Prevention, suppression, and resistance

Antiretroviral treatment for children with HIV in sub-Saharan Africa

Boerma, R.S.

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Discussion and future perspectives
Since the beginning of this millennium, access to antiretroviral treatment (ART) for children living with HIV has increased exponentially. Currently, more than 800,000 children are on ART representing about half of all HIV-infected children worldwide, compared to only 18,000 in the year 2000\textsuperscript{6,10}. Now that access to ART for children is improving, it is becoming increasingly important also to evaluate the quality of the care provided. The limited availability of antiretroviral drugs for pediatric use, difficulties with accurate pediatric drug dosing, and poor treatment adherence are among the most important obstacles for effective long-term pediatric HIV treatment in resource-limited settings. Furthermore, the development of HIV drug resistance is an increasing threat to HIV treatment in general and is especially prevalent in children. Providing good quality care for children living with HIV does not only prevent morbidity and mortality for the individual child but also contributes to the health and wellbeing of a generation of perinatally infected children growing up to be young adults. The aim of this thesis is to give informed recommendations for sustainable antiretroviral treatment for children living with HIV in low- and middle-income countries (LMIC) while taking into account the additional challenges of pediatric HIV treatment.

**SUMMARY**

**Part I: prevention of mother-to-child transmission**

In Chapter 2 we study the risk factors for mortality among HIV-exposed infants who were part of a prevention of mother-to-child transmission (PMTCT) program in Cameroon. In this study, conducted from 2004 to 2012, 44 out of 285 children (15.4\%) died in the first 18 months of life. Children who were prematurely born, received both formula feeding and breastfeeding (mixed feeding), and whose HIV-infected mothers did not take antiretroviral drugs for PMTCT had a higher risk of dying. In most children who died, it was not possible to establish if they were HIV-infected or not because HIV PCR testing— which is needed to diagnose HIV in children <18 months of age— was not widely available.

Since the beginning of this study in 2004, significant improvements have been made in HIV prevention and treatment efforts in LMIC. The number of children acquiring HIV through mother-to-child transmission has been reduced by more than half, from approximately 500,000 children per year in 2004 to 220,000 in 2014. Single-dose nevirapine, frequently used for PMTCT in our study, has been phased out, and option B plus (lifelong ART for HIV-infected pregnant women plus a short course of nevirapine or zidovudine for
infants) is now the preferred PMTCT approach\textsuperscript{6}. Moreover, formula feeding for infants of HIV-infected mothers is no longer recommended. Diarrhea-related mortality, due to the unsanitary preparation of formula milk, outweighs the risk of HIV transmission by breastfeeding, which is low when the mother is on ART\textsuperscript{19–21}. Finally, early infant diagnosis has improved and access to ART has increased for HIV-infected infants. These observations show how quickly and radically HIV guidelines have changed over the past decade, and how the accelerated global HIV response has led to improved prevention and better treatment outcomes.

In \textbf{Chapter 3} we show the consequences of prior exposure to PMTCT for the development of HIV drug resistance among children in a systematic review of the literature, summarizing the prevalence of pre-treatment HIV drug resistance (PDR) in sub-Saharan Africa. In children who had prior exposure to PMTCT, 43% had at least one drug resistance mutation before first-line ART initiation. Most of the detected drug resistance mutations conferred resistance towards non-nucleoside reverse transcriptase inhibitors (NNRTI). The prevalence of PDR was almost four times higher in children who were exposed to PMTCT (which usually contains an NNRTI), compared to those without prior PMTCT exposure. However, including in unexposed children, the pooled proportion of children with PDR was >15%. We found that this prevalence has increased over time, as the highest prevalence was reported in the most recently conducted studies. Since 2013, the World Health Organization (WHO) no longer recommends NNRTI-based first-line ART for young children, instead, recommends the use of a protease inhibitor (PI)\textsuperscript{20}. However, in many resource-constrained settings, children are still started on NNRTI-based first-line treatment because PIs are less widely available, more expensive, and require refrigeration. The results of our systematic review further stress the importance of implementing PI-based treatment as a first-line regimen for all children under three years of age, although substantial financial and logistic barriers need to be overcome.

