Early Initiation of HAART in Children with HIV Infection and Severe Malnutrition

Master`s thesis submitted to the Charité Universitätsmedizin Berlin,
Freie Universität and Humboldt Universität Berlin
in partial fulfilment of the requirements for the award of a
Master of Science degree in International Health

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August 2009

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Acknowledgements

First of all, I would like to thank Dr. August Stich and Dr. Christa Kitz for their supervision, support and advice in the whole process of planning, conducting and writing this research and thesis.

Furthermore, I am very grateful to Dr. Charlotte Adamczick who invited me, not only to collect the data in the paediatric department in Zomba Central Hospital, but also to stay with her during the time of conducting the research. She was a great help in a practical as well as in a theoretical way, and also a good friend. It was a pleasure to live and work with her.

In addition, my thanks goes to the staff of Zomba Central Hospital, especially to the staff from the Nutritional Rehabilitation Unit. They showed me great hospitality and always took time to answer my questions, in spite of very busy working days. And in the same way, I want to address my gratitude to the people from Dignitas International who helped me with further information, and also the staff from the health centres, especially the health surveillance assistants, who did a really great job in finding the children in their homes.

I would like to give special thanks to Henning Guldhammer who did a great job in proofreading this work for English wording and grammar, as well as to Dr. Thomas Pundt and Helge Christiansen who proofread this thesis for medical and statistical consistency.

Last but not least, I am very grateful to my family, my friends and the members of my church. There are too many to name each one, but they supported me in every possible way and without them I would not be where I am today.

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List of abbreviations

ARV / ART	Antiretroviral therapy
BMI	Body mass index
CD4 %	Cluster of differentiation 4 percentage
CTC	Community-based therapeutic care
DHO	District Health Office
HAART	Highly active antiretroviral therapy
IRIS	Immune reconstitution inflammatory syndrome
MDG	Millennium Development Goals
MICS	Multiple indicator cluster survey
MoH	Ministry of Health
MUAC	Mid-upper-arm circumference
NAIDS	Nutritional AIDS
NAF	National HIV / AIDS action framework
NGO	Non government organization
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NRU	Nutritional Rehabilitation Unit
OTP	Outpatient therapeutic program
PCR	Polymerase chain reaction
PI	Protease inhibitor
PMTCT	Prevention of mother to childhood transmission
RUTF	Ready-to-use therapeutic food
SAM	Severe acute malnutrition
SC	Stabilisation Centre
SD	Standard deviation
SFP	Supplementary feeding program
TFC	Therapeutic Feeding Centre
W/H	Weight for height
WHO	World Health Organisation
ZCH	Zomba Central Hospital

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1. Executive Summary

Background: HIV infection and childhood malnutrition remain serious public health problems that hinder the further development of many countries in the world, especially in sub-Saharan Africa. Addressing these issues is therefore of international interest and should be tackled with combined efforts as described in the Millennium Development Goals (UN 2008). The mortality rates of children with HIV infection are still extremely high, while treatment options are far behind compared to services for adults (Fergusson and Tomkins 2008b). HIV positive children are more likely to become malnourished than their non-reactive counterparts and at the same time they show lower cure rates if admitted to therapeutic feeding centres (TFCs). There is an ongoing debate about the optimal timing of antiretroviral therapy (ART) for children who present with HIV infection and severe malnutrition in TFCs (WHO 2004). Even though the WHO recently updated the guidelines for treatment of children below 12 months of age (WHO 2008c), initiation criteria, especially for older children, are still not very specific and thus interpretation remains with the respective clinician (Heikens et al. 2008). After observing extremely high mortality rates in this specific patient group, the paediatrician in Zomba Central Hospital (ZCH) in southern Malawi initiated ART earlier during enrolment in the feeding program. This study aims at a retrospective evaluation of the data resulting from this change in treatment in order to provide more detailed and evidence-based recommendations about the optimal timing of ART in children with severe malnutrition.

