Long-term effects of HIV treatment in sub-Saharan Africa: from access to quality
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Virological suppression among HIV-infected children in low- and middle-income countries: a systematic review and meta-analysis.


Submitted.
SUMMARY

Background
This review and meta-analysis aims to summarize virological suppression rates in HIV-infected children <18 years, up to five years after initiation of non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based first-line antiretroviral treatment (ART) in low- and middle-income countries (LMIC).

Methods
We searched Medline, Embase, the Cochrane Central Register for Controlled Trials (CENTRAL) and the Literatura Latino Americana de Ciencias de Salud (LILACS) for randomized controlled trials, cohort studies and cross-sectional studies. We extracted data on virological suppression six to 60 months after first-line treatment initiation and summarized the proportion of children with virological suppression at six-monthly time intervals using random-effects meta-analysis.

Findings
Seventy-two papers, reporting on 51,347 children, were included in the analysis. Summary estimates of virological suppression after six, 12, and 24 months of ART were 71.3% (95%CI 67.9-74.6), 69.6% (95%CI 66.3-72.9), and 78.3% (95%CI 75.0-81.6), respectively. For NNRTI-treated children these rates were 65.5% (95%CI 56.7-74.3), 64.6% (95%CI 57.0-72.2), and 76.8% (95%CI 71.7-82.0), and for PI-treated children 77.2% (95%CI 66.8-87.6), 70.3% (95%CI 61.0-79.6), 74.2% (95%CI 58.6-89.7), respectively.

Interpretation
In the most comprehensive literature overview of first-line ART in children in LMIC to date, virological suppression rates were 70-80%, which is lower compared to adults in LMIC and to children in high-income countries. Children in LMIC continue to be a vulnerable population. More attention should be given to strategies to increase virological suppression rates, including improved monitoring, increased access to and accelerated development of adequate and affordable first- and second-line ART.
HIV suppression in children in LMICs

INTRODUCTION

Treating HIV in early childhood is life-saving. However, children are vulnerable to developing virological failure. Variability in pharmacokinetics, limited pediatric treatment options, and lack of adherence support are among the potential reasons for this increased risk [1]. In addition, drug exposure as part of the prevention of mother-to-child transmission (PMTCT) can lead to the emergence of HIV drug resistance [2, 3], thus increasing the risk of virological failure.

The World Health Organization (WHO) recommends all children below three years of age to receive a PI-based regimen (lopinavir/ritonavir [LPV/r]), regardless of history of PMTCT exposure [4]. Unfortunately, despite these recommendations, the use of PIs for young children in low- and middle-income countries (LMIC) in routine programs is limited due to practical barriers. PIs are more costly than NNRTIs, and infant formulations were to date only available as a liquid that requires refrigeration, although new formulations are on their way [5–7].

Previous systematic reviews on virological suppression in children only focused on sub-Saharan Africa, only on young children, or only included randomized controlled trials (RCTs) in which circumstances are usually well controlled and less likely to represent ‘real life’ settings [8, 13–15]. This review and meta-analysis is the first attempt to analyze virological outcomes up to five years after treatment initiation, in children up to the age of 18 years, on three different continents, and including all types of study designs.

The goal of this comprehensive assessment of available data was to provide summary estimates of virological suppression rates in children retained on first-line ART six to 60 months after treatment initiation. In addition, we stratified results of children on NNRTI- or PI-based first-line ART and compared results of children with and without prior PMTCT exposure.

METHODS

Search strategy and selection criteria

This study was performed in accordance with the PRISMA statement for reporting systematic reviews and meta-analyses [8]. The systematic review protocol is provided in Supplement V. We systematically reviewed relevant literature in Medline (through PubMed), Embase, the Cochrane Central Register for Controlled Trials (CENTRAL)
and the Literatura Latino Americana de Ciencias de Salud (LILACS), using the search strategy as provided in Supplement I. In short, a search was conducted (by RB) to find articles on virological outcomes in HIV-infected children <18 years of age living in LMIC [9], including information about viral load outcomes in the first five years of first-line ART. We searched for articles published between January 2005 and May 2015, in English, French and Spanish. Additionally, online databases of the International AIDS Society 2012-2014, the Conference on Retroviruses and Opportunistic Infections 2012-2015, and the HIV pediatric workshop 2012-2014 were screened for relevant conference abstracts. Snowballing techniques were used to retrieve any additional articles.

