METHODS
Search strategy and selection criteria

Primary search—We performed a systematic search of peer-reviewed, published reports using the Medline, EMBASE, and LILACS (Latin American and Caribbean Health Sciences Literature) electronic databases and the Cochrane Controlled Trials Register. Observational studies and clinical trials published between 1/1/1997 and 10/15/2008 were included. Search terms referred to HIV infection, children, and resource-limited settings. Additional citations were selected for review from discussion with experts and review of bibliographies of published reports.

Abstract review—Publications were selected for review if study subjects were children (ages 0–17), living in a country with International Monetary Fund designation of emerging or developing economy,\(^14\) and treated with combination ART (defined as \(\geq\)3 drugs, including at least two nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or both), and if publications reported on changes in HIV RNA levels and CD4 cells.

Manuscript review—Publications were included in the final analysis if they reported the proportion of patients with HIV RNA level below assay limit of detection (virologic suppression) or the change in CD4 percentage (ΔCD4%) at 12 months after ART initiation, or if they reported sufficient information to perform these calculations.
Citations were limited to reports in which ≥95% of children were treatment-naive (having received no prior antiretroviral drugs, except for prevention of mother-to-child transmission (PMTCT)). Cohorts including both adults and children were included if pediatric outcomes were reported separately. When more than one publication reported outcomes from the same cohort, the most recent publication (or the largest study cohort, if two publications occurred within a 1-year period) was used. Citations were not included if they reported only on outcomes among critically ill children.

Titles and abstracts were independently reviewed by three authors (AB, AC, AM). If disagreements between authors were encountered, eligibility for inclusion was determined by consensus.

Data extraction and outcomes definitions

Data were extracted independently by two authors (pairs of AB, AC, AM), and discrepancies in data extraction were resolved by repeat manuscript review and consensus. Baseline data, collected at the time of ART initiation (or, if not available, at the time of enrollment), are outlined in Table 1.

Primary outcomes

**Virologic suppression:** Virologic suppression was defined as the proportion of children reported to have RNA <400 copies/ml after 12 months of ART. When virologic suppression thresholds were reported as RNA <50, <100, <250, or <300 copies/ml, we conservatively analyzed these results as <400 copies/ml.

**ΔCD4%:** When the mean or median ΔCD4% was reported for all children with 12-month data, this value was used in the meta-analysis. When ΔCD4% was not reported, or was reported for only a subset of children with baseline and 12-month values, the ΔCD4% was calculated by subtracting the mean (or median) CD4% at baseline from the mean (or median) 12-month value. Most of the reported interquartile ranges (IQRs) of CD4% showed symmetry around the reported medians, supporting the assumption that CD4% or ΔCD4% might be nearly normally distributed. Mean and median values were therefore analyzed together.

Secondary outcomes—Secondary 12-month outcomes included growth parameters (weight-for-age, height-for-age, or weight-for-height Z-scores); mortality and loss-to-follow up (LTFU) rates; and number of children with 12-month RNA and CD4 data. Secondary outcomes were not aggregated into pooled estimates, but were collected to describe the effect of ART on growth and mortality and to evaluate the impact of missing data.

Data analysis

**Methods for combining estimates**—Analyses were performed using SAS v9.1 (Cary, NC). Because all studies included in the analysis were cohort studies without control arms, we used a straight-forward pooling method of weighting each study by the number of children with 12-month RNA or CD4 data (patient-level analysis). For comparison, we also calculated pooled estimates using two traditional meta-analytic methodologies: 1) a fixed-effects model approach (weighted by the inverse of the variance from each study), and 2) a random-effects model approach (based on the DerSimonian-Laird method; weighted by the inverse of the sum of between- and within-study variances).

**Methods for examining heterogeneity, bias, and study quality**—Statistical heterogeneity was assessed using Q statistics with Chi-square tests and was summarized by the I² statistic, which reflects the proportion of total variation across studies that is due to heterogeneity rather than to chance. The presence of publication bias was assessed using Begg’s
and Egger’s tests.\textsuperscript{19} We also examined the relationship between several clinical and programmatic factors and the primary outcomes to better understand sources of anticipated statistical heterogeneity. Information regarding study quality and comparability was collected according to published guidelines.\textsuperscript{21,22}

**Sensitivity analyses -- effects of missing data**—The majority of reported viral suppression and $\Delta$CD4\% results were derived from “on-treatment” analyses; children who initiated ART, but for whom 12-month RNA and CD4\% data were missing, were excluded. To examine the effects of missing data on the patient-level estimates, we conducted two sensitivity analyses.

First, we excluded studies in which 12-month data were available for $<50\%$ of children initiating ART, in which data to calculate this proportion were not reported, or in which missing data could not be assessed because cohorts were limited to children with complete follow-up data. Second, we calculated a proxy for “intention-to-treat” outcomes for each study. For the viral suppression outcome, we used as the denominator all children who began ART >12 months prior to the date of analysis, or all children in the cohort when entry dates were not specified. The numerator remained the number of children known to have RNA<400/ml. This analysis assumed that children who died or lacked RNA data at 12 months in fact had RNA levels $>400/ml$. For the $\Delta$CD4\% outcome, we assumed that all patients who initiated ART but lacked 12-month follow-up data had zero CD4\% change.

**Supplementary information**—Additional details regarding the literature search, data extraction, and data analysis are available from the authors upon request.

**RESULTS**

**Literature search**

**Primary search and abstract review**—436 citations were retrieved from Medline, 168 from EMBASE, 16 from the Cochrane Clinical Trials registry, 52 from LILACS, and 10 from expert discussion and bibliography review. After duplicate citations were eliminated, 591 citations remained; 546 abstracts were excluded for the reasons outlined in Figure 1.

