Prevention, suppression, and resistance

Antiretroviral treatment for children with HIV in sub-Saharan Africa

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Chapter 8: Multicentre analysis of second-line antiretroviral treatment in HIV-infected children: adolescents at high risk of failure

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[Submitted]
ABSTRACT

Background
The number of HIV-infected children and adolescents requiring second-line antiretroviral treatment (ART) is increasing in low- and middle-income countries (LMIC). Data on pediatric second-line ART outcomes in LMIC and potential risk factors for virologic failure are essential to improve HIV care in LMIC, where pediatric third-line ART is not routinely available.

Methods
We performed a multicenter analysis by systematically reviewing the literature to identify cohorts of children and adolescents receiving second-line ART in LMIC, contacting the corresponding study groups, and including patient-level data on virologic and clinical outcomes. Kaplan-Meier survival estimates and Cox proportional hazard models were used to describe cumulative rates and predictors of virologic failure. Virologic failure was defined as two consecutive viral load measurements >1000 copies/ml after at least 6 months of second-line treatment.

Results
We included 12 cohorts representing 928 children on second-line protease inhibitor (PI)-based ART in 14 countries in Asia and sub-Saharan Africa. Data on second-line ART after failure of a first-line PI-based regimen were too limited to include in our analysis. After 24 months, 16.4% (95%CI 13.9-19.4) of children experienced virologic failure. Adolescents (10-18 years) had failure rates of 14.5 (95%CI 11.9-17.6) per 100 person-years compared to 4.5 (95%CI 3.4-5.8) for younger children (3-9 years), p<0.001. Risk factors for virologic failure included adolescence (adjusted hazard ratio [aHR] 3.93, p<0.001) and short duration of first-line ART before treatment switch (aHR 0.64 and 0.53, p=0.008, for 24-48 months and >48 months, respectively, compared to <24 months).

Discussion
The rate of virologic failure in children on second-line ART was comparable to results among adults on second-line ART and lower than among children on first-line ART in LMIC. Adolescence was strongly associated with virologic failure.
Conclusions
In LMIC, pediatric PI-based second-line ART is associated with relatively low virologic failure rates. However, adolescents show exceptionally poor virologic outcomes in LMIC and optimizing their HIV care requires urgent attention. In addition, for those children and adolescents who fail PI-based treatment in LMIC, access to salvage regimens, most notably integrase inhibitors, must be improved.
INTRODUCTION

Worldwide, the number of HIV-infected children receiving antiretroviral treatment (ART) has more than doubled since 2010 to an estimated 823,000 in 2014. In low- and middle-income countries (LMIC), 97% of children on ART are on first-line treatment, and only 3% receive second-line ART. However, with the increasing paediatric ART coverage in LMIC, the absolute number of children failing first-line and requiring second-line options will rise.

Currently, the World Health Organization (WHO) recommends HIV-infected children ≥3 years of age to start non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART as a first-line regimen, and to switch to a protease inhibitor (PI)-based second-line regimen in case of treatment failure. Children <3 years are recommended to start PI-based first-line ART. As PI-based treatment is costly and logistically challenging, many local guidelines in LMIC, however, still recommend a NNRTI-based regimen as first-line ART in young children. Moreover, due to late diagnosis and linkage to care, perinatally HIV-infected children may only start ART after the age of 3 years. As a consequence, most children in LMIC still receive an NNRTI-based first-line regimen and switch to PI-based ART in case of failure.

Children and adolescents are found to have higher rates of first-line ART failure compared to adults. The population of HIV-infected adolescents is growing as perinatally infected children now survive until adulthood, and HIV treatment in adolescents is found to be especially challenging. In order to ensure adequate long-term treatment for these populations, evaluation of current second-line treatment outcomes is essential. Data, however, are scarce. We performed a multicentre analysis of children and adolescents in LMIC to evaluate the effectiveness of second-line ART by describing the rate of virologic failure and identifying its predictors.