\textbf{Part II: first-line antiretroviral treatment}

In \textbf{Chapter 4} and \textbf{Chapter 5}, we report on two cohort studies of children initiating first-line ART in west and eastern Africa between 2010 and 2013. In \textbf{Chapter 4} we describe a cohort of 90 children, all unexposed to PMTCT, initiating first-line ART in Lagos, Nigeria. One in six children in this cohort had drug resistance mutations before treatment initiation, conferring resistance to both NNRTIs and nucleoside reverse transcriptase inhibitors (NRTI). Almost 60% of children with PDR failed first-line ART within 24 months. The presence of PDR was the strongest predictor of failure- increasing the odds of failure by
more than 7. In **Chapter 5**, we report the outcomes of a cohort of 289 children initiating first-line ART in Uganda. Similar to our cohort in Nigeria, the presence of PDR was the most important predictor of treatment failure after 24 months of follow-up. The presence of PDR was also associated with the accumulation of additional drug resistance mutations during first-line treatment. In both MARCH cohorts in Nigeria and Uganda, 32-33% of all children failed their first-line treatment. Therefore, this implies that within two years one-third of children starting first-line ART will need to switch to a second-line regimen, which is more expensive and less widely available.

In **Chapter 6**, we conduct a systematic review and meta-analysis to evaluate the proportion of children achieving virological suppression on ART in LMIC. We found that 60% to 75% of children achieved virological suppression in the first two years on first-line ART, which is considerably lower than the rates found in adults in LMIC or children in high-income countries. Data on long-term virological outcomes beyond two years were very scarce, indicating that this is an area in need of urgent research attention. The results of this systematic review confirm the additional challenges of pediatric HIV treatment compared to adult treatment and show that increased efforts are a pressing need to reach the target of 90% virological suppression among children in LMIC.

**Part III: second-line antiretroviral treatment**

In **Chapter 7** we study a cohort of children in Uganda who have failed first-line treatment and start a second-line regimen containing a PI. Of these children, 20% failed second-line treatment within two years after the switch. This failure rate is lower than the failure rate in Ugandan children on first-line ART, as described in **Chapter 6**, of whom one-third experienced virological failure. This difference might be due to the higher potency and higher genetic barrier of PI-treatment compared to NNRTI-based ART. None of the children developed resistance towards PIs in the first two years after switching the treatment. For children who had developed resistance against NRTIs on their first-line regimen, treatment failure was not more prevalent than for children who did not have resistance against NRTIs. Children with poor adherence were more likely to fail treatment compared to those with optimal treatment adherence. These findings are reassuring, as it implicates that these children do not need to be switched to a third-line regimen. The findings also indicate that virological suppression on second-line ART with improved adherence support could be achieved. However, it should be noted that PI resistance will develop in the long term in children who have prolonged exposure to inadequate drug levels as a result of poor adherence (see **Chapter 8**). Adherence support programs, therefore, are key to
providing children with adequate long-term HIV treatment and prevent the development of HIV drug resistance in the long term.

**Chapter 8** describes the rate of virological failure in children on second-line PI-based ART in a multicenter cohort analysis of studies conducted in fourteen countries in Asia and Africa. In general, the rate of virological failure was low compared to the failure rates found in children on first-line ART, as we also found in the Ugandan cohort described in **Chapter 7**. An alarming finding, however, was that adolescents had a three times higher rate of virological failure compared to younger children. This finding aligns with previous studies which have identified adolescents as an exceptionally challenging population for HIV treatment\textsuperscript{122,152,153}.

