Long-term effects of HIV treatment in sub-Saharan Africa: from access to quality
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General introduction
INTRODUCTION

The human immunodeficiency virus (HIV) epidemic remains a major global health burden. In 2014, more than 36.9 [34.3–41.4] million people were living with HIV worldwide [1]. Access to antiretroviral treatment has changed the HIV epidemic drastically. Because of this treatment, HIV-positive people can now live long and healthy lives. An estimated 7.8 million HIV-related deaths were averted between 2000 and 2014 [2]. As of June 2015, an estimated 15.8 million people had accessed to treatment, which is an exponential increase from 200,000 people in 2002 [3]. More than 11 million people access HIV treatment in sub-Saharan Africa, the region that carries the largest HIV-burden. Increasing levels of HIV drug resistance in sub-Saharan Africa could jeopardize the long-term treatment success [4–6]. As HIV treatment programs in sub-Saharan Africa mature, there are rising concerns about the long-term sustainability and quality of these programs.

HIV: the human immunodeficiency virus

HIV is a retrovirus, belonging to the genus *Lentiviridae* which is characterised by a long incubation period (*lentus* = slow). There are two types of HIV: HIV-1, which is most common globally, and HIV-2 which is less pathogenic and mostly found in west-Africa [7]. HIV-1 can be divided in four groups: M, N, O, and P. HIV-1 group M is responsible for the global epidemic, and is the virus generally referred to as simply ‘HIV’. HIV-1 group M can be divided into nine different subtypes: A, B, C, D, E, F, G, H, J and K. These subtypes can also form hybrid viruses, known as circulating recombinant forms (CRFs). For example CRF02_AG is a subtype A/G recombinant, which is circulating widely in West and Central Africa [8,9]. Subtype B is the predominant subtype in Western Europe, Australia and North America. As a result, most HIV research has focused on subtype B, while it is responsible for only 12% of the infections worldwide. In contrast, less is known about other subtypes like A and C, which are frequently found at a global scale and the dominant subtypes found in sub-Saharan Africa [1,10].

HIV is an enveloped virus, enclosing viral enzymes, a capsid and core with two single RNA strands. The viral enzymes are involved in HIV replication: reverse transcriptase, converting RNA to DNA; integrase, integrating the viral DNA into the host DNA; and protease, cleaving the viral proteins (Figure 1). Every HIV virion produces ~100,000,000,000 new virions per day [11]. The replication of HIV through reverse transcriptase is error-prone. With each life cycle, at least one random mutation in the HIV genome occurs. This creates a large pool of different versions of HIV, so
called ‘quasispecies’. The process of continuous viral alteration complicates drug and vaccine development.

HIV can be transmitted from one person to the other through body fluids [12]. The most common ways of transmission are sexual intercourse, needle sharing, using unsterilized medical equipment, occupational exposure (e.g. needlestick injury), or through blood transfusion. Additionally, vertical transmission of HIV from mother to child can occur during pregnancy, delivery and through breastmilk [13].

After infection, HIV replicates within and destroys cells of the human immune system, which are mostly CD4⁺ T-cells, macrophages and dendritic cells. Early HIV-infection is often asymptomatic, or characterised by flu-like symptoms for about a week, often going unnoticed. This is followed by an asymptomatic period of on average 8-10 years [14]. Without treatment, the immune system will deteriorate, leading to the most advanced stage of infection: acquired immunodeficiency syndrome (AIDS). When a person has AIDS, the level of CD4⁺ T cells has become dangerously low and the immune system is no longer able to fight off (opportunistic) infections, eventually leading to death.

**HIV treatment: combination antiretroviral therapy**

HIV was discovered as the cause of AIDS in 1983 [15,16]. In 1987, the first antiretroviral (ARV) drug became available on the market: azidothymidine (AZT), which is a nucleoside reverse transcriptase inhibitor (NRTI). Despite the impressive survival benefit of HIV-positive people taking AZT, the effect was of limited duration as HIV developed resistance against the drug [17]. The new ARVs prescribed as mono- or duo-therapy also lost their effect due to the development of drug resistance.

In 1996, the introduction of highly active antiretroviral therapy (HAART; currently referred to as ART) drastically improved the life-expectancy of HIV-positive people [16]. New drug classes, non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), were developed, each targeting different viral enzymes involved in HIV replication (Figure 1). ART, consisting of a triple-therapy combination of three different ARVs from two different drug classes, was able to suppress HIV replication for a long time with minimum development of drug resistance [16]. After the introduction of NNRTI- and PI-based ART, new ARV drug classes have been developed: integrase inhibitors, fusion/entry inhibitors and maturation inhibitors.
HIV treatment in sub-Saharan Africa: the public health approach

