Long-term effects of HIV treatment in sub-Saharan Africa: from access to quality
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Summary & General discussion
LONG-TERM EFFECTS OF HIV TREATMENT IN SUB-SAHARAN AFRICA: FROM ACCESS TO QUALITY.

Since the early 2000s, international partnerships, major donor funding, political commitment and community activism have transformed the global HIV/AIDS epidemic [1]. As of June 2015, 15.8 million people had access to antiretroviral therapy (ART), of whom over two-third reside in sub-Saharan Africa [2]. This has led to large reductions in HIV-related morbidity and mortality, and improved national life-expectancy. Furthermore, access to ART has reverted the HIV epidemic and reduced transmission. Increasing numbers of HIV-positive pregnant women receive antiretroviral (ARV) drugs, which protects both themselves against HIV progression and prevents vertical transmission of HIV to their babies. Since 2000, there has been a reduction of 35% in all new HIV infections, with a 58% decrease in new infections among children [3]. At the same time, the epidemic is still ongoing with an estimated 2 million people newly infected with HIV and the death of 1.2 million in 2014 due to AIDS-related disease [3].

The recent international 90-90-90 targets are aiming for continued expansion of access to and lifelong treatment with ART [4]. According to these targets, 90% of all people living with HIV should know their HIV status; 90% of all people with diagnosed HIV infection should receive sustained ART; and 90% of all people receiving ART should have viral suppression, by 2020. If these targets are reached, 73% of all people living with HIV worldwide will achieve suppression. Modelling suggests that if these targets are met by 2020, it will be possible to end the AIDS epidemic by 2030. This will be possible through the prevention of AIDS and onward transmission of HIV as a result of durable HIV suppression. While the global response to the HIV epidemic has been a major effort with promising results, the job is certainly not yet complete. Scale-up must continue and new challenges lie ahead to secure long-term HIV treatment success in all steps of the cascade of HIV care. Without scale-up, the HIV/AIDS epidemic will continue to outrun the response, increasing the long-term need for HIV treatment and increasing future costs [5].

One of the challenges of long term ART success is durable viral suppression, in the context of increasing HIV drug resistance in sub-Saharan Africa [6]. The studies presented in this thesis evaluate the effect of HIV treatment programmes and the emergence of HIV drug resistance in adults and children, in sub-Saharan Africa. First, we described pretreatment challenges for HIV-infected children in sub-Saharan Africa. Second, we described the long-term virological suppression rates in HIV-infected children and adults receiving first-line ART in low- and middle-income countries. Third, we described the future ARV drug options for people who are failing standard
first- and second-line ART. This chapter provides a summary and general discussion of the study findings, followed by future perspectives.

Part I - Starting HIV treatment: pretreatment challenges

Chapter 1 provides a general introduction of this thesis. In Chapter 2, we studied the barriers to ART initiation for 306 HIV-infected children aged ≤12 years, in three clinics in Uganda. We found that the children reported very late for treatment: 72% of the children were diagnosed with advanced HIV disease at ART initiation (i.e. WHO clinical stage 3 or 4). The risk factors for late presentation were: being younger than two years of age, living without parents, caregiver unemployment, lack of prevention of mother-to-child transmission (PMTCT) services, and high transportation costs to the clinic. We confirmed these risk factors through interviews with both health workers and caregivers of children attending the clinics. In addition, these interviews revealed that inconsistent referral from perinatal care, caregivers’ lack of awareness of HIV symptoms, fear and stigma also contributed to late presentation.

It is important to start ART early, especially in children. To improve access to (paediatric) HIV care, there is a need for better psychosocial support for mothers, community and orphanage outreach programs, and linkage of antenatal care systems to ART providers. Our study added insight into the challenges of identifying HIV-infected infants directly after birth and recruiting them into care. Knowledge of these factors and their potential solutions is important to help health workers and ART program planners to create interventions that reach HIV-infected infants as early as possible. This will in turn avoid preventable child morbidity and mortality [7]. Children are not only at higher risk when HIV-infected, they are also taking longer to get diagnosed and require special attention to reach the first 90-90-90 target (90% of all people living with HIV knowing their status). In addition, an improvement in HIV diagnosis in children could also increase the number of HIV diagnosis in adults (the mother and father), preventing future infant infections.

