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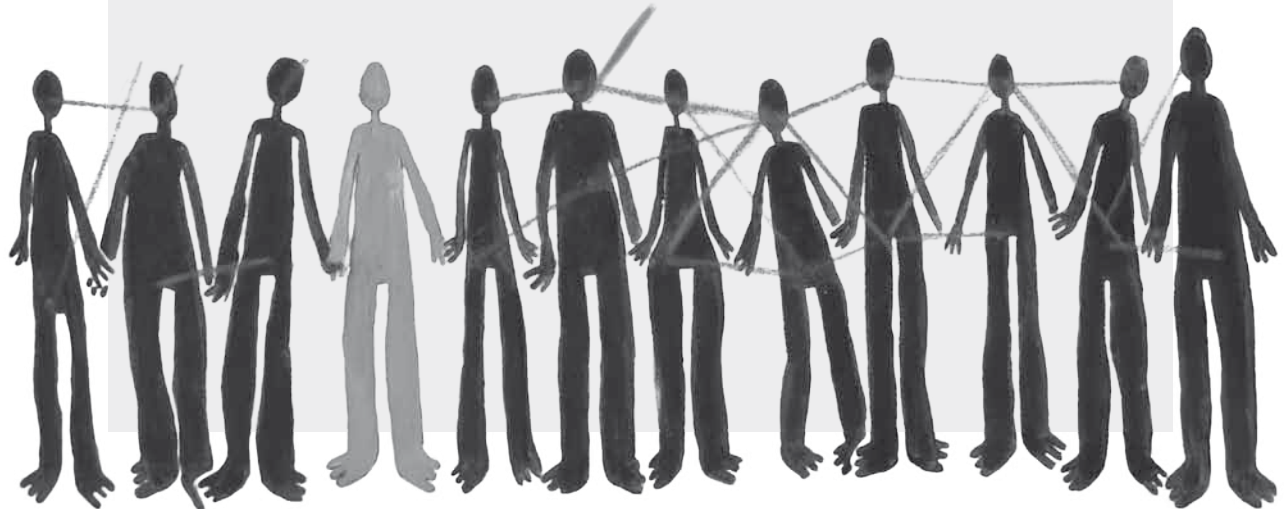
Chapter 1
General introduction



HIV IN SUB-SAHARAN AFRICA

The human immunodeficiency virus (HIV) epidemic remains a major global public health challenge, with a total of 34 million people infected with the virus worldwide.[1] Sub-Saharan Africa bears an inordinate share of the global HIV burden. Although the rate of new HIV infections is decreasing, the total number of people living with HIV in this region continues to rise. In 2010, that number reached 23 million, 68% of the global total.[1] Unlike most areas, the epidemic in Africa disproportionally affects women, and the virus is mainly transmitted during unprotected heterosexual intercourse. This sets the African epidemic apart from other regions where HIV transmission is largely limited to particular risk groups, such as men who have sex with men. With a high prevalence of HIV among women of reproductive age, onward transmission of HIV to newborns and breastfed babies is unfortunately also common in Africa. The estimated total number of children living with HIV is 3.4 million, of which over 90% reside in Africa.[1] Although the overall growth of the epidemic appears to have stabilized, HIV continues to have a profound impact on many aspects of African society. The epidemic has affected millions of households, reversed life expectancy in many countries, overburdened health care systems, and severely hampered productivity and economic development.

VIRAL CHARACTERISTICS

HIV is a retrovirus encasing in its core single-stranded RNA, structural proteins and enzymes. The pol gene of HIV codes for the enzymes reverse transcriptase, integrase and protease. Reverse transcriptase converts the single-stranded RNA of HIV to double-stranded DNA that can be incorporated in the chromosomal DNA of the host. Integrase participates in the insertion of viral genome into the cell genome. Protease breaks down proteins into small pieces for placement into new virions.