Methods

We conducted a systematic review of the literature to identify cohorts of children receiving second-line ART in LMIC. We systematically searched the literature in Medline through Pubmed, Embase, the Literatura Latino Americana de Ciencias de Salud (LILACS), and the African Index Medicus, as well as conference abstracts of the International AIDS Society, the Conference on Retroviruses and Opportunistic Infections, and the HIV Pediatric Workshops of 2014 and 2015 to identify second-line cohorts of which results had not yet been published. The complete search strategy is provided in supplementary Table S1.
Study selection

We searched for cohort studies, cross-sectional studies and randomized controlled trials reporting second-line virologic treatment outcomes of children and adolescents living in LMIC (according to the World Bank 2016 definition). Studies were eligible if they reported on at least five children on a PI-based second-line regimen. Exclusion criteria were: age <3 years or >18 years at switch to second-line ART; children who had received less than six months of first-line ART before switching; children having either a first- or second-line regimen consisting of dual- or monotherapy; and children without any viral load (VL) results during the first five years of second-line ART. In order to create a homogeneous group of participants, we selected only children on ritonavir-boosted lopinavir (LPV/r)-based ART, reflecting the 2013 WHO guidelines on paediatric second-line ART. Because of the various changes in treatment guidelines for children <3 years (from NNRTI-based first-line and PI-based second-line in 2010, to PI-based first-line and raltegravir-based second-line in 2016) we included only participants >3 years of age. Study selection was done independently by two reviewers and any disagreement was resolved by discussion between both. Authors of eligible articles were approached by email with a request to share the patient-level data of their cohort. If the study group agreed to share data, a data sharing agreement was signed by both parties. Anonymized data sets were shared by email and were collected in one central database. If different study groups had included participants from the same study sites, we checked with the corresponding authors that none of the participants were included in our data set twice. Only the first author had direct access to all data in order to maintain confidentiality.

Data management

Data sets were provided by the corresponding authors in Stata®, SPSS®, or Excel® format. The following variables were requested: sex; age at switch; calendar year at switch; country of residence; duration of first-line ART; drugs used in first-line regimen; reason for switching to second-line ART; drugs used in second-line regimen; VL, CD4 count/CD4 percentage, and WHO/CDC HIV stage at switch; VL during follow-up and period between switch and VL measurement; status at moment of censoring (in care, dead, lost to follow-up, transferred out), and date of end of study.

Risk of bias assessment

To assess the potential risk of bias in each cohort, we developed a list of five criteria relevant for this analysis, based on existing checklists of the Newcastle Ottowa Scale.
the Strengthening the Reporting of Observational studies in Epidemiology (STROBE)\textsuperscript{156}, and the Cochrane Collaboration tool for assessing the risk of bias\textsuperscript{157}. For each criterion, a study could score 1 if the criterion was met and 0 if the criterion was not met or not reported. Each cohort could obtain a maximum score of 5. Cohorts with a score of $\geq 4$ were considered to have a lower risk of bias, and below 4 a higher risk. Criteria and scores of each study are provided in supplementary Table S2.

**Data analysis**

We defined young children as individuals aged $\leq 9$ years, and adolescents as individuals aged 10-18 years at switch. Baseline characteristics of young children and adolescents were described using counts and percentages or medians and interquartile ranges. We did not use multiple imputation to adjust for missing data if these data were missing at the cohort level. For categorical variables, we added a ‘missing’ category for individuals with missing data for that variable. Kaplan-Meier survival analysis was used to assess the cumulative incidence of virologic failure overall, and separately for younger children and adolescents. Difference in virologic failure rates between groups was assessed using a log-rank test. In the primary analysis, we defined virologic failure according to the WHO definition of two consecutive VL measurements $>1000$ copies/ml after at least six months of second-line ART\textsuperscript{29}. As not all studies used a second confirmatory VL measurement to define failure, we conducted a secondary analysis in which we defined failure as a single VL $>1000$ copies/ml after at least six months of second-line ART. Associations between virologic failure and age, sex, time spent on first-line ART, calendar year of switch and VL and CD4 count/percentage at switch were assessed using a Cox proportional hazard model, clustered by study cohort and by number of VL results per child ($<5$ results, 5-15 results, and $>15$ results). The proportional hazard assumption was tested by calculating Schoenfeld residuals. To test for the robustness of our data, we conducted three sensitivity analyses in which we only included children in sub-Saharan Africa, only children with known VL and CD4 count/percentage results at switch to second-line ART, or only studies with a perceived lower risk of bias. A two-sided p-value of $\leq 0.05$ was considered significant. Data were analysed using Stata 12\textsuperscript{\textregistered} (StataCorp LP, TX, USA).
RESULTS

Search
Our search strategy retrieved a total of 370 articles and 371 conference abstracts, of which 340 articles and 367 abstracts were excluded. Main reasons for exclusion were: not concerning second-line treatment, inclusion of adults rather than children, or not reporting virologic treatment outcomes. All four remaining abstracts had been published and were already included as article in the 30 remaining papers. After full text screening of the remaining articles, 21 authors were contacted to participate which resulted in 12 contributing datasets, including our own cohort of Ugandan children receiving second-line ART158 (Figure 1).

