HIV-infection in sub-Saharan Africa

From quantity to quality of care

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Chapter 1

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Chapter 1

Human Immunodeficiency Virus (HIV)

In the early 80s a mysterious and deadly disease was reported in the United States of America (1). Men who had sex with men suffered from various and ultimately lethal infections that appeared to be caused by an impaired immune system. Other at-risk groups that were later described included intravenous drug users, donor blood recipients and, lastly, heterosexuals. The disease was named Acquired Immune Deficiency Syndrome (AIDS), due to the clinical presence of a malfunctioning immune system. In 1984, Human Immunodeficiency Virus (HIV) was identified as the virus responsible for AIDS (1). HIV is a retrovirus that disrupts the host immune system by targeting and reducing the CD4-expressing white blood cells that regulate the immune response. Once infected, the host is unable to eliminate HIV, leading to progressive HIV infection, depletion of CD4 cells, immune deficiency and severe (opportunistic) infections from otherwise non-hazardous pathogens, ultimately leading to death.

HIV | The global burden
Since its recognition, the number of HIV infections has increased rapidly and the HIV epidemic has become one of the biggest challenges facing global health (1). So far, over 70 million people worldwide have been infected. Sub-Saharan Africa is the continent with the highest burden of HIV, where AIDS is the number one cause of death (2). Overall, in 2017 an estimated 36.7 million people were living with HIV worldwide, of which 1.8 million were children. Almost 90% of these children live in sub-Saharan Africa (2, 3).

HIV | Anti-Retroviral Treatment
Initially, successful treatments for HIV/AIDS involved drugs that had been developed to treat cancer (4). Azidothymidine, the first anti-retroviral treatment (ART), became available in 1987, and is a Nucleoside Reverse Transcriptase Inhibitor (NRTI). It directly inhibits reverse transcriptase, an enzyme that the HIV-virus uses to transcribe viral RNA into DNA, a crucial step in the replication of the virus. Initially Azidothymidine was given as a single agent, and markedly improved survival of HIV-infected patients. Unfortunately resistance to these treatments developed rapidly, a pattern that repeated each time new NRTI drugs were launched (5). Furthermore,
new drug classes, such as non-Nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) were discovered. It was found that when drugs were given in combinations, the problem of resistance development was partly overcome. The first combination therapies were known as Highly Active Retroviral Therapy (HAART) and later as combined ART (cART). Currently, cART is called ART and includes a combination treatment of three types of ART from two or more different drug classes. Because NNRTIs and PIs act at different steps of the HIV life cycle (figure 1), a combination of these drugs maximally suppresses the replication of the virus.

In the last decade more classes of ART were discovered including integrase inhibitors, fusion inhibitors and CCR5 antagonists. Currently these newer medications are not regularly available in sub-Saharan Africa. Despite these rapid developments and some interesting case reports, HIV can still not be cured as ART only suppresses HIV replication.

Figure 1: The life cycle of the Human Immunodeficiency Virus.
The different mechanisms of antiretroviral medication: X\textsuperscript{1/2} (non) nucleoside reverse transcriptase inhibitors ((N)NRTI), X\textsuperscript{3} protease inhibitors, X\textsuperscript{4} integrase inhibitors, X\textsuperscript{5} entry inhibitors including CCR5 antagonists (x\textsuperscript{5*}), x\textsuperscript{6} fusion inhibitors. Source: Wikipedia.
HIV| The public health approach

Despite the huge success implementing ART in the developed world at the end of the 20th century, the vast majority of HIV-infected people lived in low and middle-income countries (LMIC) and did not have access to the treatments. By the end of 2001, of the estimated 40 million people who were infected with HIV, only 1 million had access to adequate ART (6). Furthermore, HIV treatment guidelines emerging in the developed world required therapeutic and advanced laboratory resources that were not available in LMIC. A public health approach to make ART accessible and available in LMIC was introduced in 2002 (6). It included guaranteed supplies of drugs, minimal laboratory monitoring and standardized and simplified treatment protocols using a decentralized approach, with tasks distributed to all levels of health-workers.