HIV has several intrinsic mechanisms that ensure rapid viral evolution. First, the reverse transcriptase of HIV lacks proofreading activity and is therefore error-prone, introducing on average one mutation for each viral genome transcribed.[2] Second, HIV infection is characterized by high viral turnover with a production of approximately 10^{10} virions per day.[3] Third, HIV recombination can lead to further viral diversity and occurs when one person is co-infected with two separate strains of the virus.[4,5] The production of millions of viral variants results in genetically diverse populations of viral species in each infected individual, a phenomenon termed 'quasispecies'.

Phylogenetic analysis of HIV samples has led to the classification of two serotypes: HIV-1, the most common throughout the world, and HIV-2, a less pathogenic variant which is concentrated in West Africa.[6] HIV-1 is further classified into three genetic groups: M (major), O (outlier) and N (non-M, non-O). Over 95% of people throughout the world are infected with HIV-1 belonging to group M, which consists of at least nine subtypes, designated by the letters A–D, F–H, J and K.[7] Advances in full-genome sequencing of HIV have led to the identification of circulating and unique recombinant forms (CRFs and URFs, respectively), which are the result of recombination between subtypes within a dually infected person. The different subtypes and recombinant forms have distinct global distribution patterns, with the highest diversity found in Africa.[8] While subtype B is most predominant in developed countries, the majority of infections worldwide are with the subtype C virus.

NATURAL HISTORY

HIV is transmitted through sexual contact, sharing of injection paraphernalia, transfusion of blood products, or from mother to child during pregnancy, delivery or breastfeeding. HIV targets, infects and replicates in CD4 T lymphocytes and CD4-positive monocytes and macrophages. The subsequent gradual depletion of CD4 T lymphocytes renders the host increasingly susceptible to opportunistic infections and malignancies. Following acute infection, which may be accompanied by a flu-like syndrome, most patients enter a clinically latent phase which may last from several months to more than 15 years. With continued viral replication and progressive decline of CD4 T lymphocytes, the immune system eventually collapses, leading to the acquired immunodeficiency syndrome (AIDS) and death, if untreated.

ANTIRETROVIRAL THERAPY

Since its introduction over 15 years ago, treatment with combination antiretroviral therapy (ART), also referred to as highly active antiretroviral therapy (HAART), has increased the life-expectancy of HIV-infected people. The goal of therapy is to suppress the HIV viral load, allow immunological recovery and prevent the occurrence of opportunistic infections. The classification of HIV medication is based on where in the viral infection or replication cycle the drug acts. Nucleoside reverse transcription inhibitors (NRTIs) were the first drugs approved for the treatment of HIV infection in 1987. In 1996, the non-nucleoside reverse transcription inhibitors (NNRTIs) and protease inhibitors (PIs) were introduced, resulting in major advances when clinicians started treating patients with

potent combinations of three or more drugs. From 2002 onward, an enormous scale-up of access to ART in Africa has been achieved, owing to high-level political commitment and substantial international funding. Today, more than five million HIV-infected Africans are estimated to be receiving ART, impacting nearly 50% of those in need (Figure 1).[1]