Characteristics of included studies
The 12 remaining cohorts represent 928 children receiving LPV/r-based second-line ART in 14 countries in Asia and sub-Saharan Africa Figure 2). Characteristics of children included are shown in Table 1 and study characteristics are described in supplementary Table S3. Median age at switch was 9.0 years (IQR 6.1-12.0). Fifty-six children (6.0%) were enrolled in a randomized controlled trial, all other children were included in observational cohort studies. Median time on first-line ART prior to switch was 36.0 months (IQR 21.6-51.6). The most common first-line regimen was zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) in 235 children (25.8%), and the most common second-line regimen was AZT/3TC/LPV/r in 194 children (21.3%). A median of 3 VL results (IQR 2-6) per individual were reported during follow-up. At the time of censoring, 717 (77.3%) children were in care and on treatment, 20 (2.2%) were lost to follow-up, 24 (2.6%) had died, 72 (7.8%) had transferred out, and for 95 (10.2%) children the status at end of follow-up was not recorded. Of all young children, 436/480 (90.8%) were still in care and on treatment at censoring, compared to 281/353 (79.6%) of adolescents, p<0.001.

Virologic failure
Of the 928 children on second-line PI-based ART, 722 (77.8%) children had at least two VL results during follow-up, were still in care and on treatment after six months of second-line ART, and were included in the primary analysis (virologic failure defined as two consecutive VL>1000 copies/ml). Over a total follow-up time of 1,882 person-years, 154 children experienced virologic failure, resulting in a failure rate of 8.2 (95%CI 7.0-9.6) per 100 person-years. After 12, 24 and 60 months, failure rates were 10.0% (95%CI 8.0-12.5), 16.4% (95%CI 13.9-19.4) and 25.3% (95%CI 21.7-29.2), respectively. In children,
Figure 1. Flow chart of study and participant selection

Retrieved:
- 369 database search
- 1 snowballing

Excluded:
- on title and abstract: 327
- on full text: 13
- duplicates: 9

Contact authors:
21

- ineligible after contact: 5
- refused: 2
- no reply: 3

11 cohorts included from literature search

Add data own research group

12 cohorts included in final analysis

Data available of 1509 participants

Excluded:
- less than 6 months on first-line: 23
- no NNRTI-based first-line: 26
- no LPV/r-based second-line: 188
- no VL results within 60 months after switch: 196
- aged < 3 years or > 18 years: 148

928 participants included in final analysis
Figure 2. Map of countries included in the multicentre analysis.
the failure rate was 4.5 (95%CI 3.4-5.8) and in adolescents 14.5 (95%CI 11.9-17.6) per 100 person-years. After 24 months, 9.1% (95%CI 6.6-12.4) of younger children and 26.3% (95%CI 21.7-31.8) of adolescents had experienced virologic failure, p<0.001 (Figure 3a).

Out of 928 children, 911 (98.2%) children had at least one VL result, were still in care and on treatment after six months of second-line ART and were included in the secondary analysis (virologic failure defined as a single VL>1000 copies/ml). Over a total follow-up time of 2,058 person-years, 307 children experienced virologic failure, resulting in a failure rate of 14.9 (95%CI 13.3-16.7) per 100 person-years. After 24 months, 17.5%

Table 1. characteristics of children and adolescents included in the multicentre analysis

<table>
<thead>
<tr>
<th></th>
<th>Children (3-9 years old)</th>
<th>Adolescents (10-18 years old)</th>
<th>Total</th>
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<tr>
<td></td>
<td>N</td>
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<tr>
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<td>Gender</td>
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<tr>
<td>Boys</td>
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<td>Girls</td>
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<td>Viral load at switch (copies/ml)</td>
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<td>&lt;1000</td>
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<td>CD4 status at switch*</td>
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<tr>
<td>Diminished</td>
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<td>22.9</td>
<td>117</td>
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<tr>
<td>Immunodeficient</td>
<td>44</td>
<td>8.3</td>
<td>52</td>
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<tr>
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<td>Duration of first-line antiretroviral treatment</td>
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<tr>
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<td>0.2</td>
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</tr>
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</table>

*Normal: CD4 count>500 or CD4% >25; diminished: CD4 count 100-500 or CD4% 10-25%; immunodeficient: CD4 count <100 or CD4% <10%. Status is based on CD4% for children <5 years, and on CD4 count for children ≥5 years.
(95%CI 14.4-21.2%) of young children and 34.4% (95%CI 29.7-39.5) of adolescents failed, p<0.001 (Figure 3b).