In Chapter 3 and 4, we assessed the prevalence of HIV drug resistance mutations (DRMs) before first-line ART initiation among children in Uganda and Nigeria. In the same cohort of children in Uganda as described in chapter 2, we found that 28 out of 279 (10%) children initiating first-line ART had DRMs (Chapter 3). Previous exposure to ARV drugs for PMTCT was a significant contributor to the presence of DRMs: 8% of ARV-naïve children versus 36% of ARV-exposed children had DRMs. Interestingly, 16% of children with unknown ARV exposure also had DRMs. Further significant risk factors for HIV drug resistance were younger age, maternal ART use and breastfeed-
ing. In **Chapter 4**, we found that 13 out of 82 (16%) ARV-naïve children aged ≤12 years in Lagos, Nigeria initiating first-line ART had DRMs.

To put these findings into context, we systematically reviewed all published literature on the prevalence of DRM in children in sub-Saharan Africa (**Chapter 4**). We included 16 studies, including our own studies, from 11 African countries (2,057 children). In a meta-analysis, we found an overall prevalence of 28% of DRMs among children in sub-Saharan Africa. The prevalence of children harbouring at least one DRM was four times as high in children who received PMTCT: 40% in ARV-exposed children versus 10% in ARV-naïve children, respectively. Among ARV-naïve children, the prevalence has increased over the past decade.

For the survival of HIV-infected children, early identification of HIV infection in infancy and prompt initiation of effective ART is critical [7,8]. Our studies (**Chapter 3 and 4**) indicate that knowledge of ARV-exposure (ie, PMTCT) is not enough to clearly rule-out children at risk of harbouring DRMs. The high and increasing prevalence of HIV drug resistance underlines the need for protease inhibitor (PI) based, rather than non-nucleoside reverse transcriptase (NNRTI) based first-line ART regimens for children in sub-Saharan Africa, irrespective of ARV exposure through PMTCT [9]. Since 2013, the WHO recommends initiation of PI-based first-line ART for children under 3 years of age [10,11]. However, implementation of PI-based ART for children is not always feasible due to the higher costs, and the limited availability of paediatric formulations which require a cold-chain [12,13]. Efforts should focus on making paediatric formulations for PIs available for Africa. Surveillance of pretreatment drug resistance remains essential in the optimization of first-line ART regimen, especially in children.

**Part II - Long-term outcomes of first-line antiretroviral therapy**

In **Chapter 5 and 6**, we systematically reviewed all published literature and conference abstracts reporting on virological outcomes among HIV-positive adults and children on first-line ART, in low- and middle-income countries. We investigated the proportion of adults and children reaching virological suppression from 6 months up to five years after ART initiation. In total, we included 72 paediatric and 165 adult studies in these meta-analyses.

In **Chapter 5**, we found that 70-80% of children on first-line ART in low- and middle-income countries reached virological suppression after 6-24 months. After up to five years, 60-80% remained virologically suppressed, but few studies reported long-term outcomes. When using an intention to treat approach (accounting for children who were lost to follow-up, died, or stopped therapy and assuming that these children
experienced virological failure) suppression rates were much lower, at 45-55% after 6-24 months. To assess the guideline change from NNRTI-based to PI-based first-line ART, we compared children receiving an NNRTI- versus PI-based first-line ART regimen. Our findings indicated that PI-based regimens are favourable compared to NNRTI-based regimen for children in a programmatic setting. Furthermore, virological suppression rates at 6-12 months were significantly better in children without PMTCT exposure.

In Chapter 6, we found high and stable levels of virological suppression (>80%) among adults retained in care during the first five years of first-line ART in low- and middle-income countries. When accounting for adults who were lost to follow-up, died, or stopped therapy and assuming all of them had virological failure, available data suggest that suppression rates declined from 75% to 62% during the first four years of ART. Early virological suppression rates (i.e. after 6-12 months) were significantly higher in Asia compared with sub-Saharan Africa, but differences tended to disappear over time (24-60 months).