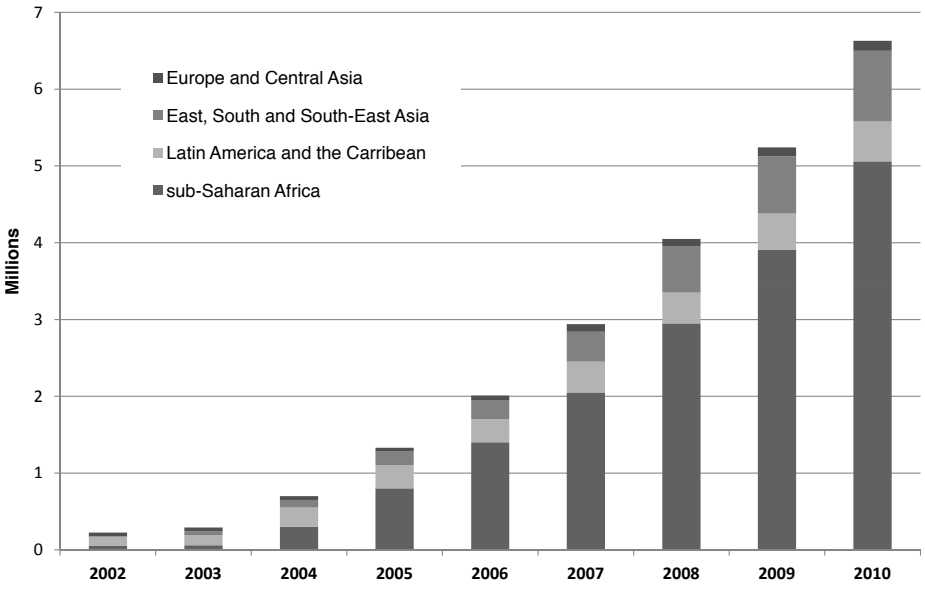


Figure 1. Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002–2010. Adapted from the WHO/UNAIDS/UNICEF progress report 2011.[1]

To support the establishment of treatment programs that reach as many people as possible, the World Health Organization (WHO) has developed a public health approach to ART delivery.[10, 11] This is in contrast to the individualized, specialist care in developed countries, that includes routine plasma viral load monitoring, drug resistance testing and a wide choice of antiretroviral drugs.[12, 13] Low-income countries are encouraged to use simplified treatment guidelines and a decentralized service delivery model. Standard first-line regimens consist of an NNRTI and a dual NRTI backbone, available in some countries as generic fixed-dose combinations. In the absence of routine virological monitoring, the diagnosis of treatment failure is generally based on clinical status and/or CD4 count. In case the decision is made to switch to second-line therapy, recommended regimens combine a ritonavir-boosted PI with two previously unused and/or recycled NRTIs.[11]

As part of the strategy to prevent mother to child transmission of HIV and eliminate pediatric infection, the WHO recommends administrating ART to women who need

treatment for their own health, and a short course of antiretroviral prophylaxis for their infants.[14] Women with higher CD4 counts who do not require treatment for their own health should receive antiretroviral prophylaxis, consisting of mono-, dual- and/or triple-therapy, to reduce transmission during the perinatal period and while breastfeeding.[14] These interventions for the prevention of mother to child transmission (PMTCT) are highly effective if used appropriately.[15, 16] The use of a peripartum single-dose of nevirapine, which is easily administrated to both mother and child but much less effective than longer prophylactic regimens, is no longer recommended. Nevertheless, it is still widely used in resource-limited settings.

Despite the major advances in scaling-up ART, most countries are still far from achieving universal access goals. Obstacles include weak health care infrastructure, a critical shortage of human resources and lack of sustainable, long-term funding. These deficiencies can lead to suboptimal drug prescribing practices, interrupted drug access and high patient attrition rates. Furthermore, treatment monitoring strategies, i.e. viral load measurements, are not routinely integrated in ART delivery programs. All factors mentioned above threaten the long-term success of HIV treatment programs and could create conditions for the accelerated development of HIV resistance to antiretroviral drugs.

HIV DRUG RESISTANCE

In the absence of therapy, the many genetic variants of HIV present in each infected person exist as minor populations only. However, under the selective pressure of antiretroviral drugs, certain variants may have an evolutionary advantage, thus overgrowing the wild-type virus. The speed of this process depends on the level of selective advantage conferred by the mutation, the prevalence of the mutant and the potency of the antiretroviral regimen.[17] In patients receiving antiretroviral drugs, the emergence of viral resistance is possible only if HIV continues to replicate in the presence of drug levels that are insufficient to completely block viral replication but sufficient to exert a selective pressure on variants with decreased drug susceptibility (Figure 2).