**Manuscript review**—Forty-five published abstracts were selected for full manuscript review. Thirty manuscripts were excluded (Figure 1), leaving 15 papers\textsuperscript{8--10,23--34} eligible for at least one of the primary analyses (Table 1).

**Characteristics of included cohorts**

Table 1 describes characteristics of the included cohorts, from 15 countries in Asia, Africa and the Caribbean. Numbers of children initiating ART in each program ranged widely (16--2,938; total: 5,928), as did age at ART initiation (mean/median, 0.1--10.0 years; range, 0.0--15.2 years). Overall, children initiated ART with low immune function: mean/median baseline CD4\% ranged from 3.8--30.0\% (mean 8.1\%). First-line ART was NNRTI-based in 81\% of children for whom regimens were described. All but one of the studies were observational. The single trial randomized infants to initiate ART before three months of age or to defer ART until WHO 2006 criteria for ART initiation were met.\textsuperscript{23} To remain consistent with other included studies, reflecting ART initiation in accordance with pre-2008 guidelines,\textsuperscript{35,36} we included only data from the deferred ART arm of this study in the pooled analyses. Eleven studies\textsuperscript{8,10,24--31,34} reported baseline growth parameters. In five\textsuperscript{25--27,29,30} of these studies, mean or median values indicated at least moderate underweight (weight-for-age), stunting (height-for-age), or wasting (weight-for-height), defined as Z-scores $<-2$. Only three manuscripts\textsuperscript{8,23,32} specifically reported on prior receipt of antiretroviral drugs for PMTCT.
Primary outcomes 12 months after ART initiation

Virologic suppression—Nine papers reported proportion of children with RNA <400 copies/ml at 12 months,\(^9,10,23–26,32–34\) representing 1,457 children initiating ART (Table 2, Section I). Twelve-month RNA data were available for 1,097 children (75%). The patient-level pooled estimate of the proportion with virologic suppression was 70% (95%CI: 67–73) (Table 2, Section IIA, and Figure 2). Estimates from the fixed-effects (72%, 95%CI: 70–75) and random-effects (70%, 95%CI: 62–79) models were similar.

\(\Delta CD4\)%—Twelve studies reported on 12-month CD4% outcomes,\(^8,9,23–31,33\) representing 5,329 children initiating ART (Table 3, Section I). Of these, 2,676 were reported to be eligible for 12-month CD4% data, and 12-month CD4% data were available for 1,839 children (35% of total, 69% of “eligible”). The patient-level pooled estimate of \(\Delta CD4\)% at 12 months was an absolute increase of 13.7% (95%CI: 11.8–15.7, Table 3, Section IIA and Figure 3), which was similar to the estimate generated by both the fixed- and random-effects models (14.3%, 95% CI: 11.3–17.3).

Heterogeneity and bias—There was no statistically significant heterogeneity in either the RNA \((p=0.26)\) or \(\Delta CD4\)% outcome \((p=0.99)\). The percentage of variation due to heterogeneity \((I^2)\) was 20.4% for the RNA outcome and 0% for the \(\Delta CD4\)% outcome. There was no evidence of publication bias for the RNA (Begg’s test: \(p=0.40\), Egger’s test: \(p=0.53\)) or \(\Delta CD4\)% outcome (Begg’s test: \(p=0.78\), Egger’s test: \(p=0.12\)).

Graphical visualization of scatter plots did not reveal any association between the primary outcomes and geographic region, study size, year of program initiation, type of ART (PI- vs. NNRTI-based), or stage of disease or age at ART initiation.

Sensitivity analyses -- effects of missing data (Table 2 and Table 3, Sections IIB) —Exclusion of studies with high proportion of missing data. In three studies, >50% of children initiating ART lacked 12-month data;\(^8,10,31\) in two studies, data to calculate the proportion of children with missing data were not reported;\(^29,34\) and in two studies, cohorts were limited to children with complete data\(^28,33\) (Table 4). When these studies were excluded, the pooled estimate of viral suppression was 72% (95%CI: 69–75), and the pooled estimate of \(\Delta CD4\)% was 14.0% (95%CI: 8.9–19.1).

Proxy for “intention-to-treat” analyses. When we assumed that children without 12-month RNA data had RNA levels >400/ml, the pooled estimate for viral suppression was 53% (95% CI: 50–55). When we assumed that children without 12-month CD4 data experienced a \(\Delta CD4\)% of zero, the pooled estimate for \(\Delta CD4\)% was 8.5% (95%CI: 5.5–11.4).

Secondary outcomes (Table 4)

Reported mortality after 12 months of ART ranged from 0.0–18.8%;\(^8,9,23–26,29–32,34\) Gains in weight-for-age Z-score ranged from 0.3–1.4;\(^25–27,29–31,34\) gains in height-for-age Z-score ranged from 0.2–1.0;\(^25,26,29,31\) and gains in weight-for-height Z-score ranged from 0.1–1.1.\(^24,26,28\) Loss to follow-up (LTFU) was defined in only three studies: children \(\geq 30\) days\(^27\) >2 months, or <3 months\(^24\) late for appointments and not known to have died or transferred care. Rates of LTFU at 12 months after ART initiation were reported in six studies (range, 0.0–7.1%);\(^9,23,26,31,32,34\) with others reporting LTFU at time points other than 12 months,\(^8,10,24,27,29\) not reporting LTFU,\(^33\) or limiting cohorts to children with complete follow-up data.\(^28,30,31\)
DISCUSSION

We performed a systematic review and meta-analysis of 12-month virologic and immunologic outcomes for treatment-naïve, HIV-infected children initiating antiretroviral therapy in resource limited settings. Data from nine studies, representing 1,097 children with complete follow-up data, contributed to a pooled estimate of 70% virologic suppression (RNA<400/ml); data from 12 studies and 1,839 children with complete data contributed to a pooled estimate of 13.7% absolute ΔCD4%. These findings are similar to reported ART outcomes for treatment-naïve children in the US and Europe, which include 12-month virologic suppression rates (<400/ml) of 53–84%2,5,11,37–43 and median ΔCD4% of 10–13%.5,38–40 As has been reported for adults,44 our study highlights that comparable outcomes in children are observed in resource-limited and developed settings, despite advanced stages of disease at ART initiation, predominantly NNRTI-based ART, and substantial barriers to ART delivery in resource-limited settings. In addition, clinically significant improvements in growth parameters are noted after 12 months on ART.45 However, missing data remain an important concern, and a proxy for an “intention-to-treat” analysis generates much lower estimates: 53% virologic suppression and 8.5% ΔCD4% at 12 months.