Study screening
Eligible studies included prospective and retrospective cohort studies, cross-sectional studies and RCTs. Participants of the study had to be children (<18 years of age) with an HIV-1 infection, on first-line ART, and receiving treatment in LMIC. Both children with and without prior exposure to PMTCT were eligible for inclusion. We included studies reporting on pre-defined six-monthly time points up to 60 months after treatment initiation. For studies reporting a suppression rate at a median time after treatment initiation, we included these if the interquartile range was ≤12 months. The selection of studies was done independently by two reviewers (RB and TSB) and any disagreement was resolved by mutual discussion. Study selection was done first based on the title, subsequently on the abstract, and finally based on reading the full text of the article.

Data extraction
Data were extracted using a data extraction form designed for this purpose in MS Access 2013®. Data extraction (by RB and AB) was done separately for each pre-defined time point at which the proportion of participants with virological suppression was reported. The virological suppression threshold used in each study was extracted and was later pooled into three categories: <50 cps/ml, <400 cps/ml or <1000 cps/ml. The extraction was done separately for participants on PI- or NNRTI-based regimens, and for participants with and without PMTCT exposure, when reported. This yielded multiple ‘analysis cohorts’ extracted from a single study. The following additional data were extracted from each study: year of study; country of study; number of study sites; percentage female; median age; ART regimen. If needed, study authors were contacted to clarify or confirm the extracted data. Study quality and risk of bias was assessed by two independent reviewers (RB and AB) using an adapted version of the Newcastle Ottowa Scale [10] (Supplement II).
Statistical analysis
The primary analysis was done on an on-treatment basis, defined as the number of children with virological suppression divided by the number of children who were on treatment and had viral load results at that time point. The results were pooled for each pre-defined time point (6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months after ART initiation). All analyses were done using a random effects model, because of the heterogenic nature of the included studies. Heterogeneity of outcomes was assessed through calculation of $I^2$-statistics. The variance of the raw proportions was stabilized using a Freeman-Tukey arcsine square root transformation and was subsequently back-transformed to the original scale.

Subgroup analyses were performed among participants on NNRTI- or PI-based regimens and with or without PMTCT exposure at each time point. A meta-regression was performed to obtain p-values for comparison of proportions between NNRTI- and PI-treated children, and PMTCT-exposed and unexposed children. To test for the robustness of our data, we performed sensitivity analyses, which included, only: 1. studies performed after 2005; 2. studies conducted in sub-Saharan Africa; 3. studies in which the participants’ median age was <3 years; 4. studies yielding the maximum score on the Newcastle Ottowa Scale for quality assessment. In addition, we conducted an intention-to-treat analysis, in which we calculated the virological suppression rate by dividing the number of suppressed children at each time point by the number of children who had started treatment at baseline, thus considering all children with unknown viral load results, who stopped ART, had deceased or were lost to follow-up, as having virological failure. All data analyses were performed using Stata 12.1® (StataCorp. 2011. College Station, TX: StataCorp LP).

RESULTS
We retrieved 1,580 articles through our literature search and one article through snowballing. Additionally, we found 1,009 potentially relevant conference abstracts. Of the 1,581 retrieved papers, 855 were excluded based on the title, 345 after reading the abstract and 267 after reading the full text. After removal of 44 duplicate cohorts, 70 full-text papers were included in this review. Of the 1,009 conference abstracts found, 680 were excluded on title and 327 after reading the abstract. Two conference abstracts were included in this review (Figure 1).

We included 72 studies, reporting on a total of 51,347 children. Of the 72 included studies, we extracted 188 analysis cohorts, based on time after ART initiation; NNRTI
or PI regimen; and previous PMTCT exposure. A median of two cohorts were extracted per study (range 1-12). Fifty-two (72.2%) studies had a maximum score of six on the Newcastle Ottowa Scale. Further details are described in Table 1. A complete overview of all studies is provided in Supplement III.

Figure 1. Flow diagram of the study selection process.

Hundred and sixty six of 188 cohorts (88.3%) reported virological outcomes in the first two years after treatment initiation, i.e. at six, 12, 18 or 24 months. The summary estimates of the proportion of participants with virological suppression, using a threshold of virological suppression of <1000 cps/ml, were 71.3% (95%CI 67.9-74.6, n=18,730) at six months, 69.6% (95%CI 66.3-72.9, n=20,622) at 12 months, 68.2% (95%CI 58.8-77.7, n=3,778) at 18 months, and 78.3% (95%CI 75.0-81.6, n=6,262) at 24 months after ART initiation. Suppression rates using a virological suppression threshold of <1000 cps/ml, <400 cps/ml, and <50 cps/ml are reported in Table 2.

The intention-to-treat analysis yielded summary estimates of virological suppression of 53.8% (95%CI 45.2-62.4, n=33,288) at six months, 46.0% (95%CI 38.5-53.6, n=42,725)
### Table 1. Characteristics of included studies and cohorts within included studies.

