Prevention, suppression, and resistance

Antiretroviral treatment for children with HIV in sub-Saharan Africa

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CHAPTER 1:
General introduction
The first report of the disease which later became known as the Acquired Immunodeficiency Syndrome (AIDS) was in 1981. This article described five previously healthy young men who had been diagnosed with Pneumocystis Carinii pneumonia, an infection only known to occur in severely immune-depressed patients. Soon after this report, more cases were described, initially mostly occurring among homosexual men. The term AIDS was coined in 1982, and the virus responsible for this disease, human immunodeficiency virus (HIV), was discovered shortly thereafter. Although the first official reports of the disease were published only 35 years ago, it has recently been shown that the virus was already present in Kinshasa, Democratic Republic of the Congo in the 1920s. Rapid population growth, changes in sexual behavior and the use of unsterilized medical equipment in this area are likely to have contributed to the spread of this virus which would lead to a pandemic by the end of the 20th century. Initially unjustly described as a disease pertaining to the ‘4Hs’ (homosexuals, hemophiliacs, heroin users, and Haitians), AIDS was diagnosed soon in other populations as well, including children. Worldwide, the number of people diagnosed with AIDS increased rapidly, and Africa became the continent with the highest burden of HIV, with AIDS being the number one cause of death in sub-Saharan Africa. Currently, an estimated 36.7 million people are living with HIV worldwide, of whom 1.8 million are children. Almost ninety percent of these children live in sub-Saharan Africa (Figure 1).

HIV LIFE CYCLE AND ANTIRETROVIRAL DRUGS

HIV is a retrovirus containing single-stranded RNA in its core. Different antiretroviral drugs act on the various steps of the HIV life cycle (Figure 2). To invade a human CD4+ T-cell, HIV uses co-receptors CCR5 or CXCR4 to attach to the cell surface before entering the cell. Entry inhibitors, such as maraviroc, can inhibit this step in the HIV life cycle. When HIV binds to the cell’s surface, the HIV envelope and the cell membrane of the CD4+ cell fuse, allowing HIV to enter the cells. This process is blocked by fusion inhibitors, such as enfuvirtide. Reverse transcriptase is an enzyme used by the virus to transcribe viral RNA into DNA. Nucleoside reverse transcriptase inhibitors (NRTI) inhibit the process of reverse transcriptase by providing NRTI triphosphates to be incorporated into the viral DNA; this disrupts the construction of DNA, thereby stopping the process of reverse transcription. NRTIs were the first class of antiretroviral drugs to be developed, with zidovudine (AZT) being first introduced in 1987. Non-nucleoside reverse transcriptase
inhibitors (NNRTI) bind directly to the reverse transcriptase enzyme to inhibit its function. Many of the first-line antiretroviral treatment (ART) regimens consist of two NRTIs, combined with one NNRTI, such as nevirapine (NVP) or efavirenz (EFV). Integrase is responsible for integrating the viral DNA into the host’s DNA, a process which can be blocked by integrase inhibitors. Integrase inhibitors are a relatively new class of antiretroviral drugs; raltegravir (RAL) was the first drug to be introduced in this class in 2007. After integration of HIV DNA into the host’s DNA, it is transcribed into RNA and then translated to form HIV proteins. Protease is used to cleave protein precursors into smaller particles that are used to assemble new viral particles. Protease inhibitors (PI), such as lopinavir (LPV), block this process of protein cleavage. An overview of antiretroviral drugs and their characteristics is provided in Table 1.

Figure 1. Total number of people and number of children living with HIV worldwide in 2015
Source: UNAIDS
HIV has a very fast replication cycle and creates about 10 billion virions per day. As the virus lacks a proofreading system to check the process of reverse transcription, the replication process is prone to error and mutations occur frequently. Without exposure to antiretroviral drugs, mutant variants of the wild type virus (called quasispecies) only exist in minority populations. However, in the presence of a particular antiretroviral drug, the proportion of variants with a mutation rendering them resistant to this drug may increase because of a survival benefit. The wild-type virus will be suppressed by the drug, while drug-resistant variants continue to replicate and become the majority variant in the body. This type of resistance is called acquired or secondary drug resistance.