Two recent systematic reviews without meta-analysis summarized responses to pediatric ART in Africa11 and in a variety of resource-limited settings.12 A pooled patient-level analysis from 16 African sites also provided mortality and LTFU estimates for children on ART.13 The current study reinforces the findings of these analyses, including similar ranges of 12-month viral suppression rates11, ΔCD4%,11 and mortality;12 advanced stage of disease and large proportion of children aged >5 years at ART initiation,11–13 wide variation in study size,11 and notable inconsistency in data reporting.11

Our analyses suggest that the pooled estimates were not significantly affected by statistical heterogeneity. However, we anticipated that variation in clinical and programmatic factors (clinical heterogeneity) would contribute to differences in the primary outcomes. Although we found no association between RNA or ΔCD4% outcomes and many such factors, including age at ART initiation and PI- vs. NNRTI-based ART, our ability to formally assess such associations was limited due to the relatively small number of included studies. Additionally, incomplete data precluded examination of the effects of receipt of medications for PMTCT, nutritional status, resource-related factors (pharmacy stockouts; free provision of medications), and prevalence or incidence of tuberculosis, malaria, anemia, and diarrheal disease.

This analysis has several limitations. First, because conference proceedings may be of more variable quality than published reports and did not change study results when added to published reports in a previous review,11 we included only published reports. This may have omitted very recent reports of ART outcomes. Second, we included only 12-month treatment outcomes, because 12-month data were provided in the greatest number of reports. Third, programs made use of HIV RNA assays with varying limits of detection. We conservatively designated all children with RNA <50, <250, or <300/ml as having RNA levels <400/ml, thus underestimating true rates of suppression to <400/ml. Finally, consistent with most reports from both developed and resource-limited settings,9,46,47 the included studies did not report clinical correlations between ΔCD4% or RNA suppression and risks of AIDS-related morbidity. However, ΔCD4% and RNA suppression are likely to serve as reliable surrogate outcomes for these events.48 Analyses using individual patient data from a large pediatric cohort are anticipated, and these will avoid many of the limitations of meta-analysis.13,49

Our study also has several notable strengths. First, we expand upon the previous literature by reviewing studies from resource-limited settings outside Africa and by analyzing 10 new reports not included in the prior published review.11 Next, in addition to narrative review, we
use recommended techniques for meta-analyses of observational studies\textsuperscript{21} to provide, to our knowledge, the first pooled estimates of the virologic suppression rate and $\Delta$CD4\% for children on ART in resource-limited settings. Finally, we conduct two sensitivity analyses demonstrating the impact of missing data.

Data were incomplete for many children who initiated ART. Of 5,928 children initiating ART, 81\% lacked 12-month RNA data and 69\% lacked 12-month CD4\% data. Children who lack follow-up data may be more likely to have died than those who were followed, as has been observed in adults,\textsuperscript{50,51} and thus may be assumed to have inferior virologic and immunologic outcomes. If true, this would lead our pooled estimates to overestimate the benefit of ART. However, lack of CD4\% or RNA data may not reflect true loss to follow-up to programs. Instead, ART initiation may have occurred $\leq$12 months before data reporting, absolute CD4 cell count may have been obtained in preference to CD4\% for children $<$5 years old, or laboratory testing may have been unavailable on the occasions on which children were seen (in the single study reporting this outcome, 25\% of children still in care at 12 months lacked CD4\% data\textsuperscript{27}).

In sensitivity analyses, virologic suppression rates and $\Delta$CD4\% did not change substantially when we excluded studies with a high proportion of missing data. However, when we assumed that all children who died or lacked 12-month data had HIV RNA$>$400/ml, the pooled estimate of viral suppression fell to 53\%. This estimate likely comprises the lower bound of expected 12-month viral suppression rates. Similarly, when we assumed that children with missing CD4\% data had true $\Delta$CD4\% of zero, the pooled estimate of $\Delta$CD4\% fell to 8.5\%. Because children who die or are lost to follow-up may have a decline, rather than zero change, in CD4\%, it is possible that the true $\Delta$CD4\% may be even lower than 8.5\%. However, due to some expected decline in CD4\% with increasing age,\textsuperscript{16,35} small gains in CD4\% may represent true improvements in immune function.

Definition and reporting of loss to follow-up (LTFU) and clear descriptions of reasons for missing data are therefore important considerations in interpreting reports of pediatric ART effectiveness and the success of ART programs. Given the high mortality in the first 3–6 months after ART initiation observed in children as well as adults,\textsuperscript{9,11,27,52} programmatic efforts to retain children in care will be crucial to improving clinical outcomes during the first year on ART.

**CONCLUSIONS**

This systematic review and meta-analysis demonstrates that the pooled 12-month HIV RNA suppression rate (70\%) and $\Delta$CD4\% (13.7\%) for children initiating ART in resource-limited settings are comparable to those seen in developed countries. This work also highlights important inconsistencies in the reporting of data which may guide the interpretation of clinical and programmatic outcomes, such as definitions of LTFU and descriptions of patient disposition. As pediatric ART programs are expanded worldwide, clear and comprehensive reporting of these data will be crucial to interpreting and comparing the effectiveness of ART in resource-limited settings.