**Part IV: Epilog**

In **Chapter 9** we provide an overview of the current treatment options for children with HIV in LMIC, and possible regimens to be introduced in the near future. Although PI-based first-line treatment is now recommended by the WHO for all children <3 years, little is known about the outcomes of children who fail first-line PI-based ART and need to be switched to second-line ART. Since 2016, WHO recommends, in this case, a second-line regimen containing either an NNRTI (efavirenz) for children >3 years or an integrase inhibitor (raltegravir) for children <3 years\textsuperscript{29}. However, studies have shown very poor results in children on second-line NNRTI-based ART, which is likely due to the high rate of resistance to NNRTIs, especially in PMTCT exposed children, as shown in **Chapter 3**. Integrase inhibitors are a relatively new and costly class of antiretroviral drugs and are not widely available in LMIC. Although advances in pediatric HIV treatment have been made over the past 15 years, significant challenges still lie ahead.

**FUTURE PERSPECTIVES**

**The state of the pediatric HIV/AIDS response**

Since the year 2000, the global response to fight the HIV/AIDS epidemic has improved dramatically. HIV prevention and treatment made enormous progress; in 2000, 3.1 million people were newly infected with HIV each year, which fell to 2.1 million in 2015. Over the same period, the number of AIDS-related deaths decreased from 2.0 to 1.1 million. The number of people receiving ART worldwide has increased exponentially from less than 700,000 to more than 17 million by the end of 2015\textsuperscript{6,10}. HIV caused the overall life
expectancy of many African countries to drop in the mid-2000’s, but life expectancy is now increasing again to levels found at the start of the HIV epidemic\textsuperscript{6}. Although these advances are reasons for optimism, it must be noted that in children the improvements in HIV prevention and treatment have not been realized on the same scale as in adults.

The pediatric ART coverage has for years been lower than the adult coverage, but this changed in 2015 when 49\% of children versus 46\% of adults were reported to have access to ART\textsuperscript{209}. However, when interpreting this figures, it must be noted that approximately 50\% of children with HIV die before their second birthday if they do not receive ART\textsuperscript{12}. Therefore, the 49\% coverage could be misleading since it does not include a considerable number of children who already died even before ART could have been initiated. Diagnosis of HIV and linkage to care has been proven to be difficult in children in LMIC, as no standard serological test for antibodies can be performed in young children, who still carry maternal antibodies to HIV. Instead, costly and elaborate HIV PCR tests need to be conducted on infants up to the age of 18 months. Consequently, in 2015, only 51\% of children born from an HIV-infected mother in sub-Saharan Africa received an HIV test after birth\textsuperscript{209}. Again, given the high early mortality among HIV-infected infants, this figure does not take into account the large number of children who died before they could be tested for HIV (see Chapter 2). The rate of mother-to-child transmission has decreased substantially over time, but still more than 200,000 children acquire HIV in LMIC each year\textsuperscript{6}. This is especially striking when considering that vertical transmission can be virtually eliminated by using adequate treatment and monitoring of HIV-infected pregnant women- as seen in high-income countries. In contrast to adult infection, pediatric HIV infection is very rare in high-income countries and therefore not of public health concern. This might be one of the reasons pediatric HIV has generally received less research attention and funding compared to adult HIV infection\textsuperscript{31}. Moreover, as efforts to decrease the rate of mother-to-child transmission of HIV worldwide are becoming increasingly successful, the market for pediatric antiretroviral drugs will further shrink, reducing the financial incentive for pharmaceutical companies to invest in pediatric formulations. Initiatives such as the Drugs for Neglected Diseases initiative (DNDi) and the Accelerating Children’s HIV/AIDS Treatment (ACT) initiative will be needed to secure funding for pediatric drug development.