Despite initial concerns about this public health approach, access to ART increased and life expectancy for HIV-infected patients in LMIC improved drastically. In 2014, a decade after the introduction of widespread ART to LMIC, two major programs were developed in addition to optimize the treatment of HIV worldwide. The Joint United Nations Program on HIV/AIDS (UNAIDS) launched “90-90-90” with the aim that by 2020, 90% of all people living with HIV would know their status, 90% of all people with diagnosed HIV infection would receive sustained ART and 90% of all people taking ART would have suppressed viral loads. Mathematical models showed that if these goals were met, HIV transmission could be stopped and AIDS could be eliminated as a public health threat by 2030 (7). In 2016 the World Health Organization introduced the “treat all” policy, which implemented a second major public health change in the global approach to HIV treatment. The “treat all” policy aimed to start ART in all HIV-infected persons regardless of their CD4 count (8). This recommendation was based upon strong evidence that early initiation of ART resulted in better clinical outcomes for people living with HIV, as compared to those whose treatment was delayed (8), further simplifying the decision to start ART. By mid-2018, 84% of LMIC adopted the treat all policy. By the end of 2020, given current commitments, 92% of all LMIC will have adopted the World Health Organization’s “treat all” policy (9).

Despite some early scepticism both concepts proved to be feasible and HIV has changed from a lethal to a treatable disease in the eyes of healthcare professionals in LMIC (9). The number of people receiving ART increased from 1
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million in 2001 to 21.7 million in December 2017, representing 59% of HIV-infected patients worldwide (10).

Challenges

**HIV resistance**
The World Health Organization recently reported a 4-25% prevalence rate of NNRTI resistance among adults retained on ART while rates of 47%-90% were found in unsuppressed HIV-infected patients (14). Urgent action is needed to restrict the increase of HIV drug resistance in the coming decade(s) in order to prolong the current success of ART in LMIC.

HIV creates, as part of its replication, billions of viruses each day, which also generates variations in the genetic structure (mutations) of these new viruses on daily basis. When these mutations occur during replication, whilst being exposed to a particular antiretroviral treatment, drug resistance may develop. The mutated virus may co-exist with the initial virus type (wild type) and may even become the dominant virus type. This may lead to disease progression in the host despite ART and can even infect other sexual partners or children born to HIV-infected mothers. This process is defined as transmitted drug resistance (11).

It is important to recognise factors influencing the development of HIV drug resistance. These factors are commonly subdivided into patient specific and programmatic factors. Patient factors include pre-treatment drug resistance and low adherence to ART (12-14). For children and adolescents, irregular clinical follow-up and HIV-associated stigma can especially compromise compliance. Programmatic issues that result in sub-optimal delivery of HIV care are a realistic threat in LMICs. Factors such as stock-outs of ART and limited human resources have direct and indirect negative impacts on the quality of treatment. HIV drug resistance is a growing global challenge.

**HIV in children**
Over the past decade, the treatment of HIV-infected children has focused on the prevention of mother-to-child transmission (PMTCT) programmes, which has drastically reduced HIV transmission in LMIC (15) and facilitated the early diagnosis
of children who are infected despite PMTCT. Early detection and ART treatment in the first 24 months of life are of importance as they have improved life expectancy to approximately 91% (16). Despite these successes, the long-term outcome of those infected, as an increasing number of children live with HIV in LMIC, remains poor. Suboptimal viral suppression and treatment failure occurs in the first 12 months on ART in as many as one third of children (17-21). Compared to adults infected with HIV, the percentage of children harbouring resistant viral strains of HIV is very high.

The higher prevalence of resistance amongst children, as compared to adults may be explained by several factors. Firstly, children who are infected despite PMTCT have an increased risk of acquiring a drug resistant strain of HIV (19). Secondly, adherence to clinic visits and compliance with treatment may be poor since young children are fully dependent on their caregivers, who are commonly infected themselves or may even have died. Thirdly, paediatric treatment options and paediatric drug formulations are limited. This reduces the choice of alternative treatments in those who experience HIV drug toxicity or resistance (13, 17, 22). Lastly, significant changes in body weight due to malnutrition and catch-up growth during ART, as well normal physiological changes in childhood, cause constant changes in pharmacokinetics, which can result in suboptimal dosing of ART causing treatment failure and an increased risk of developing acquired drug resistant mutations (14).