**Acknowledgments**

The authors gratefully acknowledge Paul Bain, Wendy Brown, and Carol Mita at the Countway Medical Library of Harvard Medical School for their assistance with electronic database searches and document retrieval; and Jennifer Chu for assistance with document procurement and manuscript preparation.

Funding for this work was provided by the National Institute of Allergy and Infectious Disease (T32 AI07433 (Ciaranello); R01 AI058736 and R37 AI420061 (Ciaranello, Losina, Walensky); K23 AI068458 (Bassett); and P30 AI 60354 (Ciaranello, Chang, Losina)); the National Institute of Diabetes and Digestive and Kidney Diseases (T32 DK07703, Bernstein); the Harvard School of Public Health Pharmacoepidemiology Program Training Fund

*Clin Infect Dis. Author manuscript; available in PMC 2010 December 15.*
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Figure 1. Selection of publications for a systematic review and meta-analysis of pediatric ART effectiveness
Flowchart describing the results of the literature search, including the source of each publication reviewed and reasons for exclusion of studies from the final analysis. After the initial search, 546 abstracts were excluded because: they reported only on ART-experienced children (1), critically ill children (1), animals (1), or only adults (58); they provided only cross-sectional data (2) or case reports (3); they did not report on HIV (7); they reported on non-resource-limited settings (12); they described diagnostic tests (20) or cohorts not treated with ART (22); the format was commentary or review, rather than original research (119); they primarily addressed prevention of mother-to-child transmission (146); or they did not report outcomes related to viral load or CD4 cells (154). Abbreviations: ART: combination antiretroviral therapy, RLS: resource-limited setting, MTCT: mother-to-child transmission of HIV.

Primary search results: 682 publications

| 436 from Medline | 168 from EMBASE | 16 from Cochrane | 52 from LILACS | 10 from bibliography review and expert discussion |
|------------------|-----------------|------------------|----------------|-----------------------------------------------|

546 publications excluded:
1 Not ART-naive
1 Critically ill
1 Animals
2 Cross-sectional
3 Case report
7 Not HIV
12 Not RLS
20 Diagnostic test
22 Not ART
58 Adults
119 Comment/review
146 MTCT
154 No CD4/RNA

591 abstracts reviewed

45 selected for detailed review

30 publications excluded:
1 Not ART
1 May 2007 subset of Oct 2006 included cohort
3 Adults
5 No CD4/RNA
5 Not ART-naive
7 Previous reports from included cohorts
8 No 12-month CD4/RNA

Final analysis: 15 publications (Table 1)

9 publications eligible for 12-month viral suppression analysis
12 publications eligible for 12-month CD4% analysis

Clin Infect Dis. Author manuscript; available in PMC 2010 December 15.
Figure 2. Forest plot of viral suppression rates (proportion of children with HIV RNA <400 copies/ml) 12 months after ART initiation for treatment-naive children in resource-limited settings.

Studies included in the pooled analysis of the proportion of children with HIV RNA <400 copies/ml 12 months after initiating ART are shown on the left of the figure. Reported proportions of children with RNA <400 copies/ml are depicted as circles, with the size of each circle proportional to the number of children included in each study; reported estimates and confidence intervals are shown to the right. The dashed vertical line indicates the value of the patient-level pooled estimate (70%). The last column indicates the percentage of total included children contributed by each included study.
Figure 3. Forest plot of absolute gain in CD4% 12 months after ART initiation for treatment-naïve children in resource-limited settings

Studies included in the pooled analysis of the absolute gain in CD4% 12 months after initiating ART are shown on the left of the figure. Reported absolute gains in CD4% are depicted as circles, with the size of each circle proportional to the number of children included in each study; reported estimates and confidence intervals are shown to the right. The dashed vertical line indicates the value of the patient-level pooled estimate (13.7%). The last column indicates the percentage of total included children contributed by each included study. CD4%, defined as the percent of total lymphocytes that are CD4+ cells, is a more useful representation of immune function in children <5 years of age than absolute CD4 cell count (total number of CD4 cells/µL of serum), because CD4% maintains a more constant value during normal immune system maturation. As a result, CD4% is often reported for children of any age, while absolute CD4 is usually reported only for adults and children >5 years old.

