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HIV drug resistance among adults and children in sub-Saharan Africa

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SUMMARY

One of the biggest medical advances of the beginning of this century has been the expanded access to treatment for HIV-infected people living in sub-Saharan Africa. This region has been disproportionally hard-hit by the HIV epidemic: 68% of all HIV-infected people (23 million out of the global 34 million) live in Africa. Pressure by activist groups, political commitment and price-negotiations with the pharmaceutical industry have led to the implementation of large-scale treatment programs from 2002 onward, financially supported by international funds such as the 'Global Fund to Fight AIDS, Tuberculosis and Malaria' and the American 'President's Emergency Plan for AIDS Relief'. This has resulted in access to life-saving treatment for approximately 5 million Africans, which is an estimated 50% of those in need of treatment. Keys to this success have been the administration of standard first-line treatment and limited laboratory monitoring. This is called the 'public health approach' and is outlined in guidelines by the World Health Organization.

HIV treatment

HIV, the Human Immunodeficiency Virus, causes AIDS, the Acquired Immune Deficiency Syndrome. HIV infects and destroys specific human blood cells, called CD4 cells, which are crucial to fighting off infections. Without intervention, people with HIV will progress to severe immunodeficiency, AIDS and eventually death, typically within about 10 years. The goal of HIV treatment, also called antiretroviral therapy (ART), is to stop HIV from replicating, allow for recovery of the immune system, and prevent the occurrence of AIDS-related infections. HIV drugs are classified according to where they halt the virus replication cycle. Nucleoside reverse transcription inhibitors (NRTIs) was the first drug class approved for treatment in 1987. However, when treating HIV with just one drug, it soon became apparent that HIV has the ability to change its genetic code by acquiring mutations, thereby enabling the virus to 'escape' from the drug prescribed. This phenomenon is called "HIV drug resistance". In 1996, the drug classes non-nucleoside reverse transcription inhibitors (NNRTIs) and protease inhibitors (PIs) were introduced, resulting in major advances when patients could be treated with potent combinations of three or more drugs. The chance of HIV drug resistance developing in the presence of triple therapy is decreased, but near-perfect patient adherence to medication is required to maintain adequate drug levels in the blood and achieve long-term suppression of the virus. As HIV has a very high replication and mutation rate, there is always a chance of HIV drug resistance development in the long-run.

Antiretroviral resistance in Africa

A potential downside of the large-scale introduction of ART on the African continent is the emergence of HIV drug resistance. This risk is increased by the weak health systems in many African countries, characterized by poor infrastructure, intermittent drug supply, and shortage of skilled staff. As a result, there may not be enough support for patients receiving treatment, and laboratory monitoring is rarely performed. In developed countries, antiretroviral treatment is accompanied by regular measurements of the HIV viral load – which is expected to be suppressed in patients receiving adequate treatment. Before the start of treatment or in the event of suspected treatment failure, an HIV drug resistance test is performed to evaluate the susceptibility of the virus to the drug prescribed. Neither the viral load test nor the HIV drug resistance test is routinely available in Africa, owing to the high costs and technical requirements involved. Furthermore, if therapy fails, alternative treatment (also called second-line treatment) is generally not available or affordable. Therefore, if a patient in Africa does not respond well to the standard first-line therapy or experiences treatment failure, there are very limited means to diagnose the problem or to provide second-line therapy.

Resistance research

The development of resistance in a patient receiving treatment is called "acquired resistance". If the HIV viral load is not suppressed despite treatment (a phenomenon termed "virological failure") the virus can accumulate mutations which work to its benefit. The length of the duration of virological failure is directly related to the development of more complex resistance patterns. The patient is at risk of developing AIDS-related illness again, but may also be able to spread the drug resistant virus to a newly-infected person. The latter is call "transmitted resistance". In order to evaluate the extent of HIV drug resistance in Africa, PharmAccess African Studies to Evaluate Resistance (PASER) was established as a multi-national network in 2006. PASER is coordinated by the PharmAccess Foundation and the Amsterdam Institute for Global Health and Development (AIGHD). It is part of a larger Dutch initiative, called 'Linking African and Asian societies for an enhanced response to HIV/AIDS', the LAASER program. The aim of LAASER is to strengthen the capacity to measure HIV drug resistance within a network of clinical and laboratory sites in Africa and Asia. The collaborating clinical sites conduct observational patient studies and the laboratories have developed quality-assured genotypic HIV drug resistance testing. The health professionals, researchers and laboratory staff involved have received specialized training in HIV treatment and in the implications of HIV drug resistance.