People living with HIV can harbor viruses with drug resistance mutations even before they have started ART (pretreatment drug resistance). This can occur when a person gets infected with a virus which already harbors drug resistance mutations (transmitted drug resistance). In children, pretreatment drug resistance can also arise perinatally: HIV-in-
<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Acronym</th>
<th>Age limits</th>
<th>Year of first FDA approval (adults)</th>
<th>Year of first FDA approval (children)</th>
<th>Price/ year*</th>
<th>On WHO list of pediatric essential medicines, formulations available</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>Nevirapine</td>
<td>NVP</td>
<td>≥15 days</td>
<td>1996</td>
<td>1998</td>
<td>26</td>
<td>Oral liquid/ dispersible tablet; FDC with 3TC+d4T or 3TC+AZT</td>
</tr>
<tr>
<td></td>
<td>Efavirenz</td>
<td>EFV</td>
<td>≥3 years</td>
<td>1998</td>
<td>1998</td>
<td>28</td>
<td>Capsule/ tablet</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
<td>RPV</td>
<td>Not approved in children</td>
<td>2011</td>
<td>-</td>
<td>7,700</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>ETR</td>
<td>≥6 years</td>
<td>2008</td>
<td>2012</td>
<td>216</td>
<td>No</td>
</tr>
<tr>
<td>NRTI</td>
<td>Emtricitabine</td>
<td>FTC</td>
<td>All ages</td>
<td>2003</td>
<td>2005</td>
<td>1,314**</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
<td>3TC</td>
<td>All ages</td>
<td>1995</td>
<td>1995</td>
<td>16</td>
<td>Oral liquid/ tablet; FDC with ABC or AZT or NVP+d4T or NVP+AZT</td>
</tr>
<tr>
<td></td>
<td>Zidovudine</td>
<td>AZT</td>
<td>All ages</td>
<td>1987</td>
<td>1990</td>
<td>19</td>
<td>Capsule/ oral liquid; FDC with 3TC+NVP or 3TC</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
<td>ddI</td>
<td>≥2 weeks</td>
<td>1991</td>
<td>1991</td>
<td>93</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
<td>TDF</td>
<td>≥2 years</td>
<td>2001</td>
<td>2012</td>
<td>23</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
<td>d4T</td>
<td>All ages</td>
<td>1994</td>
<td>1996</td>
<td>10</td>
<td>Capsule/ powder for oral liquid; FDC with 3TC+NVP</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
<td>ABC</td>
<td>≥3 months</td>
<td>1998</td>
<td>1998</td>
<td>82</td>
<td>Oral liquid; FDC with 3TC</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Tipranavir</td>
<td>TPR</td>
<td>≥2 years</td>
<td>2005</td>
<td>2008</td>
<td>2,413**</td>
<td>No</td>
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</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Acronym</th>
<th>Age limits</th>
<th>Year of first FDA approval (adults)</th>
<th>Year of first FDA approval (children)</th>
<th>Price/ year*</th>
<th>On WHO list of pediatric essential medicines, formulations available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion inhibitors</td>
<td>Indinavir</td>
<td>IDV</td>
<td>Not approved in children</td>
<td>1996</td>
<td>-</td>
<td>303</td>
<td>No</td>
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<tr>
<td>Entry inhibitors</td>
<td>Saquinavir</td>
<td>SQV</td>
<td>Not approved in children</td>
<td>1995</td>
<td>-</td>
<td>521</td>
<td>No</td>
</tr>
<tr>
<td>Integrase inhibitors</td>
<td>Ritonavir-boosted lopinavir</td>
<td>LPV/r</td>
<td>≥15 days</td>
<td>2000</td>
<td>2000</td>
<td>75</td>
<td>Oral liquid/tablet</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>FPV</td>
<td>≥6 months</td>
<td>2003</td>
<td>2007</td>
<td>900</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Darunavir</td>
<td>DRV</td>
<td>≥3 years</td>
<td>2006</td>
<td>2008</td>
<td>249</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td>Atazanavir</td>
<td>ATV</td>
<td>≥3 months</td>
<td>2003</td>
<td>2008</td>
<td>125</td>
<td>Solid oral dosage</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
<td>NFV</td>
<td>≥2 years</td>
<td>1997</td>
<td>1997</td>
<td>1979</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Enfuvirtide</td>
<td>ENF/T20</td>
<td>≥6 years</td>
<td>2003</td>
<td>2003</td>
<td>22,203**</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Maraviroc</td>
<td>MVC</td>
<td>Not approved in children</td>
<td>2007</td>
<td>-</td>
<td>3,337**</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Raltegravir</td>
<td>RAL</td>
<td>≥4 weeks</td>
<td>2007</td>
<td>2012</td>
<td>491</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir</td>
<td>DTG</td>
<td>≥12 years</td>
<td>2013</td>
<td>2013</td>
<td>1,154**</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir</td>
<td>EVG</td>
<td>Not approved in children</td>
<td>2012</td>
<td>-</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>