While the year 1996 was a turning point for HIV-positive people living in resource-rich settings, ARVs were not available nor affordable in Africa at that time. By the end of 2001, 40 million people were estimated to be living with HIV worldwide; 25.8 million were living in sub-Saharan Africa. Three million people died of AIDS in that same year [18]. The impact of the epidemic reverted society’s development, as the estimated infection rates continued to rise, and life-expectancy continued to fall. Therefore, the 2001 United Nations General Assembly Special Session on HIV/AIDS called for urgent global action in the ‘Declaration of Commitment on HIV/AIDS’ [19]. At that time, HIV treatment guidelines were directed at resource-rich settings and based on individual patient management. Medical doctors could prescribe every ARV available, and high-end laboratory technology was available to closely monitor treatment response. This personalised approach was not feasible in resource-limited settings such as sub-Saharan Africa, where doctors and laboratory capacity were (and still are) limited. This prompted the development of the ‘public health approach’ to providing HIV treatment by the World Health Organization (WHO) in 2002. [20–29].
Key elements of the public health approach include task-shifting to lower-level health care workers, administration of standard ART regimens and minimal laboratory monitoring [20]. It has allowed the rapid scale-up of access to ART to millions of people, with efficient use of resources. However, the lack of laboratory monitoring within this approach has raised concern that treatment failure could go unnoticed.

![Figure 2. Treatment monitoring.](image)

**Treatment monitoring**

HIV/AIDS disease progression and ART success can be measured through clinical, immunological and viral load monitoring. Clinical monitoring is the assessment of clinical symptoms, and/or opportunistic infections. Immunological monitoring assesses the CD4+ T cell count (in short, CD4 count), which is a measure of immune function. Viral load monitoring comprises the quantification of the HIV RNA load in copies per millilitre plasma. This is a direct measurement of the number of viral copies in the blood. Typically, virological failure is the first sign of treatment failure (Figure 2). When the viral load in the body increases, the immune system suffers the consequences and the CD4 count will decrease, eventually leading to immunological failure. Subsequently, a person will soon suffer new or recurrent clinical event(s), which is defined as clinical failure. The 2002–2015 WHO definitions of treatment failure are summarized in the Table 1 [21–29].

Historically, the public health approach relies on clinical monitoring which allows drug resistance mutations to accumulate before clinical failure is diagnosed (Figure 2).
While viral load monitoring is increasingly being recommended as the preferred ART monitoring tool [21–29], it is often unavailable in resource limited settings, increasing the chance that drug resistance may develop [30].

**Specific issues in children**

Vertical transmission of HIV is preventable, and effective interventions have virtually eliminated new HIV infections in children in resource-rich settings [31]. The prevention of mother-to-child transmission (PMTCT) consists of a collection of measures to prevent perinatal HIV transmission [32]: routine HIV testing for all pregnant women; reduction of the maternal viral load through short-course ARVs or ART during pregnancy and delivery; elective cesarean delivery; and the use of formula feeding or

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**Table 1. Summary of the World Health Organization antiretroviral treatment guidelines for a public health approach.**

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<tr>
<td>Adults</td>
<td>CD4 counts ≤200 cells/mm³</td>
<td>CD4 counts ≤350 cells/mm³</td>
<td>CD4 counts ≤500 cells/mm³</td>
<td>All</td>
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<tr>
<td>Children</td>
<td>All: age-specific CD4 criteria</td>
<td>&lt;2 years old: all; 2.5 years old: ≥750 cells/mm³ or 25%</td>
<td>&lt;5 years old: all</td>
<td>All</td>
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<tr>
<td>Adults</td>
<td>NNRTI + 2NRTI</td>
<td>All</td>
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<tr>
<td>Children</td>
<td>NNRTI + 2NRTI</td>
<td>&lt;3 years old: PI + 2NRTI; ≥3 years old: NNRTI + 2NRTI</td>
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<tr>
<td>Adults</td>
<td>PI + 2NRTI</td>
<td>All</td>
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<td>Children</td>
<td>PI + 2NRTI</td>
<td>Stay on PI + 2NRTI, adherence counselling</td>
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<td>≥3 years old: INI + 2NRTI; ≥3 years old: PI + 2NRTI</td>
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<tr>
<td>Adults</td>
<td>Clinical and immunological monitoring, targeted viral load monitoring if available</td>
<td>All</td>
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<tr>
<td>Children</td>
<td>Routine viral load monitoring</td>
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<td>Clinical</td>
<td>New or recurrent WHO stage 4 condition</td>
<td>All</td>
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<td>Immunological</td>
<td>CD4 below baseline; or 50% fall form peak value; or persistent CD4 &lt;100 cells/mm³</td>
<td>CD4 below baseline; or persistent CD4 &lt;100 cells/mm³</td>
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<tr>
<td>Virological</td>
<td>No recommendation</td>
<td>VL ≥10,000 cps/ml</td>
<td>VL ≥5,000 cps/ml</td>
<td>VL ≥1,000 cps/ml</td>
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INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load; WHO, World Health Organization.
following strict breastfeeding guidelines. For HIV-exposed infants, a short course of ARVs is administered, followed by virological testing for early infant diagnosis. Through PMTCT, the risk of perinatal transmission of HIV can be reduced from 15-45% without intervention, to <2% with optimal PMTCT in resource-rich settings [32–34].

