HIV-infection in sub-Saharan Africa

From quantity to quality of care

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Chapter 9

Considerations, implications and overall conclusion
Considerations and implications

This thesis outlines the different challenges faced in providing care for HIV-infected children and adults living in sub-Saharan Africa, and there are several clinical implications that emerge from these results.

Considerations and implications| HIV-treatment in sub-Saharan Africa

Due to the scaling-up of ART over the last decade, the number of people receiving ART has increased enormously from 1 million in 2001 to 21.7 million, representing 59% of HIV-infected patients worldwide, by December 2017 (1). However, 90% of the USAID 90-90-90 goals for 2020 are still far from being attained. In addition, although survival rates for children affected with HIV have improved drastically, incidence of suboptimal viral suppression and HIV resistance among children are a concern and much more common than in HIV-infected adults living in LMIC. Viral suppression rates for children range from 60-75%, in contrast to 85% for adults (2, 3). Additionally, HIV drug resistance at the start of ART among PMTCT exposed HIV-infected children is 43%, in comparison to 10% for adults (2). This inequity is dangerous and the imbalance in funding between paediatric and adult HIV research is problematic and must be addressed (4, 5). If not, the next generation of HIV patients will be faced with increasing treatment failure and drug resistance.

Considerations and implications | Improved monitoring of treatment

Over the past decade, the emphasis of HIV programs in LMIC has shifted from quantity to quality of care. In addition to adherence support, viral load monitoring has become the backbone of high quality paediatric HIV care. Since 2016, the World Health Organisation has recommended routine viral load testing at 6 and 12 months after ART initiation, and thereafter every 12 months. Our data from Malawi and Uganda support these recommendations. The data presented in chapters 3 and 4 emphasize the need for viral load testing at regular intervals during the first 24 months of treatment, and at least yearly thereafter. Country guidelines should be adjusted. For instance, at the time of writing, according to the current Malawian Guideline of Clinical Management of HIV in children and adults, viral load testing is only done at 6 months, 2 years and every 2 years thereafter. Based on the data that we report from Malawi, we strongly recommend increasing the frequency of viral
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load testing, to at least the World Health Organisation’s recommended frequency, to improve treatment monitoring and to enhance the detection of early treatment failure and (future) resistance (6).

Considerations and implications | Improved antiretroviral treatment

HIV resistance rates in children are high and worrisome. Previously, we reported that pre-treatment drug resistance was around 17% among children in LMIC (7, 8). In this thesis we reported that the rate is now even higher, with a prevalence of acquired NNRTI and/or NRTI resistance of 30% after 48 months of treatment. Because of these resistance patterns, Protease-Inhibitor (PI)-based ART regimens, which are known to reduce early infant mortality and HIV disease progression in non-LMIC settings, are more important in the management of HIV-infected children (9). In line with this, the World Health Organisation now recommends PI-based first-line regimens worldwide, including in LMIC (10). PI-regimens, including one PI and two NRTI’s, have been shown to be effective and robust for adolescents and adults in LMIC (11, 12). Long-term data comparing PI-based versus NNRTI-based regimens for children, especially in LMIC, are sparse, but expected to be good as PMTCT programs do not incorporate PI-based regimens and these regimens are robust (resistance is less likely to be developed after a missed doses) (11, 12). However the feasibility of large-scale implementation of PI-based regimens in LMIC settings remains challenging (13). For example, Lopinavir/Ritonavir (LPV/r; Kaletra) is the most commonly used PI in LMIC. LPV/r is supplied in tablet, capsule (pellet) and liquid form. Treatment with LPV/r has several disadvantages. Firstly, the tablet of LPV/r is 5 times as expensive as the broadly used Nevirapine (an NNRTI) (14). Secondly, liquid paediatric formulations would be most ideal from a dosing perspective as, for example, the concentration of widely available liquid formulations is such that a child would have to ingest a large volume in order to receive an adequate dose of the medication (28 mL per dose for a 10 kg child). A more concentrated form is expensive to make and storage of the medication requires a refrigerator. This leaves the LPV/r capsules as “the best” available option for children. Capsules are opened and the pellets inside are given to children, especially if they are under 3 years of age. However, it is difficult to give pellets to small children on a spoon. In addition, the bioavailability of these pellets is uncertain (13). In conclusion, though...
the recommendation is appropriate, practicalities on the ground make meeting these recommendations challenging.