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ART, antiretroviral treatment; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PMTCT, prevention of mother-to-child transmission.
at 12 months, 45.7% (95%CI 35.6-55.9%, n=8,138) at 18 months, and 51.8% (95%CI 40.8-62.9, n=17,991) at 24 months (Figure 3 and Supplementary Table S1).

Twenty cohorts (10.6%) reported on virological suppression rates at 30-60 months after first-line ART initiation. Suppression rates fluctuated between 60.3% at 42 months (95%CI 34.6-86.0, n=162) and 79.6% at 60 months (95%CI 64.0-95.1, n=927) Virological suppression rates at other time points are reported in Table 2.

We stratified the studies according to the type of first-line regimen, NNRTI- or PI-based. In the NNRTI-cohorts virological suppression was achieved in 65.5% (95%CI 56.7-74.3, n=4,993) after six months; 64.6% (95%CI 57.0-72.2, n=6,253) after 12 months; and 76.8% (95%CI 71.7-82.0, n=1,712) after 24 months of ART. In PI-cohorts these rates were 77.2% (95%CI 66.8-87.6, n=3,426); 70.3% (95%CI 61.0-79.6, n=2,527); and 74.2% (95%CI 58.6-89.7, n=28), respectively (Figure 2 and Supplementary Table S2). Restricting these analyses to children under three years of age, who are recommended to receive PI-based treatment, yielded similar results (Supplementary Table S2).

At six months after ART initiation, 63.3% (95%CI 29.0-97.6, n=150) of PMTCT-exposed children had virological suppression compared to 76.9% (95%CI 66.2-87.6, n=501) of unexposed children, p=0.523. At 12 months, these proportions were 51.7% (95%CI -22.5-125.8, n=59) versus 70.6% (95%CI 59.4-81.8, n=460), p=0.954, and at 24 months 14.6% (95%CI -5.9-35.2, n=9) versus 66.6% (95%CI 50.3-82.8, n=107), p=0.867, for exposed and unexposed children, respectively (Supplementary Table S2). Exposed children were significantly younger than unexposed children (median age 0.7 versus 3.1 years, p=0.007). No significant difference in ART regimen was found between exposed and unexposed children. The limited amount of data did not allow for subgroup analyses.

Sensitivity analyses restricting the analysis to geographic location, calendar year, age, and study quality showed similar patterns of virological suppression rates of ~70-80% in the first two years after treatment initiation (Figure 3 and Supplementary Table S3).
Virological suppression is defined as a viral load <500 cps/ml.

Data on virological suppression after 24 months were pooled using a threshold of <1000 cps/ml only, because of limited availability of data.

95% CI, 95% confidence interval; NA, not available.
DISCUSSION

In this systematic review and meta-analysis, including 72 studies reporting on 51,347 children, we show that virological suppression rates in HIV-infected children in LMIC are between 70 and 80% in the first 24 months, and 60 to 80% up to five years after first-line ART initiation. These outcomes are considerably lower than the rates of adults in LMIC, and of children in high-income countries [11–14].

For the first two years of treatment, suppression rates were sustained at 70-80%, and were robust when accounting for calendar year of treatment initiation, continent, age groups, and assessed study quality. The proportions we found are in accordance with the findings of previous systematic reviews with shorter follow-up periods, in which a rate of 46-81% at six months of treatment [15] and a rate of 70% [16], and 49-81% [15] at 12 months were reported. Proportions are lower, however, compared to a recent systematic review on virological suppression in adults in LMIC, which found suppression rates of approximately 85% in the first two years after first-line treatment initiation [11]. Outcomes are also poorer compared to the suppression rates of >90% found in HIV-infected children in high-income countries [12–14].

Figure 3. Sensitivity analyses: summary estimates of the proportion of children with virological suppression 6–24 months after treatment initiation.

Virological suppression is defined as viral load <1000 cps/ml.
Separate analyses for studies: 1. conducted after 2005; 2. conducted in sub-Saharan Africa; 3. in which the children’s median age is <3 years; 4. with a maximum score of 6 on the adapted Newcastle Ottowa Scale; 5. intention-to-treat analysis; 6. the primary on-treatment analysis.

ITT, intention-to-treat analysis; NOS: Newcastle Ottowa Scale; OT, on-treatment analysis.
Our results indicate that HIV-infected children treated with ART in LMIC are a vulnerable population and, despite current efforts, are at high risk of treatment failure. Two other findings stress these disconcerting results: first, also in cohorts using more potent PI-based treatment, virological suppression rates were <80%; second, the intention-to-treat analysis showed suppression rates in children of only 45-55% in the first two years, while in adults these rates were 65-75% [11].