In six African countries - Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe - thirteen clinics participated in a prospective study including approximately 3,000 adults receiving ART who were followed up for at least two years. In this group, the extent of

HIV drug resistance before and after the start of treatment was measured. Additionally, two studies have been conducted among newly-diagnosed HIV-infected persons who had never been exposed to antiretroviral drugs, to evaluate transmitted drug resistance. A spin-off project, the 'Monitoring Antiretroviral Resistance in Children' (MARCH) study was initiated in Uganda and focuses on HIV drug resistance among children, a group for which access to treatment has lagged behind and for which data on drug resistance development is scarce. The studies included in this thesis were conducted as part of the PASER and MARCH programs.

Part 1: Epidemiology of transmitted HIV drug resistance

After the introduction (**chapter 1**), part 1 describes the epidemiology of transmitted HIV drug resistance among newly-diagnosed persons in Kampala, Uganda and Mombasa, Kenya. In Kampala, a study carried out among 70 recently-infected individuals revealed a drug resistance mutation in 9% (**chapter 2**). An identical study in Mombasa found a prevalence of 13% (**chapter 3**). As previous research had shown that transmitted drug resistance was below 5% in African populations, our studies suggest a rise in resistance among the urban populations of Kampala and Mombasa. It is likely that the extent of resistance is related to the length of time since the large-scale introduction of HIV treatment. In **chapter 4**, we used a mathematical model to predict trends in transmitted resistance over the next decade, during which access to ART is expected to be further scaled up. Depending on the number of people for whom ART will be available, transmitted resistance is expected to rise to a level between 12-19% in East Africa. As ART was available in East Africa ahead of other African countries, the findings of increasing HIV drug resistance in this region provide an important warning to the rest of the continent.

Part 2: Acquired HIV drug resistance in persons failing first-line antiretroviral therapy

Part 2 is an examination of patients who fail first-line therapy and become eligible for second-line therapy. In settings in which doctors do not have access to an HIV viral load test, they rely on clinical and/or immunological criteria to diagnose treatment failure. If AIDS-related clinical symptoms are present although the HIV viral load is suppressed, a doctor may inappropriately decide to switch to second-line therapy. In **chapter 5**, we point out that this is a frequent problem, occurring in almost 50% of patients who did not have a viral load test prior to switching to second-line therapy. This unnecessary switch reduces therapeutic options for the patient and increases overall costs. It is, therefore, likely that performing a viral load test in this situation is cost-effective. In the same study, we analyzed resistance mutations among 183 patients in whom the viral load was confirmed to be high. Due to the presence of extensive resistance, the virus had often lost susceptibility to two medication classes, the NRTIs and NNRTIs. This

means that second-line therapy will consist of the third class, the protease inhibitor, as the only active agent. **Chapter 6** is an investigation in more detail of HIV mutations among 142 patients in whom a routine viral load test was conducted after the first 12 months of therapy. The specific mutational patterns were less complex and consequently, susceptibility to the NRTI drug class was better preserved compared to patients in chapter 5. This difference can be explained by the fact that for patients in chapter 6 virological failure was detected "early" during a routine measurement whereas patients in chapter 5 all had AIDS-related clinical symptoms, indicative of prolonged virological failure. The findings from these two studies underscore the fact that routine viral load testing among patients receiving ART can prevent the accumulation of mutations. The speed at which this accumulation can occur was studied in **chapter 7.** Among a small cohort comprising 43 South African patients, repeated resistance testing was performed in patients with a persistently elevated viral load while during treatment. Viruses were found to accumulate mutation to NRTI drugs at an average rate 1 mutation in six-and-a-half months. Future studies should determine the optimal frequency of routine viral load monitoring to prevent HIV drug resistance and ensure the patients remain free of AIDS-related diseases.