In resource-rich settings, patterns of HIV drug resistance to the different classes of antiretroviral drugs have been well documented. Soon after the availability of the NRTI zidovudine, it was noted that mutations in HIV could lead to antiretroviral resistance and failure.[18] Since the advent of combination ART and the availability of potent and well-tolerated regimens, rates of virological failure and antiretroviral resistance in the developed world appear to be falling.[19] However, in patients who have previously been treated with mono-nucleoside and dual-nucleoside therapies, higher rates of resistance

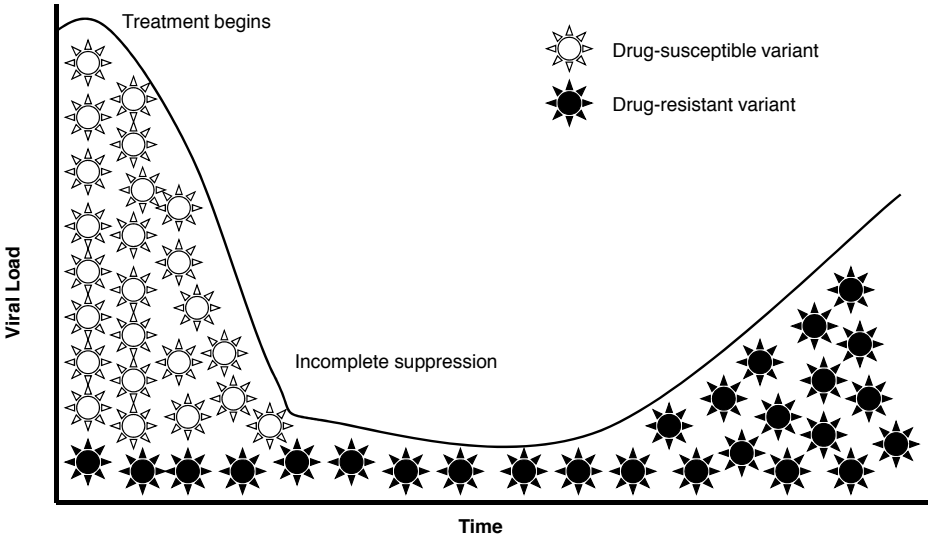


Figure 2. The selection of drug resistant variants.

will persist. HIV drug resistance which has developed in persons receiving ART is called acquired or secondary drug resistance. When drug resistant HIV is subsequently spread to newly infected individuals, this is referred to as transmitted or primary drug resistance.

AIM OF THE THESIS

It has been hypothesized that in resource-limited settings, where few patients have been previously exposed to suboptimal drug regimens, HIV drug resistance is less likely to emerge than in the developed world.[20] However, the weak health systems in many African countries may accelerate the development of resistance due to ART interruptions, poor adherence, lack of viral-load monitoring and limited drug choices.[21-23] Furthermore, the continued widespread use of peripartum single-dose nevirapine, which rapidly selects for resistance, increases the chance of virological failure when followed by NNRTI-based antiretroviral therapy for women and children.[24,25] Lastly, HIV drug resistance has been less well studied in subtypes other than subtype B and controversy remains over whether subtype diversity impacts treatment response due to different patterns of resistance-conferring mutations.[26] The aim of this thesis is to assess the extent and pattern of HIV drug resistance among treatment-naive and treatment-experienced adults and children, and to determine the effect of HIV drug resistance on the response to first- and second-line ART in routine ART programs in sub-Saharan Africa.