Methodology: Information for all 1329 admissions to the nutritional rehabilitation unit (NRU) in ZCH between December 2007 and March 2009 were extracted from hospital records and entered into a digital database. Afterwards all HIV positive children with severe wasting, aged between 6 to 60 months on the day of admission, were identified and allocated to three groups: 1.) early ART, defined as weight for height (W/H) standard deviation (SD)-score <=-2 at time of admission or initiation within 30 days after admission, 2.) late ART, defined by a W/H SD-score >-2 at time of admission or initiation more than 30 days after admission and 3.) no ART during enrolment in the feeding program.
More detailed information was collected for these children from NGO, laboratory and health centre records as well as through home visits conducted by health

surveillance assistants. The final data analysis was done with Stata 10 using logistic, multinominal logistic and multivariate regression as well as Kaplan-Meier time-to-event methods. Main outcomes were mortality rates and weight gain in the three groups of HIV positive children and these were also compared to HIV negative children.

Findings: HIV positive children are generally at significantly higher risk of death compared to HIV negative children if they arrive with severe malnutrition in a NRU. 34% of the 341 children who were tested positive died during the stabilisation phase and therefore had to be excluded from the final analysis. Of the remaining 225, 110 children had to be excluded because of not meeting the entry criteria. The final study cohort of 115 children was then allocated to the three groups of early ART (n=20), to late ART (n=10) and no ART (n=85). The observed mortality rates in these groups were 15% for early, 0% for late and 20% for no ART. However, the groups were too small to find statistical significance in the differences between these mortality rates. But if the mortality of all children who started ART during the feeding program was compared with those not on ART until end of the feeding program, it proved to be significantly lower for the first group (RRR 5.9, p=0.041). Regarding the outcome of weight gain, a statistical significant correlation was observed with less weight gain in late ART initiation compared to higher weight gains in early initiation. Surprisingly the non ART group showed an even more rapid weight gain than the late ART group, but still less than the early ART group.
Further findings are related to interactions between nutritional oedema, HIV infection and CD4-percentage (CD4%): Children with HIV infection were generally observed to have less oedema than HIV negative children. And again, HIV positive children with low CD4% had significantly less oedema than infected children with high CD4%. The mortality rate also differed: Children with HIV had the highest mortality rate when they were marasmic, while HIV negative children had the highest mortality rate when severe oedema was present. As predictor for the risk of death the CD4% was better than the CD4 full cell count, but not as strong as the weight for height (W/H) standard deviation (SD)-score at time of minimum weight.

Conclusions: Even though this study has serious limitations because of the retrospective study design, small numbers of observations and not randomly assigned treatment schemes, the evidence is strong enough to recommend

initiation of ART for all children with severe malnutrition and HIV infection during enrolment in therapeutic feeding programs. This is especially true for children presenting initially with marasmus. The explanatory power is not sufficient to derive evidence based guidelines about the optimal timing for ART during nutritional rehabilitation. Nevertheless, the data can be interpreted to suggest that ART for children who respond well to nutritional therapy should be deferred until they reach a state of moderate wasting, while children who do not respond within few days in terms of weight gain should be started right away, even if they are still in a state of severe wasting.

Regarding weight gain, early ART initiation resulted in a faster recovery from severe wasting than late ART initiation. On the other hand, the late ART group showed lower weight gains than the non ART group. A possible interpretation might be a decreased weight gain for a short period of time after commencing ART, possibly because of primary adverse drug effects, which was then overtaken by more rapid weight gain. The conclusion drawn from this observation is the importance of nutritional support and close observation of the weight during the first weeks and months after ART initiation.