Part 3: Outcomes of first- and second-line antiretroviral therapy

In part 3 we investigate the effectiveness of ART in preventing HIV drug resistance or suppressing HIV once resistance has emerged. In response to the rapid scaling up of ART in resource-limited settings, the World Health Organization has formulated Early Warning Indicators, which assess ART site characteristics, such as prescribing practices, patient attrition rates and drug supply continuity, which may be associated with the emergence of HIV drug resistance. Within the PASER network, we evaluated the Early Warning Indicators and identified vulnerable aspects of care (**chapter 8**). Of great concern is the fact that nine out of thirteen sites failed to meet the targeted goal for at least one indicator. In **chapter 9** we examined the response to ART in patients with preexisting HIV drug resistance. In the PASER study, nearly 2600 people started first-line ART, of whom 5% harbored drug resistance to at least one prescribed drug. In these patients, the risk of virological therapy failure and further acquisition of HIV drug resistance after the first year was more than double compared to patients without resistance. This study confirmed the importance of suppressing HIV with three active agents (two NRTIs and one NNRTI) in the first-line. The situation is very different when starting second-line ART after first-line failure. Guidelines recommend that for second-line ART, a protease inhibitor is combined with two NRTIs. In **chapter 10**, we studied the response to second-line ART in 243 patients who harbored substantial NRTI resistance. We found that the protease inhibitor drug class was successful in re-suppressing drug resistant HIV, even though NRTI activity was diminished. These findings bring up the question of whether

the protease inhibitor could be used as a mono-therapy, with the advantage of lower costs, fewer pills, and less NRTI-associated toxicity. Ongoing studies will hopefully be able to answer this question in the coming years.

Part 4: Pediatric studies

Part 4 focuses on pediatric studies. A review of the literature (**chapter 11**) leads to the conclusion that in children with HIV treatment failure complex resistance patterns are present. In Africa, this mainly concerns resistance to the NRTI and NNRTI medication classes. As part of the MARCH pediatric study conducted in Uganda, HIV drug resistance was studied in 50 children failing first-line ART (**chapter 12**). All children harbored drug resistant viruses, and the effectiveness of NRTIs was severely reduced. This is of particular concern in children, for whom the number of licensed HIV drugs is limited. Both the systematic review and the MARCH study in Uganda underscore the fact that second-line drug access must be improved by reducing costs and increasing the availability of new drugs for children. In **chapter 13**, we concentrate on the question of why children enter into care at relatively advanced age and with advanced disease symptoms. Mortality among HIV-infected infants is very high and therefore early diagnosis and immediate treatment are essential. The main risk factors for late entry into care were inconsistent referral from prenatal to pediatric care, high transportation costs to the clinic, caregivers' unawareness of HIV symptoms, fear and stigma. Although HIV drug resistance was not studied in this chapter, those factors influencing the motivation of people to seek health care might also influence the patient's retention in care and treatment adherence once ART is initiated.

Chapter 14 consists of a general discussion and underscores the notion that the prevention of HIV drug resistance requires long-term commitment. In the fight against the global HIV epidemic, prevention of new infections among adults and the elimination of mother-to-child transmission should be the foremost priorities. It is imperative, in addition, that those who are presently infected with HIV have access to life-saving ART. Studies included in this thesis have provided evidence for a gradual rise in HIV drug resistance in sub-Saharan Africa. As drug resistance jeopardizes the effectiveness of ART, we strongly advocate five measures to protect the standard first-line regimens for adults and children. First, African health systems must be strengthened to meet increasing demands. For example, drug supply systems must be improved to prevent treatment interruptions for patients. Second, the introduction of low-cost viral load testing should be implemented for routine monitoring for patients on treatment. This is possible, since recent technological advances have enabled lower test cost and have simplified the storage and shipment of samples. Third, surveillance of resistance should be integrated into national HIV treatment programs. As individual resistance testing is not feasible, studies should focus on representative populations prior to ART initiation. Results from

such surveillance among adults and children will be able to directly inform current ART guidelines. Fourth, ART guidelines should be adapted to the findings of local or regional surveillance efforts. In certain populations or in regions with high drug resistance, prescribing the standard first-line regimen may no longer be useful; instead, the protease inhibitor, usually reserved for second-line treatment, may have to be used immediately. Fifth, these guideline changes are only possible if protease inhibitors, as well as other second-line medicines, are available at cheaper prices. The local production of generic medicines should be strengthened and great pressure should be exerted on the pharmaceutical industry in order to secure price reductions.

In conclusion, lifelong care and effective treatment is required for the millions of HIV-infected Africans who will eventually need it. The goal of making HIV treatment available to more people is currently under pressure due to the decline of donors and resources, and to the loss of political will. Sustained investments are required to allow the scaling up of comprehensive HIV treatment, including strategies to monitor, prevent and treat drug resistant HIV.