**Comorbidities**

With the increased availability of ART in LMIC the focus of treatment is shifting from lifesaving to improving quality of life by treatment of comorbidities that negatively affect it. Common problems that occur in HIV-infected persons, especially in LMICs, include malnutrition, chronic diarrhoea and anaemia, amongst others.

**| Comorbidities| Diarrhoea**

Acute diarrhoea is a major cause of death in LMIC, especially in young children if occurring in combination with malnutrition and/or HIV (23). Among children in sub-Saharan Africa, diarrhoea is the second leading cause of death (24). Diarrhoea is defined as the passage of three or more loose/liquid stools per day, or more frequent passage than normal for the individual. In the context of HIV it may more commonly
present as a chronic condition, defined as loose stools lasting for at least 4 weeks (25). In children infected with HIV several opportunistic pathogens can cause chronic diarrhoea, resulting in worsening malnutrition and increased risk of death (26).

The most common causes of diarrhoea in HIV-infected children are opportunistic infections with bacteria, viruses, protozoa, parasites and fungi. Secondary factors include food intolerance, side effects of HIV-related medication, HIV-enteropathy and nutrition deficiencies (25). Co-trimoxazole prophylaxis, prescribed as part of PCP infection prevention, has also been shown to reduce diarrheal illness in HIV–infected patients, possibly by treating bacterial gastrointestinal super-infections, prompting the World Health Organization to recommend co-trimoxazole prophylaxis for HIV-infected patients worldwide (27). Prevalence data on protozoal infections in patients with chronic diarrhoea range widely from 1-75%, and differ in demographics, seasonal variance and diagnostic methods (28, 29). Prevalence rates are higher when tested with sensitive Polymerase Chain Reaction (PCR) techniques in comparison to traditional microscopy (30, 31). However, PCR techniques are not commonly available in resource-limited settings and therefore reliable data from these areas are scarce (32). Interestingly, the prevalence of intestinal protozoa in HIV-infected adults after the introduction of ART has had a documented decreased both in industrialized nations and resource-limited settings (32-35). However, prospective data on children receiving ART treatment is lacking. Longitudinal data is needed in order to clarify which opportunistic infection may resolve through immune reconstitution due to ART alone and which infections might require targeted therapy (32).

Comorbidities | Anaemia
Anaemia is the most common haematological disorder among HIV-infected patients worldwide with an estimated prevalence of 60-95% (36). The World Health Organization defines anaemia as haemoglobin levels below 110-120 g/l depending on age. Severe anaemia is defined as a haemoglobin levels below 70 g/l (37). In sub-Saharan Africa, 60% of HIV-infected adults are anaemic and 22% are severely anaemic (38, 39). Moreover, in these settings, HIV-associated anaemia and severe anaemia are both independently associated with an increased one-year mortality of 8% and 55% respectively (40, 41). Anaemia can present with a wide range of clinical symptoms including fatigue, palpitations, shortness of breath and dizziness.
Fatigue is the most important symptom of anaemia and is strongly associated with a reduction in quality of life (42).

HIV-associated anaemia is typically multifactorial. Aetiologies include direct effect of HIV by apoptosis of bone marrow progenitors, micronutrient deficiencies due to malnutrition, infections, neoplastic disease and side effects of anti-retroviral treatment, such as with Zidovudine and Co-trimoxazole (44-48). Consequently, even in the presence of malaria parasites, the most common cause of severe anaemia in sub-Saharan Africa, additional or alternative causes should be considered (49). Micronutrient deficiencies associated with anaemia in HIV-infected adults include shortages of iron, folate or vitamin B12. Although iron deficiency is common in sub-Saharan Africa and likely contributes to HIV-associated moderate anaemia, its role in the development of severe anaemia is not fully understood. Most of the comprehensive studies suggesting that the role of iron is not as important in HIV-infected patients when compared with non-HIV-infected patients have been performed in children (50, 51). The data on adults is limited and comprehensive clinical data are needed to support the development of evidence-based guidelines for the prevention and treatment of severe anaemia in HIV-infected adults in this setting (52).