RESEARCH SETTING

The PharmAccess African Studies to Evaluate Resistance (PASER) network was established in 2006 as a partnership of clinical sites, laboratories and research groups in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe (Figure 3).[27] PASER, together with its counterpart program TREAT Asia Studies to Evaluate Resistance (TASER) in Asia, constitutes a bi-regional capacity development program called LAASER (Linking African and Asian Societies for an Enhanced Response to HIV/AIDS; http://www.laaser-hivaids.org). From 2006 to 2011, this program was funded by The Netherlands Ministry of Foreign

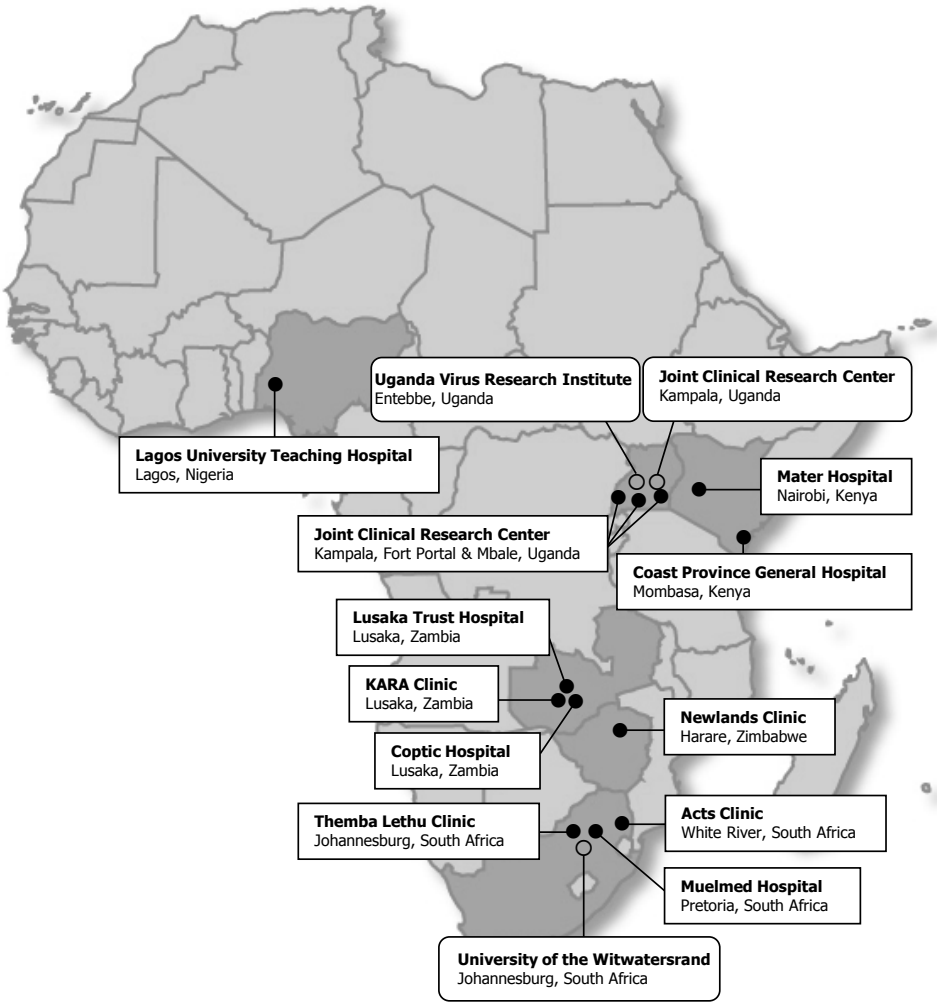


Figure 3. Geographical location of PASER sites. Closed circles represent clinical sites; open circles are reference laboratories. Reproduced from the PASER-M Cohort Profile.[30]

Affairs in partnership with the Aids Fonds. Laboratories providing genotyping results for PASER and TASER participated in the TREAT Asia Quality Assurance Scheme (TAQAS), an assessment program to build genotyping laboratory capacity.[28]

The PASER network is coordinated by the PharmAccess Foundation, a non-profit organization dedicated to the strengthening of health systems and improvement of access to quality basic health care in Africa (http://www.pharmaccess.org), in collaboration with the Amsterdam Institute for Global Health and Development (http://www.aighd.org). The program contributes to the Global HIV Drug Resistance Network (HIVResNet), developed by the WHO.[29] PASER study protocols incorporate the assessment of baseline and acquired drug resistance in adults receiving first- or second-line ART (PASER-Monitoring) and transmitted drug resistance in recently infected individuals (PASER-Surveillance).