In these two large meta-analyses (Chapter 5 and 6), we showed that rates of virological suppression in children were slightly lower (70-80%) than those found in adults (>80%). In general, satisfactory rates of virological suppression are possible in low- and middle income countries. Children remain a vulnerable population, at increased risk for treatment failure. While high (>90%) virological suppression rates have been achieved in children in high-income countries [14,15], this was not the case in low- and middle-income countries. In order to achieve optimal treatment results for HIV-infected children in low- and middle-income countries, practical and affordable paediatric formulations and regimens (i.e. PIs) and improved treatment monitoring is needed. Further research is needed to better describe virological outcomes among adults and children who are lost to follow-up and those who stop therapy, so that these results can be taken into account in future estimates of population-level virological suppression. These retention data are needed to inform a comprehensive benchmark framework, and to assess and monitor program performance, including the 90-90-90-targets [4].

In Chapter 7, we assessed the effect of pretreatment HIV drug resistance on mortality, the development of AIDS and switches to second-line ART in adults on first-line ART in sub-Saharan Africa. We included 2579 adults on NNRTI-based first-line ART with genotypic test results available from Uganda, Nigeria, Zimbabwe, Kenya, Zambia, Zimbabwe and South Africa. Before ART initiation, 14% had DRMs which were mostly NNRTI-associated. Overall, 6% of participants had DRMs associated with reduced
susceptibility to the prescribed regimen (i.e. pretreatment drug resistance). We found that among participants with pretreatment drug resistance, switching to second-line ART was nearly 4-times as common compared to those without. During the first 3 years on ART, pretreatment drug resistance was not associated with the development of new AIDS-related events or excess mortality. We found that at 3-year follow-up, 4% of patients had switched to second-line ART. Of concern, 24% of participant in this study who were switched to second-line ART either had VL < 1000 cps/mL, or VL ≥ 1000 cps/mL without presence of DRMs, which means they could still have benefited from continuing on first-line ART.

This study showed that the presence of pretreatment drug resistance diminishes the long-term effectiveness of first-line ART, and is strongly associated with switching to second-line ART (Chapter 7). The study extends previous findings of the PASER cohort, that pretreatment drug resistance is associated with increased risk of virological failure, reduced CD4 recovery and increased accumulation of additional drug resistance after one year of first-line ART [16]. Increased access and uptake of available viral load testing could avert unnecessary switches to second-line ART. These switches to more costly and toxic second-line ART impair the efficiency in the use of scarce resources available in ART programs. Increased implementation of viral load monitoring and access to affordable second-line ART is urgently needed to secure long-term virological suppression in sub-Saharan Africa.

**Part III - Salvage drug options**

In Chapter 8 and 9, we described the prevalence and patterns of acquired drug resistance and future ARV drug options for people who are failing standard first- and second-line ART. In the setting of limited or absent virological monitoring we were able to investigate the effect of ongoing viral replication on the accumulation rate and patterns of DRMs as well as predict susceptibility of future ARV drug regimens. First, we described the remaining drug susceptibility after continued virological failure on first-line ART in both adults and children (Chapter 8). Next, we described the risk of virological failure on second-line ART in adults and explored the level of PI-resistance after failure (Chapter 9).

In Chapter 8, we evaluated the virological outcomes of 2,737 adults and 289 children on NNRTI-based first-line ART in sub-Saharan Africa. We found that virological failure rates were approximately three times higher in children compared to adults: 24 and 30% versus 9% after 1 and 2 years. We included both adults (N=63) and children (N=56) with continued virological failure and a genotype test result at at least two follow-up points. At first virological failure, ≥1 DRM was detected in 87% of participants: 83%
harboured NNRTI-resistance mutations and 73% harboured NRTI-resistance mutations. While drug susceptibility was already reduced in many participants at first-time failure, the predicted susceptibility declined significantly after continued virological failure for all NNRTIs and NRTIs. Whereas virological failure rates were significantly higher in children compared to adults, we found no significant differences in the patterns and accumulation rate of DRMs.