FDA: United States Food and Drug Administration; FDC: fixed dose combination; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NR: not reported

* Median price for low- and middle income countries in sub-Saharan Africa, adult formulations
**Prices for low-income countries and/or sub-Saharan Africa not available

Sources:
http://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118951.htm
http://hivinsite.ucsf.edu/InSite?page=ar-drugs
http://apps.who.int/hiv/amds/price/hdd/Default2.aspx
fected pregnant women are advised to take antiretroviral drugs to prevent the transmission of HIV to her child during pregnancy, childbirth or breastfeeding. In addition, the infant receives antiretroviral prophylaxis after birth. These measures are called prevention of mother-to-child transmission or PMTCT. If a child becomes HIV-infected despite PMTCT, it has an increased risk of pre-treatment drug resistance, because of prior exposure to low levels of antiretroviral drugs, either intrauterine, during childbirth or breastfeeding, or as infant prophylaxis.

THE PUBLIC HEALTH APPROACH

In 1987, zidovudine (AZT) was the first antiretroviral drug to become available for the treatment of HIV infection. However, resistance against AZT monotherapy developed rapidly. In 1996, combination antiretroviral therapy was introduced, which made it possible to fully suppress viral replication in the body using a combination of drugs which have an effect on different stages in the HIV life cycle. Despite its success in resource-rich countries at the end of the 20th century, the vast majority of people living with HIV in low- and middle-income countries did not have access to this medication. ART was believed to be too expensive and its use too complicated to be able to implement in low- and middle-income countries. By the beginning of this millennium, it was estimated that 38 million people were living with HIV worldwide, while less than half a million had access to ART.

In 2002, the World Health Organization (WHO) proposed a public health approach to scale-up the provision of ART in low- and middle-income countries. This method entailed standardized treatment protocols and decentralized HIV care, making large-scale HIV treatment possible in resource-limited settings. HIV treatment in the context of a public health approach contains two sequential regimens: a patient starts on a standardized first-line regimen and is switched to a second-line regimen in case of treatment failure. Using this public health approach, combined with a massive increase in funding, the coverage of ART worldwide has increased dramatically over the past 15 years, from less than 700,000 people who had access to ART in the year 2000 to more than 17 million in 2015.
HIV IN CHILDREN

HIV can be transmitted from a mother to her child during pregnancy, during childbirth, or postpartum through breastfeeding. Without any antiretroviral treatment, the overall risk of transmission is 25% to 45%, depending on the duration of breastfeeding\textsuperscript{11}. In the year 2000, it was estimated that more than half a million children were vertically infected with HIV each year. Due to the increased efforts to prevent mother-to-child transmission in low- and middle-income countries, this number was cut by more than half to an estimated 220,000 children in 2014\textsuperscript{6}. In children who are vertically infected with HIV, disease progression is faster than in adults, and without antiretroviral treatment, over 50% will die before the age of two years\textsuperscript{12}.