Figure 3a-b. Cumulative incidence of virologic failure among children and adolescents on second-line treatment. 3a: primary analysis, 3b: secondary analysis

Virologic failure in the primary analysis is defined as two consecutive VL results>1000 cps/ml after at least 6 months of second-line treatment and in the secondary analysis as a single VL>1000 cps/ml after at least 6 months of second-line treatment. T0 is set at 6 months after treatment switch, total follow-up time is 60 months.
Predictors of virologic failure

Adolescents had a higher risk of virologic failure compared to younger children (adjusted hazard ratio [aHR] 3.93 [95%CI 2.67-5.78], p<0.001). Children who had spent more time on first-line ART had a lower risk: compared to <24 months of first-line ART, the aHR was 0.64 (95%CI 0.42-0.96), p=0.032, for those on first-line ART for 24-48 months, and 0.53 (95%CI 0.33-0.85), p=0.008, for those on first-line ART for >48 months. Sex, calendar year of switch, VL and CD4 status at switch were not associated with virologic failure.

Virologic failure is defined as two consecutive viral load results >1000 cps/ml after at least 6 months of second-line ART. Cox regression model is stratified by number of VL results per child and by study cohort. Age, calendar year, viral load and CD4 status are at moment of treatment switch. *Normal: CD4 count>500 or CD4% >25; diminished: CD4 count 100-500 or CD4% 10-25%; immuno-deficient: CD4 count <100 or CD4% <10%. Status is based on CD4% for children <5 years, and on CD4 count for children ≥5 years. 95%CI: 95% confidence interval. ART: antiretroviral treatment.
failure (Table 2). Adolescence was the only factor associated with virologic failure in three sensitivity analyses, with an aHR of 3.08 (95% CI 1.35-7.02, p=0.007) for children in sub-Saharan Africa only, an aHR of 5.11 (95% CI 2.66-9.82, p<0.001) for children with a known VL and CD4 status at switch, and an aHR of 4.32 (95% CI 1.69-11.04, p=0.002) for children in studies with a perceived lower risk of bias (Supplementary Table S4).

**DISCUSSION**

The rate of virologic failure among children on second-line PI-based ART after failure of first-line NNRTI-based ART was 8.2 per 100 person-years, with 16.4% of children experiencing virologic failure within 24 months. Adolescents were almost four times more likely to experience virologic failure on second-line ART compared to younger children.

In the first two years of PI-based second-line ART, 16% of children experienced virologic failure. In a secondary analysis using a single VL measurement to define virologic failure, 25% failed. These outcomes are better than the pooled estimates of 60-75% of children achieving viral suppression in the first two years of first-line ART\textsuperscript{151}, which might reflect the higher potency and the higher ‘forgiveness of non-adherence’ attributed to PIs as compared to NNRTIs (mainly used in first-line regimens within LMIC). Moreover, a child’s or caregiver’s improved motivation to adhere to treatment after failure of first-line treatment might also play a role. Finally, the risk of pre-treatment HIV drug resistance towards NNRTIs is typically higher than resistance towards PIs, especially after exposure to drugs for the prevention of mother-to-child transmission\textsuperscript{23,159}. Our results are comparable to previous studies among adults on second-line ART in LMIC. In a study among adults in 12 Asian countries, the failure rate was 8.8 per 100 patient-years\textsuperscript{160}. A large cohort study in six African countries among adults on second-line ART found that 15% experienced virologic failure after two years\textsuperscript{134}. When only looking at the subgroup of younger children in our study, outcomes are even better than adult results, as the failure rate was 4.5 per 100 patient-years and 9.1% failed after two years. This again underscores the necessity for increasing virologic monitoring as children grow older.

Adolescent age was the strongest predictor of virologic failure, and this finding was robust across several sensitivity analyses. This result is in line with previous paediatric studies which also identified adolescents to be at increased risk of treatment failure on first- and second-line ART\textsuperscript{140,161–163}. Studies on treatment outcomes of adolescents living with HIV in LMIC are scarce, but the available data are worrisome. In sub-Saharan Africa,
HIV is the leading cause of mortality in adolescents\textsuperscript{164}. While the number of AIDS-related deaths worldwide decreased by 24\% between 2004 and 2011, mortality increased by 50\% among adolescents over the same time period\textsuperscript{153}. The observation that perinatally infected children are now surviving into adolescence due to the large-scale introduction of ART is an enormous achievement. However, the poor treatment outcomes of these children once they reach adolescence call for increased attention for this age group, not only to prevent HIV-related morbidity and mortality, but also to decrease the risk of HIV transmission in sexually active adolescents. Treatment of adolescents is known to be challenging, because of physical, psychological and social changes in an adolescent’s life and the transition from paediatric into adult HIV care\textsuperscript{152,154,165,166}. Strategies to retain adolescents in care and to improve treatment adherence need to be explored further, and might include adherence clubs, mobile health technologies, support in dealing with stigma, and training in life skills and problem-solving\textsuperscript{152}.