Despite the success of PMTCT, an estimated 2.6 [2.4-2.8] million children were living with HIV globally in 2014, the majority (90%) of whom live in sub-Saharan Africa [1]. Although HIV-infection in children follows a similar pattern as in adults, children face specific challenges. The persistence of maternal antibodies in children under 18 months means a virological diagnostic test (DNA PCR) is required which is not readily available in resource-limited settings. This makes HIV diagnosis in this age group difficult. Without ART, over one-third of children will die before reaching two years of age [35]. Therefore, early HIV diagnosis and immediate ART initiation has been recommended by the WHO since 2010; irrespective of clinical or immunological status (see Table 1) [26–28]. However, in 2015 only an estimated 32% [30-34%] of HIV-infected children have access to treatment, compared to 41% [38-46%] of the adult population [1].

When a child has been diagnosed and is enrolled in HIV care, only limited paediatric ARV drug options and formulations are available [36]. Some children have been exposed to ARVs through PMTCT before initiation of ART, which increases their chances of having already acquired drug resistant HIV strains and in turn, limits their treatment options. The fact that children rapidly change their body weight makes correct dosing challenging, increasing the risk of treatment failure and of developing drug resistance. HIV-infected children also have higher viral loads and faster disease progression compared to adults [37]. Furthermore, children rely on their caregivers for adherence and retention in care [38,39].

![HIV drug resistance](image)

**Figure 3. HIV drug resistance.**
ART, antiretroviral therapy
Drug resistance

HIV drug resistance refers to the ability of HIV to replicate in the presence of drugs that usually suppress its replication [4]. HIV drug resistance can impede the successful suppression of HIV by ART [40]. Several mutations in the viral reverse transcriptase, protease, integrase and envelope have been found to be associated with a poor response to ART [41,42]. Drug resistant HIV can be acquired or transmitted (Figure 3). Acquired drug resistance occurs in HIV-positive people who are taking ARV drugs, for example ART or ARVs for PMTCT. Often in the context of insufficient drug levels, HIV continues residual viral replication and builds up drug-resistant variants through a process of selection and mutation. Transmitted drug resistance occurs when previously uninfected people become newly infected with these drug-resistant viruses. Pretreatment drug resistance refers to drug resistance in those who are about to initiate ART. Several factors lead to the development of HIV drug resistance: viral factors, drug specific factors, patient factors and programmatic factors [4,43]:

1. **Viral factors**

Due to the high replication rate and error-prone transcription by HIV, drug resistant variants are created on a daily basis. Pretreatment drug resistance is associated with increased risk of virological failure, and further development of drug resistance [44,45]. The risk of virological failure and drug resistance development may also vary across HIV subtypes [46,47].

2. **Drug specific factors**

Some ARVs have a higher genetic barrier than others. In drugs with a low genetic barrier (such as NNRTIs), one mutation can be enough to develop drug resistance, compared to drugs with a high genetic barrier (such as PIs), requiring multiple mutations. Also, side effects (nausea, diarrhoea) caused by ARVs can be a reason for poor adherence or malabsorption of the drugs. Furthermore, drug-drug interaction can cause suboptimal ARV drug levels, for example rifampicin for tuberculosis treatment interacts with ARVs [48].

3. **Patient factors**

Suboptimal adherence is one of the main reasons for suboptimal drug levels, which in turn leads to virological failure and the emergence of drug resistance [49]. HIV-associated stigma and fear might negatively affect adherence and retention in care. Adherence and timely clinic attendance are especially challenging for children, who depend on their caregiver [50].
4. **Programmatic factors**

Suboptimal program functioning can increase the risk of drug resistance [51,52]. Drug stock-outs and limited human resources can affect adherence and retention in care. Lack of adequate treatment monitoring in the WHO public health approach can lead to delayed switch practices. Drug resistance mutations will accumulate when treatment failure is diagnosed late and ART regimen switches are delayed; particularly in the absence of viral load monitoring.

**RATIONALE FOR THIS THESIS**

Due to the increased availability of ART for HIV in sub-Saharan Africa, there are rising concerns about the long-term sustainability of these ART programs. Increased levels of pretreatment HIV drug resistance have already been measured in sub-Saharan Africa and jeopardize treatment success [4,5,30,53–57]. This thesis presents data on the long(er)-term effects of HIV treatment in sub-Saharan Africa. We aimed to assess the issues pertinent to the next challenge of large-scale ART programs: access to quality HIV care for adults and children.