WHO GUIDELINES ON THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

In western countries, mother-to-child transmission of HIV is very rare, occurring in <1% of HIV-infected pregnant women. This low rate is due to a combination of measures, such as HIV testing in pregnancy, intensive monitoring of ART during pregnancy, elective caesarean sections for women with a detectable viral load at the end of gestation, and the avoidance of breastfeeding\textsuperscript{13}. However, not all of these interventions are feasible in resource-limited settings, and practical solutions suitable for these conditions have not been sought over the past years. In the early 2000s, single dose nevirapine (NVP) given to the mother before labor and to the child postpartum, was recommended by the World Health Organization (WHO) as a simplified option for the prevention of mother-child transmission in resource-limited settings\textsuperscript{14}. However, single-dose NVP was not always successful in preventing HIV transmission and in both mothers and children who received single-dose NVP, the risk of HIV drug resistance was increased\textsuperscript{15,16}.

In 2010, the so-called option A and option B were introduced in the WHO guidelines\textsuperscript{17}. Option A consisted of a short course of AZT for pregnant women during pregnancy, a single dose of NVP plus AZT during labor and a single dose of NVP plus AZT for one week for the infant. Option B consisting of ART (triple therapy) for the mother during pregnancy and breastfeeding, plus daily NVP or AZT up to 6 weeks after birth for the infant. In 2012, the WHO issued a programmatic update, introducing a third option for PMTCT programs. This option B plus recommends all HIV-infected women to start ART as early
as possible during pregnancy and to continue this treatment for life\textsuperscript{18}. The introduction of option B plus was meant to further simplify PMTCT programs, while at the same time preventing mother-to-child transmission in future pregnancies and sexual transmission in sero-discordant couples.

In high-resource settings, HIV-infected pregnant women are recommended not to breastfeed their infants and to use formula feeding instead to avoid HIV transmission. In resource-limited settings, however, it was found that the mortality risk was higher in formula-fed infants compared to breast-fed infants, probably because a lack of clean water and the poor hygienic preparation of formula milk led to diarrhea-related mortality\textsuperscript{19}. In resource-constrained settings, mothers are therefore recommended to give exclusive breastfeeding while taking ART\textsuperscript{20}. Children who receive both breastfeeding and other feeding (mixed feeding) under the age of six months have an increased risk of HIV-infection; mixed feeding should, therefore, be avoided\textsuperscript{20,21}.

WHO GUIDELINES ON PEDIATRIC HIV TREATMENT

Until 2010, all children who were eligible for ART were recommended to start NNRTI-based first-line treatment and to switch to second-line PI-based ART in the case of therapy failure\textsuperscript{22}. However, as it was found that children who were exposed to NNRTIs as part of a PMTCT regimen had a high risk of developing HIV drug resistance mutations towards NNRTIs\textsuperscript{15,16,23}, guidelines were changed in 2010: young children with prior PMTCT exposure were recommended to start a PI-based first-line regimen, while children without PMTCT exposure would still receive NNRTI-based first-line ART\textsuperscript{24}. In 2012, new evidence arose from the P\textsuperscript{1060} trial showing that treatment outcomes were superior in all young children on PI-based treatment, compared to NNRTI-based treatment, regardless of PMTCT exposure\textsuperscript{25,26}. Therefore, since 2013 the WHO treatment guidelines recommend first-line PI-based ART for all children under the age of 3 years\textsuperscript{20}. Many low- and middle-income countries, however, have not yet been able to implement these guidelines. PIs are about five times more expensive than NNRTIs\textsuperscript{27}, and the syrup of the recommended PI, ritonavir-boosted lopinavir (LPV/r), has an unpleasant taste and has to be stored refrigerated\textsuperscript{28}, which is not always feasible in resource-constrained settings.

Children who experience virological failure (defined as two consecutive viral load measurements >1000 copies/ml after at least six months of treatment\textsuperscript{29}) on first-line ART are recommended to switch to a second-line regimen, which consists of a PI with an NRTI
backbone in children who failed an NNRTI-based first-line regimen. In young children who fail a PI-based first-line regimen, the most recent WHO guidelines recommend to switch to a raltegravir-based regimen. Figure 3 shows the treatment sequence for children as recommended by the 2016 WHO treatment guidelines. The WHO guidelines on prevention and treatment of HIV in children over the past 16 years are summarized in Table 2.