| Study          | Year | Location  | CD4 % Change (95% CI) | % Weight |
|----------------|------|-----------|-----------------------|----------|
| Chearskul      | 2005 | Thailand  | 15.2 (-9.4 - 30.8)    | 3.6      |
| Eley           | 2006 | South Africa | 12 (-4.1 - 28.3)    | 14.2     |
| Koekkoek       | 2006 | Thailand  | 15 (-7.4 - 22.8)     | 0.9      |
| O’Brien <5yo   | 2006 | Mixed     | 11.6 (1.1 - 22.1)    | 1.5      |
| Rouet          | 2006 | Cote d’Ivoire | 11 (-1.4 - 23.4)   | 3.7      |
| Ble            | 2007 | Tanzania  | 15 (10.3 - 19.7)     | 0.9      |
| Bolton-Moore   | 2007 | Zambia    | 14.1 (-2.1 - 30.3)   | 46.9     |
| Janssens       | 2007 | Cambodia  | 17 (-7.1 - 41.1)     | 10.5     |
| Myung          | 2007 | Cambodia  | 14.9 (2.4 - 27.4)    | 3.7      |
| Puthanakit     | 2007 | Thailand  | 12 (-0.3 - 24.3)     | 9.8      |
| Kumaraswamy    | 2008 | India     | 11 (-9.5 - 31.5)     | 3.6      |
| Prendergast    | 2008 | South Africa | 17 (6.6 - 27.4)   | 0.7      |
| POOLED         |      |           | 14.3 (11.3 - 17.3)   |          |
| Studies included in a meta-analysis of the effectiveness of pediatric ART in resource-limited settings |
|---|
| **Baseline characteristics of study population** |
| **Studies** | **Author (Publication Year)** | **Program Dates** | **Location** | **Number initiating ART** | **Age (D)** | **Female (%)** | **HIV RNA (log_{10} copies/ml)** | **CD4 cell percentage (D)** | **CD4 cells/µL (absolute D)** | **Baseline growth parameters (P)** | **PMTCT (Local PMTCT coverage) (R)** | **ART characteristics** |
| | | | | | | | | | | | | | | |
| Ciaranello et al. (2005) | | 9/96–3/04 | Thailand | 66 | 5.4 (0.3–14.6)* | 38 (0.1–35.0) (L) | No VL | 12 (2.016) (L) | No VL | 11.7 (7.0–17.3) | NR | NR |
| Chearskul (2005) | | 8/02–12/04 | South Africa | 409 | 1.9 (0.7–4.6) | 5.4 (5.2–6.1) (J) | No VL | 5.0 (1.0–15.0)* | No VL | 5.0 (5.0–6.0) | NR | NR |
| Koekkoek (2006) | | | | | | | | | | | | | |
| O’Brien (2006) | | 6/01–3/05 | 8 countries (MSF, A) | 1,184 | 1.5–5y: 9.9 (6.0–13.2) | NR | NR | NR | NR | NR | NR |
| Rouet (2006) | | 10/00–9/04 | Côte d’Ivoire | 78 | 30 (12–90) | NR | NR | NR | NR | NR | NR |
| Ble (2007) | | 2002–2005 | Tanzania (B) | 59 | 30 (12–90) | NR | NR | NR | NR | NR | NR |
| Bolton-Moore (2007) | | 5/04–6/07 | Zambia | 2,938 | 6.8 (3.0–10.4) | NR | NR | NR | NR | NR | NR |
| George (2007) | | 5/03–4/06 | Haiti | 1,147 | 6.3 (4.0–11.0) | NR | NR | NR | NR | NR | NR |
| Janssens (2007) | | 6/03–3/06 | Cambodia | 212 | 6.0 (4.0–7.9) | NR | NR | NR | NR | NR | NR |
| Kamya (2007) | | 4/04–6/05 | Uganda | 250 | 9.2 (4.5) | NR | NR | NR | NR | NR | NR |
| Myung (2007) | | 8/02–10/04 | Cambodia (C) | 117 | 5.5 (2.5) (10.0–10.0)* | 7.6 (0.4–14.8)* | NR | No VL | 6.8 (6.8) | 5.0 (0.5) | 5.2 (4.9) | NR | NR |
| Puthanakit (2007) | | 8/02–3/05 | Thailand | 192 | 5.5 (2.5) (10.0–10.0)* | 7.6 (0.4–14.8)* | NR | No VL | 6.8 (6.8) | 5.0 (0.5) | 5.2 (4.9) | NR | NR |
| Zhang (2007) | | 7/05–8/06 | China | 51 | 10.0 (7.0–13.0) | NR | NR | NR | NR | NR | NR |
| Kumarasamy (2008) | | 2/96–3/08 | India (H) | 67 | 6.3 (4.2) | NR | NR | NR | NR | NR | NR |
### Baseline Characteristics of Study Population

| Studies Author (Publication Year) | Program Dates | Location | Number Initiating ART | Age (D) | Female (%) | HIV RNA (log10 copies/ml) | CD4 cell percentage (D) | CD4 cells/µL (absolute) (D) | Baseline Growth Parameters (P) | PMTCT (Local PMTCT coverage) (R) | First-line ART regimen |
|----------------------------------|---------------|----------|-----------------------|---------|------------|--------------------------|------------------------|---------------------------|-----------------------------|-----------------------------|---------------------|
| Prendergast (2008)               | 7/03- 9/05    | South Africa | 60; 53 (I)            | 0.1     | (0.0-1.1)  | 47                       | 6.0 (5.3-6.6)          | 30.0 (17-43)               | NR                          | NR                          | ZDV/3TC/NVP/NVP (94%)  |
|                                  |               |          |                       |         |            |                          |                        |                           |                             |                             | ZDV/3TC/NVP (6%)       |
|                                  |               |          | Immediate ART arm (I)  | 40      | 0.1        | 50                       | 5.8 (5.3-6.5)          | 36.0 (28-45)              | NR                          | NR                          | All received sdNVP     |
|                                  |               |          | Deferred ART arm (I)   | 20; 13  | 0.4        | 40                       | 6.5 (6.0-6.6)          | 15.0 (12-18)             | NR                          | NR                          | All received sdNVP     |

Abbreviations: ART: antiretroviral therapy, NR: not reported, MSF: Medecins sans Frontieres, WHO: World Health Organization, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, NVP: nevirapine, EFV: efavirenz, NFV: nelfinavir, ZDV: zidovudine, d4T: stavudine, ABC: abacavir, 3TC: lamivudine, WAZ: weight-for-age Z-score, WHZ: weight-for-height Z-score, HAZ: height-for-age Z-score, No VL: no HIV RNA (viral load) assay, IQR: interquartile range, SD: standard deviation, y: year; PMTCT: prevention of mother-to-child transmission of HIV; sdNVP: single-dose nevirapine.