To improve virological suppression rates in children in LMIC, a better understanding of their poor outcomes as compared to adults and to children in high income countries is required. First of all, children may be more vulnerable to virological failure after exposure to failed PMTCT, which is associated with NNRTI resistance [17, 18]. In this review, PMTCT-exposed children had lower virological suppression rates than unexposed children, although differences were not significant. Using the currently recommended PI-based treatment, clinical outcomes in young children have been shown to be better compared to NNRTI-treated children, regardless of previous PMTCT exposure [19]. Second, treatment adherence is challenging in children who are dependent on their caregivers to receive their medication and to remain in care. Little is known about the long-term treatment outcomes of children on first-line ART, as we identified only nine studies reporting on virological suppression rates more than two years after ART initiation. Third, accurate drug dosing in children is difficult, because of changing pharmacokinetics in children of different weights, and the limited availability of pediatric formulations. This increases the risk of underdosing and subsequent HIV drug resistance. In order to improve treatment response in children in LMIC, various steps will need to be taken. Implementation of PI-based treatment for young children regardless of PMTCT exposure, as recommended by the WHO [4], is essential to achieve better treatment results in this vulnerable population who will need treatment for the rest of their lives. To be able to treat all children under three years with a PI, financial and logistic barriers for LMIC to implement this strategy need to be overcome. It has been suggested that PIs might be used only to achieve initial virological suppression, after which children can be switched to less costly NNRTI-based treatment [20]. However, this is only recommended in settings where viral load monitoring is available, which is often not the case in LMIC. Cost-reduction of ARVs for LMIC, the production of generics, and harmonization of treatment guidelines are important steps to increase access to PI-treatment. In addition, the development of new antiretroviral agents, in formulations appropriate for children, should receive priority. In children who fail PI-based first-line treatment, second-line options are very limited and outcomes are poor [21, 22]. New generation PIs such as darunavir could be a second-line option after failure of first-line LPV/r-based treatment in children.
above three years of age. The new integrase inhibitor raltegravir has recently been approved for young infants. These new agents are, however, currently not available in LMIC [23]. As access to first-line PI regimens for children increases, evidence-based strategies for durable second-line options should be developed. Third, as we found that virological suppression rates in children are considerably lower than in adults, it is important that especially children are monitored closely during treatment in order to timely detect treatment failure. Implementation of viral load monitoring for this population in LMIC should be a priority. Finally, the specific aspects of pediatric HIV-care, such as blood sampling techniques, specific laboratory assays, and pediatric drug formulations, should receive more attention in the training of health workers in LMIC. Treatment protocols should be, when possible, simplified, in order to improve HIV-care for children in resource-limited settings.

Strengths of our study include the fact that it provides the largest and most comprehensive literature review of HIV treatment outcomes in children in LMIC to date, and that our findings were robust across several sensitivity analyses. In order to assess all available data on this topic, we chose to include both observational studies and RCTs. A limitation to this approach is the large heterogeneity among the studies, and care should be taken when comparing results across studies. We are aware of the fact that other factors apart from drug class and PMTCT exposure are likely to play a role in virological suppression rates in children, such as the specific drugs used within each drug class [24]. Very few studies reported the number of virologically suppressed children separately for each drug used, so we could not conduct separate analyses to correct for specific drugs used. As we did not have individual patient data of the included studies, but only study-level data, we did not correct for potentially relevant patient characteristics, such as age or clinical and immunological status. Including study averages of such data, such as mean age or mean CD4-count, would have introduced the risk of ecological bias in our analysis [25].

In conclusion, this systematic review and meta-analysis is the most comprehensive literature overview of response to first-line ART in children in LMIC to date. We show that rates of virological suppression in children are considerably lower than those found in adults and in children in high-income countries. Implementation of PI-based treatment, the development of new pediatric formulations against affordable costs, improved pediatric treatment monitoring, and specific pediatric training for health workers are necessary in order to achieve optimal treatment results for HIV-infected children in LMIC.
CONTRIBUTORS

RB did the initial search of published work, checked all full-text articles, extracted data from the full reports and conference abstracts, conceived and coordinated the analyses, and wrote the first draft of the paper. TSB also checked all full-text articles and abstracts, and AB also extracted data. KS conceived the systematic review, supervised the reviewing process and was available to resolve conflicts during data extraction. JC supervised the analysis process and interpreting the data. TRW and MBvH supervised KS and JC and assisted conceiving the study and interpreting the data. SB assisted interpreting the data. All authors participated in discussion of the results and in writing of the final paper.

DECLARATION OF INTEREST

We declare that we have no conflicts of interests.

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