![Figure 3. Current WHO recommendations on first- and second-line antiretroviral treatment for children (2016)](image)

- NRTI: nucleoside reverse transcriptase inhibitor; LPV/r: ritonavir-boosted lopinavir; EFV: efavirenz; RAL: raltegravir

**ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS**

Various adverse effects have been associated with the use of antiretroviral drugs. Some toxicities occur early after a child has initiated ART which may be a reason to switch him or her to a different regimen. Other toxicities only develop after years of treatment. These long-term effects are becoming increasingly important now that all people living with HIV are recommended to start ART as soon as possible and to continue treatment for life.
Table 2. WHO guidelines for the prevention and treatment of HIV in children since the beginning of this millennium.

<table>
<thead>
<tr>
<th>Year</th>
<th>PMTCT mother</th>
<th>PMTCT child</th>
<th>First-line ART</th>
<th>Second-line ART</th>
</tr>
</thead>
</table>
| 20004 | Any of the following options:  
- short course AZT  
- short course AZT+3TC  
- single dose NVP | Single dose NVP | | |
| 20029 | No changes | No changes | NNRTI+ 2NRTI | PI+2 NRTI |
| 200431 | Any of the following options:  
- short course AZT  
- short course AZT+3TC  
- single dose NVP  
- AZT from 28 weeks of gestation, single dose NVP during labor | | NNRTI+ 2NRTI | PI+2 NRTI |
| 200633 | Preferred option:  
AZT from 28 weeks of gestation, AZT+3TC+sd-NVP during labor, AZT+3TC for 7 days postpartum | - single dose NVP at birth and AZT for 7 days postpartum | NNRTI+ 2NRTI | PI+2 NRTI |
| 201034 | Option A:  
AZT from 14 weeks gestation; sd-NVP and AZT+3TC intrapartum; AZT+3TC 7 days postpartum  
Option B:  
Triple ART | Option A:  
daily NVP until cessation of breastfeeding; 4-6 weeks for infants on replacement feeding | PMTCT unexposed children <3 years of age:  
NNRTI + 2 NRTI  
PMTCT exposed children <3 years of age:  
LPV/r+2NRTI  
All children ≥3 years:  
NNRTI+2NRTI | After failure of NNRTI-based first-line:  
LPV/r+2 NRTI  
After failure of PI-based first-line:  
NNRTI+2NRTI |
| 201320 | Option B plus:  
Lifelong triple ART for HIV-infected pregnant women | Option B plus:  
4-6 weeks NVP or AZT postpartum | Children <3 years of age:  
LPV/r+2NRTI (regardless of PMTCT exposure)  
Children ≥3 years:  
NNRTI+2NRTI | After failure of NNRTI-based first-line:  
LPV/r+2 NRTI  
Children ≥3 years of age, after failure of PI-based first-line:  
NNRTI+2NRTI  
Children <3 years of age, after failure of PI-based first-line:  
Remain on first-line (LPV/r+2NRTI) and improve adherence |
Some of the most important side effects of antiretroviral drugs include:

- Neuropsychiatric effects, associated with use of efavirenz
- Dyslipidemia, associated with use of stavudine and all protease inhibitors
- Anemia, associated with zidovudine use
- Insulin resistance and diabetes, associated with use of stavudine, zidovudine, didanosine and ritonavir-boosted lopinavir
- Lipodystrophy, associated with use of stavudine, zidovudine, efavirenz and all protease inhibitors
- Peripheral neuropathy, associated with stavudine and didanosine use
- Systemic hypersensitivity reactions, associated with the use of any NNRTI, but especially nevirapine. Moreover, the use of abacavir is contraindicated in patients who are HLA-B*5701 positive, because of the increased risk of a severe hypersensitivity reaction to abacavir.