This thesis

This thesis | Research setting
The research presented in this thesis is based on clinical studies performed in Malawi and Uganda (figure 2).

This thesis | Research setting | Malawi
Malawi is a densely populated country located in south-east Africa with over 18 million inhabitants, of which half are under the age of 15 (Figure 3). Malawi is one of the poorest countries in the world with 50.7% of the population living in poverty and 25% in extreme poverty (53). HIV is highly prevalent with over one million people infected, of which 10% are below 15 years of age. HIV prevalence among 15-49 year-olds declined from a peak of 16.7% in 1999 to 10.6% in 2016 (54). Since 2005,
HIV treatment has been offered free of charge through the Malawi National AIDS program. In 2018 an estimated 69% of the HIV-infected patients were on ART (55).

The studies presented in this thesis were performed in Queen Elizabeth Central Hospital in Blantyre in collaboration with the College of Medicine Malawi, MLW (Malawi-Liverpool-Wellcome Trust) laboratories, Blantyre and the Global Child Health Group, Emma Children’s Hospital Amsterdam University Medical Centres. The Queen Elizabeth Central Hospital is an academic referral hospital that serves Blantyre district, a (semi-) urban area in the Southern region of Malawi.

**This thesis** | **Research setting** | **Uganda**

Uganda is located in Eastern Africa with a total population of 40 million (2017) of which 55% are below 18 years of age (Figure 2). According to the World Bank’s 2016 poverty assessment, poverty in Uganda between 2006 and 2013 declined rapidly. The population living below the national poverty line declined from 31.1% in 2006
to 19.7% in 2013 (56). In 2016 the total number of people with HIV in Uganda was 1.3 million, which is 6% of the population, reduced from 7.3% in 2011 (57).

The Ugandan study presented in this thesis formed part of the Pan African Studies to Evaluate Resistance (PASER). The PharmAccess Foundation and the Amsterdam Institute for Global Health and Development coordinated this program. PASER was established in 2006 as a multi-country capacity building and research program in collaboration with the World Health Organization Global HIV Drug Resistance Network (HIVResNet), for the assessment and prevention of HIV drug resistance in sub-Saharan Africa (58). The PASER program on African adults has been supplemented with similar paediatric studies: Monitoring Antiretroviral Resistance in Children (MARCH). 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 programs in sub-Saharan Africa (19). The MARCH cohort was a prospective, observational cohort study of HIV-infected children under 12 years of age. In 2010 over 300 children were included in three sites in Uganda (19, 59).

This thesis | Outline of this thesis
This thesis focuses on various aspects of care of HIV-infected children and adults living in Sub-Saharan Africa and aims to gain further insights that will improve HIV treatment and optimize long-term survival in vulnerable patients where resources are limited.

Part I of the thesis focuses on the treatment of HIV-infected children in sub-Saharan Africa, in particular when treatment should be started and how to monitor treatment in a low resource setting. In Chapter 2 we assess alternative diagnostic strategies to identify which HIV-infected Malawian children should qualify for ART, a decision based on regular testing (CD4 and viral load testing). Chapter 3 and 4 present treatment outcomes, including viral failure and the development of drug-resistant mutations, in two cohorts of HIV-infected children in Malawi and Uganda respectively. In addition, in Chapter 4 we focus on treatment failure and the differences between treatment failure during short (< 24 months) and long-term (24-48 months) ART in a cohort of Ugandan children.

Part II of the thesis evaluates common comorbidities of HIV in children and adults living in sub-Saharan Africa. In Chapter 5 we describe the prevalence and clinical relevance of old and new intestinal protozoa in HIV-infected children.
in Malawi using a multiplex real-time PCR platform. In Chapter 6 we describe prevalence of potential aetologies and outcome in HIV-infected adults presenting with severe anaemia (Haemoglobin (Hb) ≤ 70 g/l) in Malawi. Finally, in Chapter 7, we describe the importance of iron deficiency in this population as well as how to diagnose iron deficiency in this specific patient population.

Part III of the thesis is by Chapter 8 and 9 used for an overall summary, considerations, implications and overall conclusion.
Chapter 1

References


Chapter 1


Chapter 1