Notes:
A: Medecins sans Frontieres: Cambodia, Kenya, Malawi, Mozambique, Thailand, Uganda, Burkina Faso, and Zimbabwe.
B: Institutionalized orphans.
C: Institutionalized and community-living orphans receiving directly-observed ART.
D: Baseline values (age, HIV RNA, CD4 cell count, and CD4 percentage) are reported as median with IQR or range (range marked with *), or as mean with SD.
E: Cohort defined as children with 12-month follow-up data, not all ART initiators.
F: 1147 children started ART more than 12 months prior to analysis date (and therefore were eligible to have 12-month data).
G: 117 children were started on ART; 22 died in the first 6 months. Baseline data are only for the 95 children who survived to 6 months: 12-month data are for 68 children with follow up data at 12 months.
H: Data are reported only on children with complete 18-month follow-up, not all ART initiators.
I: A total of 63 infants were randomized (43 to immediate, 20 to deferred); 3 infants from the immediate ART arm were lost to the study before initiating ART, and were not included in the cohort reported here. Of 20 randomized to the deferred arm, 3 infants were lost to the study before initiating ART, and 4 did not start ART. To be consistent with other cohorts reporting only on ART initiators, these 7 were not included in the cohort reported here (leaving 13 in the deferred arm and 53 total ART initiators).
J: Baseline data are for the 409 children initiating ART, unless marked with (K), indicating baseline values for the 264 children with 12-month follow-up data.
K: RNA assay used only for infant diagnosis, not for treatment monitoring.
M: Not reported if median or mean, or if IQR or range.
N: Baseline values are mean (95% CI); they are also reported as median (IQR) for entire cohort (all ages): absolute CD4 count 300/µL (138–551); CD4 percentage 11.8% (7.2–17.4).
P: WAZ, WHZ, and HAZ are reported as median values, unless noted with * as mean values.
Q: Baseline and 12-month growth parameters are reported in an earlier publication from this cohort.
R: PMTCT data are provided for comparison, as receipt of antiretroviral drugs for PMTCT may impact later ART outcomes. Data not in parentheses are rates of receipt of any antiretroviral drug for PMTCT, as reported in each study. Data in parentheses are World Health Organization estimates of receipt of any antiretroviral drug for PMTCT among antenatal clinic attendees, based on the each country and the fiscal year closest to the program dates. WHO data on type of antiretroviral drug used for PMTCT are not available; however, in most cases where rates of PMTCT coverage are low, the regimen is likely to be single-dose.
Meta-analysis of viral suppression rate (proportion of children with HIV RNA <400 copies/ml) 12 months after ART initiation for treatment-naïve children in resource-limited settings.

### I. Included Studies:

| Author           | Number initiating ART | RNA assay limit of detection (copies/ml) | Proportion (%) with HIV RNA < limit of detection | Number of patients with HIV RNA < limit of detection | Number of patients with RNA data at 12 months (E) |
|------------------|-----------------------|------------------------------------------|--------------------------------------------------|------------------------------------------------------|--------------------------------------------------|
| Eley             | 409                   | <400                                     | 70                                               | 184                                                  | 264                                              |
| Koekkoek         | 16                    | <50                                      | 83                                               | 5                                                    | 6                                                |
| Rouet            | 78                    | <250/<300                                | 49                                               | 33                                                   | 67                                               |
| George           | 236                   | <50                                      | 56                                               | 56                                                   | 100                                              |
| Janssens         | 212                   | <400                                     | 81                                               | 156                                                  | 193                                              |
| Kamya            | 250                   | <400                                     | 74 (B); 69 (C)                                   | 164                                                  | 222                                              |
| Puthanakit       | 192                   | <50                                      | 68                                               | 130                                                  | 181                                              |
| Zhang            | 51                    | <400                                     | 55 (D)                                           | NR                                                   | NR                                               |
| Prendergast (A)  | 53                    | <400 and <50                             | 100 (<400); 94 (<50)                             | 49 (<400); 46 (<50)                                   | 49                                               |
| Immediate ART arm (A) | 40                  | <400 and <50                             | 100 (<400); 94 (<50)                             | 36 (<400); 34 (<50)                                   | 36                                               |
| Deferred ART arm (A) | 13                   | <400 and <50                             | 100 (<400); 92 (<50)                             | 13 (<400); 12 (<50)                                   | 13                                               |

### II. Pooled estimates:

| Pooled estimate of proportion (%) <400/ml (95% CI) |
|--------------------------------------------------|
| A. Primary analyses:                             |
| 1. Patient-level analysis                        | 70 (67–73) |
| 2. Fixed-effects model (inverse variance)        | 72 (70–75) |
| 3. Random-effects model (Dersimonian-Laird)      | 70 (62–79) |
| B. Sensitivity Analyses (patient-level estimates):|
| 1. Exclude studies with >50% missing data, or    | 72 (69–75) |
| missing data not reported (Koekkoek, George,     |
| Zhang)                                          |
| 2. Missing 12-month data: assume RNA >400 copies/ml | 53 (50–55) |

Abbreviations: NR: not reported.

Notes:
- A: By design, compared to children in the “deferred ART” arm and to children in the other included studies, children in the “immediate ART” arm of the Prendergast trial were younger and had less advanced HIV infection at ART initiation (Table 1). The immediate ART arm of this trial was therefore excluded from pooled analyses. A total of 63 infants were randomized (43 to immediate, 20 to deferred). Of 20 randomized to the deferred arm, 3 were lost to the study before initiating ART, and 4 did not start ART. To be consistent with other cohorts reporting only on ART initiators, these 7 were not included in the cohort reported here (leaving 13 in the deferred arm).
- B: Proportion with virologic suppression, including only patient for whom RNA data were available.
- C: Proportion with virologic suppression if patients lost to follow-up or deceased were assumed to have had detectable RNA.
- D: 55% reported only in abstract and graphically in Figure 2.
- E: None of the 1,457 ART initiators included in the pooled RNA analysis were reported to have <12 months of follow-up time and therefore to be ineligible for 12-month data.
### Table 3
Meta-analysis of change in CD4% 12 months after ART initiation for treatment-naïve children in resource-limited settings.