2. Introduction

Two important health issues are the subject of this work: paediatric infection with HIV/AIDS and severe childhood malnutrition. In spite of international efforts to improve health universally, both malnutrition and HIV/AIDS still cause a high burden of disease in many developing countries, especially in sub-Saharan Africa. They therefore continue to be of major public health interest and need to be further addressed in order to reach the internationally agreed targets set with the Millennium Development Goals (MDGs) by the United Nations in the year 2000 (UN 2008). Three out of these eight goals are directly linked to the topic of this thesis. They are firstly to halve, between 1990 and 2015, the proportion of people who suffer from hunger (goal 1), secondly, to reduce the under-five mortality rate by two thirds in the same time period (goal 4) and thirdly, to have halted and begun to reverse the spread of HIV/AIDS by 2015 (goal 6). With this research project, the author aims to contribute to reaching the above mentioned targets by gaining more knowledge about how treatment options can be

improved for children who suffer from severe malnutrition and HIV at the same time.

One of the countries suffering most from the consequences of the HIV pandemic, as well as from constant food insecurity resulting in high levels of malnutrition, is Malawi. This small and landlocked country in south-east Africa was therefore chosen as the location for the data collection of this study.

According to the mentioned topics, this introduction is split up into four further sections: first a review of the subject of childhood malnutrition and its management, followed by an introduction to paediatric HIV infection, its epidemiology, pathogenesis and management, then a description of the current situation in Malawi regarding these two health issues and, finally, a definition of the study hypothesis and its objectives.

2.1 Childhood Malnutrition

Malnutrition can be summarized as an “important public health problem which is caused by a deficient or excess intake of nutrients in relation to requirements” (Lucas and Gilles 2003). In developing countries undernutrition is the much more prevalent form of malnutrition and is caused by multiple factors. Most at risk are vulnerable groups like women in reproductive age and children, but also people with immune suppression, especially those with HIV/AIDS.

More than one third of all young children worldwide are estimated to suffer from chronic undernutrition. Projections show that even by 2020 still one quarter of all children worldwide will be undernourished, the majority of them in South Asia and Africa. Multinutrient undernutrition usually occurs between conception and the age of three years, because during this period the rapid growth and development of the body requires sufficient nutrient intake (Lucas and Gilles 2003).

Furthermore, malnutrition has a huge effect on the overall under-five mortality of a population. In their frequently cited study, Pelletier et al. (1994) showed that malnutrition is associated with 42-57% of all deaths in children below five years of age in developing countries, and a more recent study from rural Kenya calculated that malnutrition today still causes an attributable fraction of 51% of all hospital deaths in the under five population (Bejon et al. 2008).

According to WHO (1999), severe acute malnutrition (SAM) is defined as W/H SD of below -3 or, alternatively, below 70% (termed as marasmus or severe wasting) or / and bipedal pitting oedema (termed as kwashiorkor or marasmic-kwashiorkor), while moderate malnutrition is defined as W/H SD between -2 and -3 or, alternatively, between 70% to 80% and absence of nutritional oedema. The actualised growth standards of WHO from 2006 were used in this research as a reference for the calculation of the respective individual severity of malnutrition (WHO 2006d).

Further definitions of malnutrition are that of stunting, defined as low height for age, which is used as indicator for chronic malnutrition and that of underweight, defined as low weight for age, which is used as combined indicator including wasting as well as stunting. Generally, the strongest indicator for risk of death is wasting (W/H) which is therefore widely used as an admission criteria to therapeutic feeding programs (WHO 1999).

The aetiology of nutritional oedema it is not completely understood. While marasmus is considered to be “an adaption to low energy intakes, a real deficiency syndrome” (Heikens 2003), the aetiology of kwashiorkor seems to be a combination of multiple factors. Generally, oedema is due to retention of sodium and water and, initially, capillary leakage can be involved in association with inflammatory processes and the release of cytokines. But the causes for the retention are still debated. More recent theories about the aetiology are based on oxidative stress caused by free radical generation and aflatoxin toxicity which again can lead to cellular damage (Cook and Zumla 2003). Children with nutritional oedema may have a normal weight for height but many are also wasted at the same time. The presence of oedema increases the risk of mortality, especially in children who are severely wasted (Lapidus et al. 2009).