It is reassuring to note that children who fail first-line NNRTI-based treatment still have a good chance of re-suppressing on LPV/r-based second-line ART. However, given that WHO guidelines recommend PI regimens as first-line for young children since 2013\textsuperscript{20}, it is concerning that hardly any data exist on outcomes of children who have failed PI-based first-line and need to be switched to second-line ART. In our literature search, we identified reports of only 30 children on second-line treatment after failure of a PI-based first-line regimen, indicating that this is a profoundly understudied topic. The most recent WHO guidelines recommend the use of a raltegravir-based regimen as a second-line option after failure of first-line LPV/r-based ART in children <3 years, and the use of either raltegravir or efavirenz in children ≥3 years. Children failing second-line PI-based ART are recommended to start raltegravir, darunavir or dolutegravir plus two NRTIs as a salvage regimen\textsuperscript{29}. However, despite recent Medicines Patent Pool licensing agreements allowing royalty-free manufacturing for sale in LMIC\textsuperscript{167}, these drugs are hardly available in programmatic settings in LMIC\textsuperscript{20,76,168,169}. For children failing PI-based treatment (either as a first-line for young children or as a second-line for older children), treatment options are therefore still very limited.

Unfortunately, most cohorts included in this analysis did not perform genotypic HIV drug resistance (HIVDR) testing in children failing second-line ART. To our knowledge, only two published cohort studies in Asia described HIVDR patterns in a cohort of children on second-line ART. These reported relatively low rates of PI-resistance of 11.3\% and 8.0\% in children failing second-line\textsuperscript{140,163}. In a cohort of 64 children on second-line in Uganda, no PI mutations were detected after failure\textsuperscript{158}. Studies among adults on second-
line ART confirm that failure is driven mainly by non-adherence and not by PI resistance. Nevertheless, if adherence is suboptimal over longer periods of time, PI mutations will eventually develop\textsuperscript{134,170,171}.

One of the major strengths of this study is the fact that this is the largest analysis of paediatric outcomes on second-line ART in LMIC to date, combining data from both Asia and sub-Saharan Africa. Our results confirm the findings of previous smaller studies, showing that failure rates are relatively favourable for children, but worryingly high for adolescents. Our study also has some potential limitations. First, this was a multicentre analysis in which treatment protocols differed by study site. By definition, a child could only be classified as experiencing failure when a VL result was available, suggesting that a child with more VL results had more chance to be classified as experiencing virologic failure. To correct for this, we stratified our Cox model for different number of VL measurements per child. Second, some potentially relevant variables were not included in our analysis such as adherence, HIVDR, and clinical status, because not all studies had collected these data, or because data were too heterogeneous to include. Finally, our study concerns children on second-line PI-based ART after failure of an NNRTI-based first-line regimen, which is not the recommended ART sequence for young children anymore. However, since PI-based first-line treatment has not yet been widely implemented in LMIC, and given that many children are only diagnosed with HIV after the age of 3 years, our data are applicable to the large number of HIV-infected children who will still receive NNRTI-based first-line ART.

**CONCLUSIONS**

In conclusion, this multicentre analysis shows that treatment outcomes of children on second-line PI-based ART are encouraging with 16% experiencing virologic failure in the first two years. Data on second-line treatment outcomes after failure of a PI-based regimen are hardly available and therefore urgently needed. The poor outcomes of adolescents compared to younger children underscore the difficulties of adolescent HIV care and call for increased attention for this vulnerable population as they transition into adulthood.

**Competing interests**

None to declare
Acknowledgments

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Authors’ contributions

RSB conducted the literature review, contacted study groups, collected all patient-level data, conducted the analyses, and wrote the first draft of the paper. TFRdW, JCJC and KCES supervised the reviewing and analysis process. TB, DD, JF, AK, DL, CK, VM, PP, AS, SS, and BZ are the coordinating researchers of the study cohorts included in the analysis. All authors participated in discussion of the results of the analysis and in writing of the final paper.