| Author                  | Number initiating ART | Baseline CD4% median (IQR or range*) or mean (SD) | 12-month CD4% median (IQR or range*) or mean (SD) | Number of patients with CD4 data at 12 months (L) |
|-------------------------|-----------------------|---------------------------------------------------|---------------------------------------------------|--------------------------------------------------|
| Chearskul               | 66                    | 3.8 (0.1–35.0) (H)                                 | Gain: 15.2 (1.8–29.0)*                             | NR                                               |
| Eley                    | 409 (B)               | 11.7 (7.0–17.3)                                    | 24.0 (18.7–30.0)                                  | 261                                              |
| Koekkoek                | 16 (C)                | 5.0 (1.0–15.0)*                                    | 20.0 (IQR NR)                                     | 16                                               |
| O’Brien                 | 1.5–5y: 322           | 1.5–5y: 16.7 (7.0–17.3)                            | 1.5–5y: 21.5 (19.4–27.8)                          | >5y: 54                                          |
| Rouet                   | 78                    | 7.5 (2.1–11.1)                                     | 18.5 (IQR NR)                                     | 68                                               |
| Ble                     | 59                    | 10.3 (SD NR)                                       | Gain: 15.0 (SD NR) absolute: 45                   | percentage: 16                                   |
| Bolton-Moore            | 2,938                 | All ages: 12.9                                     | All ages: 27.0                                    | 862                                              |
| Janssens                | 1,147 (E)             | (12.5–13.3) (I)                                    | (26.3–27.6) (I)                                   | 193                                              |
| Myung                   | 117 (F)               | 6.8 (6.8)                                          | 21.7 (7.5)                                        | 68                                               |
| Puthanakit              | 192                   | 5.2 (4.9)                                          | 17.2 (7.5)                                        | 181                                              |
| Kumarasamy              | 67 (G)                | 12.0 (7.0–18.0)                                    | 12.0 (15.0–31.0)                                  | 67                                               |
| Prendergast (A)         | 53                    | 30.0 (17.0–43.0)                                   | (K)                                              | 49                                               |
| Immediate ART arm (A)   | 40                    | 36.0 (28.0–45.0)                                   | 33.0                                              | 36                                               |
| Deferred ART arm (A)    | 13                    | 15.0 (12.0–18.0)                                   | 32.0                                              | 13                                               |

#### II. Pooled estimates

| Gain in CD4% at 12 months (95% CI) |
|------------------------------------|
| A. Primary analyses:               |
| 1. Patient-level analysis          | 13.7 (11.8–15.7)       |
| 2. Fixed-effects model (inverse variance) | 14.3 (11.3–17.3)       |
| 3. Random-effects model (Dersimonian-Laird) | 14.3 (11.3–17.3)       |
| B. Sensitivity Analyses (patient-level estimates): |
| 1. Exclude studies with >50% missing data or missing data not reported (Koekkoek, O’Brien, Ble, Kumarasamy, Cearskul) | 14.0 (8.8–19.1)       |
| 2. Missing 12-month data: assume CD4% gain = 0 | 8.5 (5.5–11.4)       |

Abbreviations: NR: not reported, IQR: interquartile range, SD: standard deviation.

Notes:

A: By design, compared to children in the “deferred ART” arm and to children in the other included studies, children in the “immediate ART” arm of the Prendergast trial were younger and had less advanced HIV infection at ART initiation (Table 1). The immediate ART arm of this trial was therefore excluded from pooled analyses. A total of 63 infants were randomized (43 to immediate, 20 to deferred). Of 20 randomized to the deferred arm, 3 were lost to the study before initiating ART, and 4 did not start ART. To be consistent with other cohorts reporting only on ART initiators, these 7 were not included in the cohort reported here (leaving 13 in the deferred arm).

B: Baseline data are for the 409 children initiating ART, unless marked with (B), indicating baseline values for the 264 children with 12-month follow-up data.

C: Cohort defined as children with 12-month follow-up data.

D: 1,184 children initiated ART. CD4% data were collected only for children aged <5 years, and baseline and 12-month CD4% data are reported only for children aged 1.5–5 years. Only children aged 1.5–5 years are therefore included in the analysis.

E: 1,147 children started ART more than 12 months prior to analysis date (and therefore were eligible to have 12-month data).

F: Baseline data are only for the 95 children who survived to 6 months; 12-month data are for 68 children with follow-up data at 12 months.

G: Data are reported only on children with complete 18-month follow-up, not all ART initiators.

H: Not reported if median or mean, with IQR or range.

I: Values are mean and (95% CI).

J: Reported values are 12-month values, unless noted as “gain.”

K: CD4 percentage at 12 months not statistically significantly different between study arms.

L: Of the 5,329 ART initiators, 2,676 were reported to be eligible for 12-month CD4% data; others were ineligible because they initiated ART <12 months before data reporting or because only absolute CD4 count was recorded due to age >5 years.
Secondary outcomes: mortality and loss to follow-up 12 months after ART initiation for treatment-naïve children in resource-limited settings.