**Better drugs, better access, better treatment**

In this thesis, we assessed the clinical and virological outcomes of children on first- and second-line ART in the context of increasing levels of HIV drug resistance, and evaluated
the implications of the current World Health Organization (WHO) pediatric HIV treatment guidelines. Based on the findings of our studies, we conclude that an integrative approach is needed to improve HIV care for children in sub-Saharan Africa, combining three essential steps: better drugs, better access, and better treatment. Developing more potent drugs and adopting the recommended treatment guidelines is the first step towards improving pediatric HIV care. However, we have seen that although WHO has recommended first-line PI-based ART for young children since 2013, many LMIC fail to implement these guidelines because the availability of PIs is still limited and costs are high. Therefore, increasing access to antiretroviral drugs in LMIC is the second essential step. Finally, having accessible drugs to children at the clinic does not equal adequate medical adherence. Better treatment indicates not only providing a child with the drugs he/she needs, but also taking into account a child’s age-specific physical and social circumstances which are key to successful antiretroviral treatment.

Better drugs

**PI-based first-line ART for children aged >3 years**

In Chapter 3 we show that the prevalence of PDR towards NNRTIs is alarmingly high in young children, but also in children >3 years of age. Therefore, we recommend to consider the use of PI-based first-line ART for older children as well. Two previously conducted trials did not find superior outcomes of PI-based ART versus NNRTI-based first-line ART in children >3 years of age, however, these studies were carried out in a context with much lower PDR prevalence\textsuperscript{210,211}. Given the increasing PDR prevalence amongst children, as we showed in Chapter 3, we predict a further increase in the need for PIs as first-line regimen. Initiating new trials, comparing PI-based versus NNRTI-based first-line regimens for this age group, should be considered.

**Improved second-line options after failure of first-line PI-based ART**

Applying the WHO guidelines, more children will be started on first-line PI-based ART and, consequently, this will increase the need to evaluate second-line options after failure of a first-line PI-based regimen. In Chapter 8 we found that data on second-line ART, after failure of a first-line PI-based regimen, are very scarce. The few available studies on NNRTI-based second-line ART show alarmingly poor results as we described in Chapter 9. Nevertheless, current WHO guidelines still recommend an NNRTI-based second-line regimen in children >3 years who failed PI-based first-line ART. Given the increasing trend of resistance towards NNRTIs over the past years, as we identified in Chapter 4,
these children are expected to fail NNRTI-based second-line ART soon after switch. Integrase inhibitors are likely to constitute more sustainable options for second-line ART but are currently hardly available in LMIC.

**Better access**

*Increased availability of new pediatric antiretroviral drugs in LMIC*

Integrase inhibitors are a relatively new class of antiretroviral drugs and have several advantages over the drugs which are currently routinely available in LMIC: side effects are generally mild, drug-drug interactions are uncommon, and the genetic barrier (especially for dolutegravir) is high which reduces the risk of HIV drug resistance. WHO currently recommends dolutegravir as an alternative first-line option for adolescents. It has a very high genetic barrier and development of resistance against dolutegravir has not yet been observed in treatment-naïve patients. In addition, it can be taken once a day, which reduces the pill burden. The use of dolutegravir has not been approved yet for children weighing <30kg, although pediatric trials are currently ongoing. Raltegravir is currently recommended by WHO as a second-line option for children failing a first-line PI-based regimen. Raltegravir has been approved for use in children ≥4 weeks of age and is available both as a tablet and as a liquid for use in infants. Disadvantages of raltegravir include the fact that it needs to be taken twice a day and that HIV drug resistance may develop over time. Elvitegravir is the third drug within the integrase inhibitor class but has not been approved yet for pediatric use. Although recommended by WHO as part of first-, second- or third-line regimens, access to integrase inhibitors for children in LMIC is still very limited and usually restricted to research settings. Similarly, the PI darunavir is a recommended component of second- or third-line treatment, but is not available on a large scale. If WHO guidelines are to be followed, these drugs need to become readily available for routine use in LMIC as soon as possible. The Medicine Patent Pool has signed agreements with pharmaceutical companies for the license-free production of the pediatric formulations of these drugs to be sold to an agreed number of LMIC, which is a monumental step.