In Chapter 9, we found that among 227 adults on PI-based second-line ART in sub-Saharan Africa, ≥85% reached virological suppression at any time point during 2-3 years of follow-up. The risk factors for having a detectable VL were non-standard or PI-based first-line ART, PI-resistance at switch and poor adherence. While we found high rates of virological suppression, major PI resistance was detected in 22% of those participants failing second-line ART. After virological failure, most participants retained susceptibility to darunavir (81%), and less than half retained susceptibility to second-generation NNRTIs (etravirine 47%, rilpivirine 31%).

High rates of acquired drug resistance after failure of NNRTI-based first-line treatment were common in both adults and children, requiring second-line PI-based ART. After virological failure on PI-based second-line ART, 1 out of 5 adults required third-line ARV drugs due to acquired PI resistance which are currently unavailable and/or unaffordable in the public sector sub-Saharan Africa. According to our findings, new drug classes (i.e. second-generation PIs and integrase inhibitors) are required to construct fully-active second- and third-line ART regimens for Africa. The role of second-generation NNRTIs in both second- or third-line regimens is expected to be limited. To ensure long-term ART success, intensified adherence support, virological monitoring and third-line drug options are urgently needed.

Epilogue – from AIDS to global health impact

In the epilogue (Chapter 10), we paid a tribute to the late Professor Joep Lange and Jacqueline van Tongeren. We reported on the symposium held on October 14th 2014 at the Academic Medical Center of the University of Amsterdam, titled 'Research in action: from AIDS to global health to impact. A symposium in recognition of the scientific contributions of Professor Joep Lange'. The scientific symposium traced Joep's career, starting in the early eighties with the treatment of the first AIDS patients and the design of ART, moving towards the emerging field of global health and ending with his most recent focus: using knowledge derived from scientific research to improve access to quality health care in real-world settings.
As discussed in this thesis, the future of good quality HIV care is only feasible if it forms part of a high quality sustainable healthcare system in sub-Saharan Africa. Access to care for all, long-term retention in care, continuous annual viral load monitoring and adherence to treatment are important topics for durable HIV treatment programmes. Sustainable healthcare delivery systems and healthcare financing are essential to ensure long-term (HIV) care of high quality in sub-Saharan Africa.

**FUTURE PERSPECTIVES**

**HIV diagnosis and treatment initiation**

Immediate ART initiation after HIV diagnosis is recommended in adults and children, due to both the proven clinical and epidemiological benefits [11]. Therefore, the first two 90-90-90 targets entail increased HIV testing (90% of all people living with HIV should know their HIV status) and prompt ART initiation (90% of all people with diagnosed HIV infection should receive sustained ART) to prevent AIDS and onward HIV transmission [4]. Results from randomized clinical trials have shown that early initiation of ART in asymptomatic individuals with high CD4 counts provides a large clinical benefit, effectively reducing morbidity and mortality [17,18]. Besides the clinical benefit, this ‘test & treat’ approach also simplifies the process of ART initiation, as the moment of treatment initiation no longer depends on a clinical assessment or CD4 count testing. Point-of-care tests for HIV diagnosis are a good and cost-effective tool to improve diagnosis and linkage to care in adults [19,20].

The effects of early treatment initiation on morbidity and mortality are particularly important in young children [7]. However, diagnosis of children through ‘early infant diagnosis programs’ remains challenging [20]. This is due to a high rate of loss to follow up as well as reliance on DNA PCR for children under 18 months of age [21,22]. While 41% [38-46%] of all people living with HIV in sub-Saharan Africa had access to ART, only 30% [28-32%] of children received ART in 2014. The proportion of children living with HIV who receive ART more than doubled from 14% [13–15%] in 2010 to 32% [30–34%] in 2014. Community support, and improved access to and knowledge of early infant diagnosis services are needed to increase paediatric HIV diagnosis and uptake of paediatric HIV services [23–25].

**Antiretroviral therapy in sub-Saharan Africa**

The public health approach has been very successful in the administration of standard NNRTI-based first-line and PI-based second-line ART regimen in resource-limited settings [3,26,27]. Access to affordable first-line NNRTI-based ART has led to major
success in the prevention of HIV-related morbidity and mortality, and will continue to be important to reach the target of providing ART to 90% of all people with an HIV diagnosis. This was confirmed by our studies, which showed that the large majority of adults and children are reaching good levels of virological suppression on first- and second-line ART (Chapter 5 and 6) [28,29].