The thirteen participating clinical sites represent a variety of clinic types in terms of available resources, administration (public, nongovernmental, private or faith based), and the level of experience with HIV treatment and research, which has been described in the study's cohort profile.[30] PASER developed a number of spin-off projects and studies related to HIV drug resistance. One of these is the MARCH (Monitoring Antiretroviral Resistance in Children) program, a pediatric cohort study in Uganda.

STUDY POPULATION

The PASER-Monitoring observational cohort recruited HIV-1 positive adults who were eligible for the initiation of a first-line ART regimen or switch to second-line ART after first-line failure, in accordance with national guidelines. Patients re-initiating a first-line regimen <30 days after stopping the previous three-drug regimen were excluded; other previous use of antiretroviral medication was allowed. Pregnancy at enrolment and HIV-2 infection (tested in endemic countries only) were additional exclusion criteria. Thirteen clinical sites collaborated on PASER-Monitoring in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe. The site specific target was 240 participants and this was achieved in 12 out of 13 sites, enrolling a total of nearly 3000 participants.

PASER-Surveillance studies were conducted in Kampala and Mombasa in 2009-2010 and recruited newly-diagnosed HIV-1 infected persons who were either below 25 years of age or had laboratory evidence of recent infection (i.e. documented seroconversion in the past 12 months). Exclusion criteria were previous use of antiretroviral drugs, the presence of an AIDS-defining illness and previous pregnancy in females. The target sample size was 85 persons per geographic setting.

The MARCH study, conducted in three sites in Uganda was initiated in 2010. It aimed to enroll HIV-1 positive children who were eligible to start first-line ART or switch to second-line ART. For children initiating a first-line regimen, previous three-drug ART was an exclusion criterion; previous use of antiretroviral drugs for the prevention of mother to child transmission was allowed. The three sites jointly recruited over 360 children.

OUTLINE OF THE THESIS

Part 1 describes the epidemiology of transmitted drug resistance in East-Africa. We conducted two cross-sectional PASER-S surveys in Kampala, Uganda and Mombasa, Kenya (Chapters 2 and 3). Additionally, we used a mathematical model based on data from both PASER-M and PASER-S studies to predict future trends of transmitted drug resistance in the region (Chapter 4).

In Part 2, mutational patterns after first-line ART failure are characterized. In a cross-sectional study, we assessed the diagnostic accuracy of clinical and/or immunological criteria for ART failure as well as drug resistance patterns present at time of switch to second-line ART (Chapter 5). As part of a prospective study, we analyzed mutational patterns detected during routine viral load measurement after 12 months of therapy (Chapter 6). Finally, the rate of mutation accumulation was assessed in patients with prolonged failure and repeated viral load measurements on first-line ART (Chapter 7).

In Part 3 we investigated the effectiveness of ART in preventing HIV drug resistance or suppressing HIV once resistance has emerged. The WHO-defined site-level Early Warning Indicators for HIV drug resistance were assessed and evaluated within the PASER-M network (Chapter 8). The impact of drug resistance mutations on the clinical outcomes of patients receiving either first- or second-line ART were prospectively investigated in Chapters 9 and 10, respectively.

Part 4 is dedicated to pediatric studies. First, we summarized the literature on acquired drug resistance in children after therapy failure in a systematic review (Chapter 11). As part of the MARCH study, mutational patterns in children experiencing first-line ART failure are described (Chapter 12). Lastly, a qualitative investigation was performed evaluating the barriers to access to care for HIV-infected children and their caregivers in Uganda (Chapter 13).

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