Because overall drug resistance in HIV is a major problem and second line treatments (PI-based regimens) for children are not optimal, new treatment options are urgently needed. Introduced in 2007, integrase inhibitors are relatively new to the market and therefore research on effectiveness, especially in children in LMIC, is limited. However, integrase inhibitors have several advantages including mild side effects, uncommon drug-to-drug interactions and a high genetic barrier, reducing incidence of drug resistance. The US Food and Drug Administration and European Medical Agency currently approve three integrase inhibitors for children and adolescents who have HIV-1 infection. Raltegravir is approved for children aged 4 weeks to 18 years, while Dolutegravir and Elvitegravir, co-formulated with Cobicistat, Emtricitabine, and Tenofovir Alafenamide (E/C/FTC/TAF), are approved for children from 6 years of age and above 30 kg of weight (15). Studies of integrase inhibitors in children and adolescents, with the exemption of Dolutegravir, are scarce and therefore additional studies investigating the safety and efficacy of these drugs in children are needed (15). Raltegravir is recommended as a second and third-line treatment in LMIC, but is rarely available in LMIC, including in Malawi and Uganda (6). Stakeholders are making efforts to improve availability and cost-effectiveness for integrase inhibitors, especially for Dolutegravir. For example, in Malawi, by 2019 administration of Dolutegravir will be commenced in boys above 30 kg (16, 17). Implementation of integrase inhibitors as a treatment, especially in children in LMIC, will take time.

Finally, as the result of the successful scaling-up of ART, including PMTCT, over the last decade, fewer young children are getting infected with HIV. Increased prevention of mother-to-child transmission will ultimately reduce the need for paediatric antiretroviral drugs and thus limit the financial incentives for pharmaceutical companies to invest in paediatric drug formulations. The children who require ART will become increasingly difficult to treat over time. New trials that compare PI-based and Integrase inhibitor-based regimes in children living in LMIC are therefore urgently needed, alongside efforts to increase drug availability for those most in need.
Considerations and implications | Comorbidity during HIV-infections

With increasing survival rates due to the availability of ART, advances in HIV care will focus more and more on the impact of comorbidities on survival and quality of life. Two major contributors to the comorbidity of HIV-infected patients in LMIC are diarrhoea and (severe) anaemia. Improving care at this level will become increasingly important.

Diarrhoea is a common and important comorbidity of HIV-infected patients, especially with regard to children, where diarrhoea is associated with a high mortality (18). In LMIC, the available investigations do not usually identify specific pathogens. PCR-techniques offer fast and reliable results for the detection gastrointestinal protozoa and can be helpful in the detection of causative pathogens of diarrhoea (19). Novel combined PCR panels are even more efficient since more pathogens can be detected with a single test. Identification of causative agents may lead to specific treatments that could improve acute and chronic diarrhoea and malnutrition, thus impacting morbidity and high mortality rates among children with HIV in LMIC (20, 21). Surprisingly, E. bieneusi was the most prevalent opportunistic intestinal protozoa in our study cohort. It might be clinically relevant, as it was associated with both gastro-intestinal complaints and possible reduced BMI recovery. New PCR results are interesting but additional clinical research is needed to follow-up long-term consequences and possible treatment options in these children.

Severe anaemia in HIV-infected patients in a resource-limited setting, such as Malawi, is a critical condition with high rates of mortality, where various factors may be simultaneously responsible (22). Guidelines for diagnosis and treatment of severe anaemia in HIV-infected adults or children are rarely available in sub-Saharan Africa, including in Uganda and Malawi (22, 23). Based on our results we recommend a more comprehensive approach to the diagnosis of severe anaemia that includes the evaluation of HIV treatment failure, exclusion of TB, identification of renal failure and adequate nutritional support. Iron deficiency has also been identified as a major cause of severe anaemia in this patient population. However, diagnosis of iron deficiency remains difficult in severely anaemic HIV patients in LMIC. Finally, in view of these challenges, we recommend the use of Hepcidin, a hormone involved in the metabolising of iron, for improvement on diagnostics. However more research is needed to confirm this recommendation. Addressing the diagnosis and treatment of severe anaemia among HIV-infected patients is vitally important. Improved diagnosis...
and trials to compare multifactorial treatment protocols may yield impactful results for this vulnerable population.

Overall conclusion

Altogether, this thesis emphasizes the importance of the early initiation of ART, the need for more intensive viral load monitoring and awareness of supportive care among HIV-infected patients in sub-Saharan Africa. Towards more and, above all, improved HIV care in LMIC for both adults and children; “From quantity to quality of care”!
References