Since the introduction of ART in 2001, safer and more efficacious ARV drugs are becoming available, and new drug classes are becoming more affordable in resource-limited settings. To ensure the future success of the public health approach for ART in sub-Saharan Africa, it is important to know which ARV drugs are cost-effective. Generic NNRTI-based first-line ART is now available in sub-Saharan Africa for US$115 per person per year. Prices of second-line PI-based ART have also fallen to US$330 per person per year but third-line drug options cost at least $1500 per person per year, and are therefore not affordable for most HIV-positive people in sub-Saharan Africa. While prices of generic ARV drugs have declined by 90% over 15 years’, further price reductions and sustainable healthcare financing are essential for long-term HIV treatment in sub-Saharan Africa [1]. Continued global advocacy and community activism are needed to reduce the price of ARVs and associated healthcare in resource-limited settings [13,30].

Since the end of 2015, the integrase inhibitor dolutegravir is recommended by the WHO as an alternative first-line drug for adults [11]. This follows ART guidelines from resource-rich settings, where integrase inhibitors are increasingly being recommended and implemented because of the favourable toxicity profile, once-daily dosing and high barrier for drug resistance [31–34]. While NNRTI-based ART is much cheaper and effective for most people in sub-Saharan Africa, the introduction of integrase inhibitors could become appropriate in regions with high levels of pretreatment drug resistance. It is not yet concluded however, what level of pretreatment drug resistance should constitute a change in recommended first-line regimen within national guidelines. Mathematical modelling and economic analysis showed that, with increasing levels of transmitted drug resistance, recommending viral load testing 6 months after ART initiation will be preferred over changing to a PI-based first-line regimen [35]. As shown in Chapter 7, timely detection of virological failure on NNRTI-based first-line regimen, followed by prompt switching to second-line, could precede HIV-related morbidity and mortality [29]. This is reflected in current HIV treatment guidelines which recommend access to ART as a priority, followed by access to viral load monitoring [10,11].

While the absolute number of children becoming newly infected with HIV is decreasing because of PMTCT success, infants and children who do get infected have a
high risk of pretreatment drug resistance ([Chapter 3 and 4]) [9,26]. This supports the recommended use of protease-inhibitors (PIs) in first-line regimen for children under 3 years of age. Where feasible, it is recommended to extend the initiation of PI-based first-line ART to children ≥3 years of age [36,37]. The limited availability of paediatric formulations of PIs is of concern. Considering high rates of virological failure in children, next-line regimens (i.e. integrase inhibitors) are urgently needed for children [38].

**Laboratory monitoring**

To monitor the response to ART, viral load testing is the preferred approach to detect and confirm treatment failure [10,11]. Sustainable virological suppression on ART is also the third target of the 90-90-90 targets (90% of all people receiving ART should have viral suppression). Viral load monitoring can also be used as an adherence enhancement tool, leading to viral (re)suppression after targeted adherence counselling [39,40]. Early detection of treatment failure, followed by switching to second-line ART if needed, can enable re-suppression and prevent the accumulation of drug resistance mutations [41].

At current prices of viral load assays and second-line ARV drugs, cost-effectiveness analyses shows that viral load monitoring should be considered only after high ART coverage has been achieved [42]. Viral load monitoring strategies could be improved however and costs should be reduced, for example by means of centralized viral load testing using dried blood spots, which has been found to be a cost-effective strategy to improve treatment monitoring [43,44]. The logistics used for centralized viral load testing could pave the way for drug resistance testing which will become cheaper and therefore more accessible in the future.

The implementation of viral load monitoring requires more than the availability of viral load technology; uptake of viral load test results [45,46]. When viral load testing is available, the turnaround times of viral load results from the lab to the clinician need to be optimized [47]. Logistical challenges need to be overcome to effectively integrate viral load testing within HIV care. Subsequently, uptake of viral load results in clinical decision making can improved, as switching to second-line regimens is currently limited. Availability of affordable second-line and eventually third-line ARV drugs could reduce the reluctance to switch to different regimen.