| Author          | Number initiating ART | Proportion initiating ART 12 months (or as noted) | Mortality | Growth | Patient Disposition and Completeness of Available Data | Proportion reported lost to follow-up | Proportion with CD4% data at 12 months (U) | Proportion with RNA data at 12 months (U) |
|-----------------|-----------------------|---------------------------------------------------|-----------|--------|----------------------------------------------------------|---------------------------------------|-------------------------------------------|-------------------------------------------|
| Chearskul       | 66                    | 3.0% (F)                                          | 93% (N)   | WAZ: 0.7 | HAZ: 0.3 | 2/66 = 3.0% (F) | NR | No VL                                           |
| Eley            | 409                   | 15.4%                                            | 84% (80–87%) | WAZ: 1.2, HAZ: 0.6, WHZ: 1.1 | 19/409 = 4.6% | 261/409 = 63.8% | 264/409 = 64.5% |
| Koekkoek        | All ages: 1,184       | NR                                               | NR        | NR     | NR (A) | 16/16 = 100% (A) | 6/16 = 37.5% |
| O'Brien         | 1.5–5y: 322           | NR                                               | NR        | NR     | NR (A) | 89/1184 = 7.5% (G) | 1.5–5y: 27/222 = 8.4% (G) |
| Rouet           | 78                    | 10.3%                                            | NR        | WAZ: 0.6*, HAZ: 0.2 (R)* | 0.0% | 16/59 = 27.1% | No VL |
| Ble             | 59                    | 0.0%                                             | NR        | WAZ: 1.1* | HAZ: 1.0* | 382/2938 = 13.0% (H) | 862/1,147 = 75.1% |
| Bolton-Moore    | 2,938 (B)             | 6.7% (H)                                         | NR        | WAZ: 0.6* | 4/212 = 1.9% (K) | 193/212 = 91.0% | 193/212 = 91.0% |
| George          | 236                   | 9.0% (I)                                         | NR        | WAZ: 0.7 | 24/236 = 10.2% (I,J) | (T) | 100/236 = 42.4% |
| Janssens        | 212                   | 61.1% (K)                                       | NR        | WHZ: 0.8 | 4/212 = 1.9% (K) | 193/212 = 91.0% | 193/212 = 91.0% |
| Kamya           | 250                   | 5.2%                                             | NR        | NR     | 3/250 = 1.2% | (V) | 222/250 = 88.8% |
| Myung           | 117 (C)               | 8.8%                                             | NR        | WAZ: 1.4 | 68/117 = 58.1% | No VL |
| Puthanakit      | 192                   | 6.3%                                             | NR        | NR     | 0.0% | 181/192 = 94.2% | 181/192 = 94.2% |
| Zhang           | 51                    | 0.0–3.9% (L)                                    | NR        | WAZ: 0.3** | 0–1/51 = 0–2% (L) | (V) | NR |
| Kumarasamy      | 67 (D)                | NR                                               | NR        | WHZ: 0.1* | 67/67 = 100.0% (D) | No VL |
| Prendergast     | 53 (E)                | 7.5% (M)                                         | NR        | NR     | 1/54 = 1.9% (T) | 49/53 = 92.4% | 49/53 = 92.4% |
| Immediate ART   | 40                    | 10.0%                                            | NR        | NR     | 0.0% | 36/40 = 90.0% | 36/40 = 90.0% |
| ART arm         | 13                    | 0.0%                                             | NR        | NR     | 1/14 = 7.1% (T) | 13/13 = 100.0% | 13/13 = 100.0% |
| ART arm         | 51                    | 0.0%                                             | NR        | NR     | 0.0% | 18/51 = 35.3% | 18/51 = 35.3% |

Abbriviations: NR: not reported, No VL: no viral load (HIV RNA) assay available.

Notes:
A: Cohort defined as children with 12-month follow-up data
B: 1,147 children started ART more than 12 months prior to analysis date (and therefore were eligible to have 12-month data).
C: 117 children were started on ART; 22 died in the first 6 months. 95 children contributed baseline data; 68 children had follow-up data at 12 months.
D: Data are reported only on children with complete 18-month follow-up, not all ART initiators.
E: A total of 63 infants were randomized (43 to immediate, 20 to deferred); 3 infants from the immediate ART arm were lost to the study before initiating ART, and were not included in the cohort reported here. Three infants from the deferred ART arm were lost to the study before initiating ART, and 4 did not start ART; these 7 were not included in the cohort reported here (leaving 53 ART initiators: 13 in the deferred arm and 40 in the immediate arm).
F: Over entire duration of follow-up (median follow-up 26 months)
G: Over entire duration of follow-up (median follow-up 6 months, range 2–12 months). In addition to 7.5% reported lost to follow-up, 3% had "unknown outcomes."
H: Over entire duration of follow-up (median follow-up 378 days)
I: Over entire duration of follow-up (median follow-up 20 months, range 0–36)
J: 171 children were “in follow-up > 1 year.” Over median 20 months of follow-up, 42 were reported lost to follow-up and 21 (9%) deceased. Not reported if those remaining (not dead or lost to follow-up at 12 months) had initiated ART <12 months prior and therefore were ineligible for 12 month data. It is reported that 98% of those in care at 12 months had absolute CD4 cell count data (not included in meta-analysis) and 58% had RNA data.
K: Over entire duration of follow-up (median follow-up 16.8 months)
L: Not reported if both children who died and 1 child who was lost to follow-up were among the 51 ART-naive children included in this analysis; the possible range is reported here.
M: Proportion reported is among children who initiated ART (13 in deferred group, 40 in immediate group), rather than among children randomized to each strategy, in order to achieve consistency with other included studies.
N: Kaplan Meier mortality estimated from figure.
O: When endpoint is defined as loss to follow-up or death.
P: This is the Kaplan-Meier estimate for number of children alive and in care at 12 months.
Q: Increases in WAZ, WHZ, and HAZ are reported as difference in median values from baseline to 12 months, unless noted with * (difference in mean values) or with ** (median difference reported).
R: Final growth parameters are not at 12-months, but over median follow-up of 620 days, and are reported in an earlier publication from this cohort. 53
S: Over entire duration of follow-up (median follow-up 36 months).
T: One infant from the immediate arm reached criteria to start ART, but was either lost to follow-up or died (not reported which) before 12 months. As it is not reported whether this infant initiated ART, s/he was not included in the pooled RNA and CD4 analyses, but s/he is considered lost to follow-up, raising the total number of children in the cohort to 54 (total) and 14 (deferred ART).
U: Note that it is not clear if missing data are because of death, loss to follow-up, or lack of resources to measure CD4 and RNA, or because some children started ART <12 months prior to the analysis date (and therefore would not have been able to contribute to 12-month data).
V: These studies were not included in the pooled CD4% analysis.