Children starting ART (and their caregivers) should receive careful instructions how to minimize the side effects, such as taking the medication with food (protease inhibitors) or at bedtime (efavirenz). If side effects are severe, the drug should be replaced with another drug, preferably from the same drug class.
TREATMENT CHALLENGES IN CHILDREN

The ultimate goal of antiretroviral therapy is to achieve virological suppression and immune reconstitution, and to prevent clinical complications and progression to AIDS. Treating children with HIV infection is complicated by several factors, compared to adult HIV treatment. First, fewer antiretroviral drugs are approved for use in children compared to adults, as is shown in Table 1. Therefore, treatment options are limited for children who experience toxicities or treatment failure and need to switch to another regimen. Second, the constant change in pharmacokinetics and body weight in a normally growing child makes accurate dosing difficult. Underweight children who experience catch-up growth when they start ART might remain on a drug dose which is too low for their actual weight, increasing the risk of treatment failure and the development of drug resistance. Third, children who have been perinatally exposed to drugs for PMTCT have an increased risk of developing HIV drug resistance, even before initiating ART. Fourth, young children are dependent on their caregivers, who are often sick themselves, to receive their medication and attend clinic visits, which means they cannot always take their medication on time. Finally, in older children and adolescents, the fear of stigma upon disclosure of their HIV status to their peers plays an important role and might decrease their motivation to adhere to treatment.

Despite these additional challenges, pediatric HIV has generally received less attention and research funding compared to adult infection, which has been reason to consider it as a neglected disease.31 Until recently, infants who were born with HIV in sub-Saharan Africa had little chance to survive. With the large scale roll-out of ART over the past decade, the prospects of children living with HIV on this continent are much better and HIV-infected children now grow up to become adolescents and adults. Therefore, it is becoming increasingly important to study the long-term pediatric outcomes of ART to ensure adequate treatment for children living with HIV, who still have a full life ahead. An emerging threat to long-term HIV treatment in sub-Saharan Africa is the development of HIV drug resistance. The challenges of pediatric HIV treatment as described above all increase the risk of developing HIV drug resistance. Despite this increased risk, very little is known about the prevalence of HIV drug resistance in African children and the consequences for long-term antiretroviral treatment.
AIM OF THIS THESIS

The objectives of this thesis are:

1. to assess the clinical and virological outcomes of HIV-infected children on first-line and second-line ART in sub-Saharan Africa;
2. to estimate levels of HIV drug resistance among HIV-infected children both before and during ART;
3. to evaluate the current ART guidelines in the context of the public health approach.

Based on these findings, we give recommendations for sustainable pediatric HIV treatment to be incorporated in future pediatric ART guidelines for low- and middle-income countries.

THESIS OUTLINE

In this thesis, we follow the different phases of a child living with HIV in sub-Saharan Africa, from birth until adolescence.

Part I describes the earliest phase of HIV infection and discusses the outcomes and the consequences of measures to prevent mother-to-child transmission. Chapter 2 describes a PMTCT program in rural and urban Cameroon, and evaluates the risk factors for mortality among children of HIV-infected mothers participating in this program. Chapter 3 provides an overview of the literature on the prevalence of HIV drug resistance in children in sub-Saharan Africa, who have and have not been previously exposed to PMTCT.

Part II follows children living with HIV who are starting first-line antiretroviral treatment. Chapters 4 and 5 describe the treatment outcomes of a cohort of children in Nigeria and Uganda on first-line ART and the effect of pre-treatment HIV drug resistance on these outcomes. Chapter 6 is a systematic review of the literature and a meta-analysis on the proportion of children who achieve virological suppression after 6 months to 5 years of first-line ART.

Part III describes children who have already failed their first-line regimen and need to switch to second-line ART in order to adequately suppress the virus again. In Chapter 7, we follow a cohort of children who start second-line ART in Uganda. Chapter 8 is a multicenter cohort study in countries in Africa and Asia, in which we evaluate the rate of virological failure in children and adolescents on second-line ART and identify risk factors for virological failure in this population.
To conclude, the epilog of this thesis gives an overview of antiretroviral treatment in children in low- and middle-income countries in the context of a public health approach. In Chapter 9, we evaluate the current state of pediatric ART and possible future treatment options.