The scale up of ART is not uniform within each country. The prevalence of transmitted drug resistance varies across geographical regions, and is associated with the year of ART roll-out [6]. National and regional surveys of HIV drug resistance are required...
in both populations starting ART (pretreatment drug resistance) and receiving ART (acquired drug resistance) to inform national guidelines on preferred ART regimen [48–51]. The implementation of prospective surveys has been challenging, especially in areas of concentrated or low prevalence HIV epidemics, and where service delivery is decentralized. Since 2012, the World Health Organization changed strategies moving from prospective surveys to cross-sectional surveys among adults and children initiating ART and among those receiving ART [52]. As international efforts are concentrating more on key populations and locations [2], national representative surveys remain important to benchmark the success of focussed interventions. Personalized genotyping at first- or second-line treatment failure is challenging and underlines the importance of monitoring and surveillance. Only few African laboratories are accredited for genotypic resistance testing and costs are high. After virological failure on second-line PI-based ART, individual genotype resistance testing is recommended to distinguish drug resistance from poor adherence. Like with viral load testing, the rollout of genotype resistance testing requires implementation strategies to yield optimal results in clinical practice.

Challenges for laboratory strengthening are numerous: specimen transport, equipment breakdown, shortage in trained personnel, and weak laboratory information management systems and laboratory infrastructure [53,54]. Improvements to laboratory capacity are vital for HIV treatment and the benefits incurred will extend beyond this specific field. The rising levels of antimicrobial resistance have reached the international security agenda, because of its threat to global health as well as the associated costs [55]. In the long term, national surveillance of pretreatment and acquired HIV drug resistance should be part of systematic global surveillance systems, to track the spread of both infectious diseases and antimicrobial resistance.

**Long-term HIV care**

There is currently no HIV vaccine available and there is no cure [56]. ARVs are a powerful weapon, but also the only weapon against HIV. Therefore, ARVs should be used wisely, to keep the development of drug resistance to a minimum and sensibly target drug resistant HIV with new drugs. The demand for second- and third-line ART will increase as access to viral load monitoring improves and first-line ART continues to be scaled up [57].

ARV drugs are also very effectively used in the prevention of HIV transmission. Successful viral suppression reduces the risk of HIV transmission between serodiscordant couples, and prevention of mother-to-child transmission (PMTCT) during pregnancy, labour and breastfeeding. In order to eliminate HIV/AIDS, we must protect children...
from becoming infected with HIV through optimal use of PMTCT interventions. With increased ART use during pregnancy (PMTCT option B+), the number of HIV-infections among infants is decreasing [26]. Still, 2.3 [2.2-2.5] million children were living with HIV in sub-Saharan Africa in 2015 [26]. Even with continued progress in prevention of mother-to-child transmission, the WHO and UNICEF project that 1.9 million children will require HIV treatment in 2020 [4]. Additionally, ARV drugs can protect HIV-negative people with a high risk of HIV acquisition through pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) [58–60]. Strong adherence to PrEP and periodic HIV testing are required however, to maximize its protective effect and prevent emergence of drug resistance [61]. Future research should evaluate the impact of PrEP on new HIV-infections and drug resistance in a real-life, programmatic setting [62].

Historically, healthcare systems in sub-Saharan Africa have not been designed to provide chronic care. Currently, international HIV treatment targets need to shift from access to ART to long-term, high-quality HIV care. Continued international funding and political commitment remain essential in the HIV response [63]. To optimize HIV diagnosis, direct ART initiation and durable viral suppression, healthcare services need improved referral systems, good patient retention in care, and an efficient clinic-laboratory interface. To combat rising levels of HIV drug resistance, efforts are needed to provide quality HIV care for those failing standard treatment regimen. Prevention of drug resistance development in a proportion of the population will limit overall levels of HIV drug resistance. Laboratory capacity and the availability of affordable second- and third-line drugs for adults and children are needed to achieve long-term virological suppression in sub-Saharan Africa.
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