*Increased efforts to implement PI-based first-line ART for all children <3 years*

Since 2013, WHO has recommended PI-based first-line ART for children aged <3 years. National guidelines of many LMIC, however, still recommend PI-based ART only for children with prior PMTCT exposure, due to the higher costs and logistical barriers to PI-based treatment. The high rates of PDR towards NNRTIs, as we observed in children
before initiating first-line ART (Chapter 3, 5 and 6), and the relatively low rates of virological suppression on current first-line ART (Chapter 4), stress the importance of implementing PI-based first-line ART. The high costs of PIs (ritonavir-boosted lopinavir is about five times more expensive than nevirapine) are one of the major barriers for LMIC to implement current guidelines.

**Better treatment**

*Improved pediatric formulations*

Besides the limited number of antiretroviral drugs approved for use in young children, the correct dosing and administration of these drugs to children is an additional obstacle for better treatment. Ritonavir-boosted lopinavir, recommended as part of first-line ART for children <3 years, is only available as a liquid which needs a cold-chain and has a very unpleasant taste. In addition, parents report difficulties in measuring the correct dose of a liquid and in carrying heavy bottles of liquid formulations from the pharmacy back home. For example, a 10 kg child would need 28 ml of first-line drugs per day, which means parents have to carry 2.5 liters of ART home after each 3-monthly clinic visit. Aside from the latter logistical drawbacks, this may also disclose the child’s HIV status as the large number of bottles taken from the pharmacy are difficult to hide. The introduction of pellets, which are heat-stable and can be sprinkled on food or milk is an important first step in addressing the logistic barriers of ritonavir-boosted lopinavir use. Efforts to mask the unpleasant taste are underway. Furthermore, the Drugs for Neglected Diseases initiative (DNDi) is currently working on a 3-in-1 formulation-combining ritonavir-boosted lopinavir with two NRTIs in one single formulation as first-line treatment for children under the age of three years.

*Specific attention for adolescents living with HIV*

Until recently, most perinatally HIV-infected children died in their first years of life because they did not have access to ART. Therefore, treatment for adolescents with perinatal HIV infection has for long been an understudied topic. Due to the large-scale roll-out of ART in the mid-2000’s, HIV-infected children now survive their childhood and the first generation of perinatally infected children with widespread access to ART now reaches adolescence. In Chapter 8 we found that adolescents on second-line ART have a three times higher risk of virological failure compared to younger children. HIV has been shown to be the number one cause of death among adolescents in sub-Saharan Africa. To ensure HIV-infected adolescents are adherent to treatment and remain in care, clinics
providing healthcare for adolescents should adopt age-specific adherence programs. When implementing interventions to improve adherence among adolescents, areas of attention should include but not be limited to: the important role of peer support and peer pressure in an adolescent’s life; the changing pharmacokinetics in their growing bodies; the increasing responsibility of adolescents taking care of siblings or sick family members; changes in living circumstances when moving away to boarding school or finding a job; and the tendency of this age group to experiment and to engage in high-risk behaviors\textsuperscript{152}.

**CONCLUSIONS**

In this thesis, we have shown that, although major improvements in the global HIV/AIDS response have been made over the past 15 years, advances in prevention and treatment of pediatric HIV infection are still lagging behind. We found that HIV drug resistance among children is a serious problem in sub-Saharan Africa and its prevalence is increasing. Also, children who start ART have much poorer treatment outcomes compared to adults and data on long-term treatment outcomes of these children are largely missing. Adolescents living with HIV constitute a population which has, until now, received very little attention. We show that these adolescents are at high risk of treatment failure and need a specific approach to keep them healthy and alive. In addition, treatment of adolescents with HIV is of major importance from a public health perspective by preventing sexual transmission of HIV.

Development of potent antiretroviral drugs and increasing the availability of these drugs in sub-Saharan Africa alone is not enough to improve HIV care for children. Better treatment also entails providing child-friendly formulations of drugs, implementation of adherence support programs, and provision of age-specific HIV care. Only a combination of better drugs, better access, and better treatment can assure a healthy and productive future for children and adolescents living with HIV in sub-Saharan Africa.