The research objectives of this thesis are:
- To assess factors associated with the timing of HIV treatment initiation in children.
- To evaluate the prevalence and predictors of pretreatment HIV drug resistance in children.
- To summarize long-term HIV suppression rates in adults and children on first-line ART in low- and middle-income countries.
- To assess the long(er)-term effects of pretreatment HIV drug resistance on morbidity, mortality and ART regimen switches in adults.
- To assess the remaining HIV drug susceptibility after failing standard first- and second-line ART in adults and children.

**Research setting**

PASER, Pan African Studies to Evaluate Resistance (formerly known as PharmAccess African Studies to Evaluate Resistance) was established in 2006 as a multi-country capacity building and research program, for the assessment and prevention of HIV drug resistance in sub-Saharan Africa. PASER was established in coordination with WHO’s HIV drug resistance prevention strategy and contributes to the WHO Global HIV Drug Resistance Network (HIVResNet), a global network advising WHO on the control and surveillance of HIV drug resistance [59]. While WHO focussed on the public sector, PASER chose to focus on the private sector (profit and not-for-profit)
to complement WHO efforts. The primary PASER objectives were to build capacity in the monitoring and surveillance of HIV drug resistance in Africa, and to disseminate information, perform advocacy and realize policy support (coordinated with WHO HIVResNet). PASER was coordinated by PharmAccess Foundation and the Amsterdam Institute for Global Health and Development.

The PASER network and its sister network TASER in Asia (TREAT Asia Asian Studies to Evaluate Resistance) were part of the bi-regional network called LAASER (Linking Asian and African Societies for an Enhanced Response to HIV/AIDS), with the primary aim to build capacity on the surveillance and monitoring of HIV drug resistance [58].
Over the past several years, the PASER program on African adults has been supplemented with a similar studies on paediatric ART and HIV drug resistance: Monitoring Antiretroviral Resistance in Children (MARCH).

The PASER cohort
The PASER-Monitoring observational cohort enrolled HIV-positive adults in thirteen public and private clinical sites in six countries: Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe (Figure 4). At each site, 240 HIV-positive adults were enrolled when initiating standard first-line ART, or when switched to second-line ART because of presumed first-line treatment failure. A total of ~3000 participants were followed prospectively and received routine HIV care according to national guidelines, which were in line with the WHO HIV treatment guidelines; see Table [21–29].

The MARCH cohort
The aim of MARCH was to strengthen the capacity of HIV drug resistance monitoring in children, and to optimize care and treatment guidelines for paediatric ART programmes in sub-Saharan Africa. The MARCH cohort was a prospective, multi-centre, observational cohort study of 460 HIV-infected children under 12 years of age at clinical sites already participating in the established PASER network (Figure 4). PASER and MARCH were conducted using harmonized study protocols. In 2010, the MARCH cohort enrolled 360 children when initiating first-line ART, or switching to second-line ART at three clinical sites of the Joint Clinical Research Centre in Uganda. At each site in Kampala, Fort Portal and Mbale, 120 children ≤12 years of age were enrolled. In 2012, the MARCH cohort enrolled an additional 100 children initiating first-line ART at the Lagos University Teaching Hospital in Nigeria. All children received routine care according to national guidelines which were in line with WHO guidelines; see Table [21–29].

OUTLINE OF THIS THESIS

Part I of this thesis describes pretreatment challenges of HIV-infected children in sub-Saharan Africa. First, we assess the reasons for late entrance into HIV care, with advanced disease, among children in Uganda (Chapter 2). Next, we assess the prevalence and patterns of pretreatment HIV drug resistance in children from both Uganda (Chapter 3) and Nigeria (Chapter 4). Furthermore, we summarize the published literature on prevalence of pretreatment HIV drug resistance in children in sub-Saharan Africa (Chapter 4).
Part II describes the long-term outcomes of first-line ART. We systematically review the long-term virological suppression rates in HIV-infected children (Chapter 5) and adults (Chapter 6) receiving first-line ART in low- and middle-income countries. Additionally, we assess the effect of pretreatment HIV drug resistance on mortality, progression to AIDS and switches to second-line ART in adults on first-line ART (Chapter 7).

Part III examines the potential future ARV drug options for people who are failing standard first- and second-line ART. First, we describe the remaining drug susceptibility in both adults and children experiencing continued virological failure on first-line ART (Chapter 8). Next, we describe the risk of virological failure on second-line ART and quantify the need for and requirements of third-line ART (Chapter 9).

In the epilogue, we pay tribute to the work of the late Professor Joep Lange (Chapter 10). His efforts were fundamental in enabling access to ART in Africa and Asia, and he was one of the co-initiators of the PASER cohort.
REFERENCES