The first choice for nutritional rehabilitation today is the community-based therapeutic care (CTC) approach (WHO 2005a, Heikens 2003). Following this concept, most children with severe malnutrition can be rehabilitated at community level by using so-called ready-to-use therapeutic food (RUTF) without being admitted for in-patient treatment in a NRU. The RUTF, which is usually used in rehabilitation of severe malnutrition, is the peanut-based Plumpy-nut^{TM}. In order to identify children in need of in-patient treatment, the

CTC approach differentiates severe acute malnutrition into complicated and uncomplicated malnutrition depending on the grade of oedema, clinical complications and the appetite or ability of the child to take RUTF. As an additional admission criteria in the CTC approach, the MUAC (mid upper arm circumference) is used: less than 110 mm defines severe malnutrition while 110 to 125 mm defines moderate malnutrition. The MUAC is especially helpful for screening because it is easy to use and consequently less prone to calculation or measuring errors. It also needs little equipment (compared to above described W/H SD-score) and is still highly sensitive as an indicator for the risk of mortality (Valid International 2006). For more details about the classification see Graph 14 in the annexes on page 71.

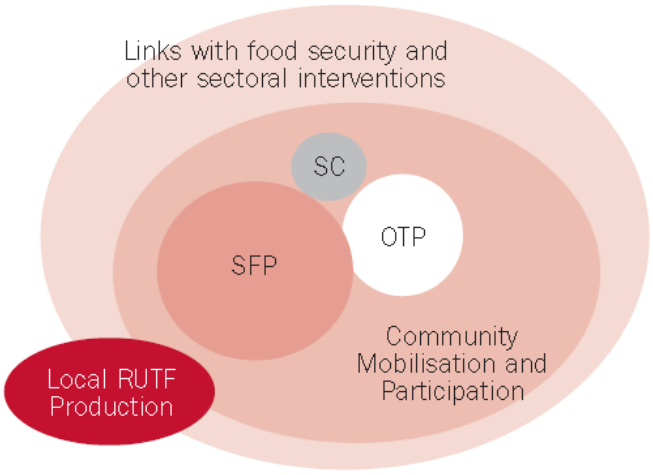
The CTC approach is based on four components:

1. Community mobilisation
2. Supplementary Feeding Program (SFP)
3. Outpatient Therapeutic Program (OTP)
4. Stabilisation Centre (SC) or Nutritional Rehabilitation Centre (NRU)

Through community mobilisation, communities are sensitized to recognise malnutrition early and to bring malnourished children to established centres for assessment before malnutrition becomes severe and complications arise. It also includes active follow-up of discharged and/or defaulted children. The second component is the SFP which is meant for children with moderate malnutrition and for those who are discharged from OTP after recovering from severe malnutrition. Children admitted to the SFP receive every two weeks a certain amount of cereal flour (usually a mixture of soya and maize) fortified with vitamins and minerals as well as cooking oil which is mixed into the porridge. The distribution ends once the child reaches its target weight of 85% W/H SD for at least two consecutive visits for moderately malnourished children. For children who were previously severely malnourished it continues for at least two months after discharge from OTP. In the OTP only children with severe malnutrition, who are clinically stable, are enrolled. Entry point is either direct in case of uncomplicated malnutrition or after some days of stabilisation in the SC/NRU for children with complicated malnutrition. Children admitted to the OTP receive a ration of RUTF every two weeks, calculated according to their

body weight. On the day of food collection all children are reviewed by a clinician or nurse and the guardians are taught about a healthy diet, sanitation and hygiene, etc.. Once children are discharged from the OTP they continue for further two months with a SFP as described above. Children with complicated malnutrition are admitted to the SC/NRU where they receive, at first, the F-75 formula recommended by the WHO. After few days, when the oedema is subsiding, the ability of the child to eat RUTF is assessed and once it is able to take at least 75% of the calculated daily RUTF ration it can continue exclusively with RUTF. As soon as a child is stable and taking sufficient amounts of RUTF, it can be discharged from the SC/NRU and transferred to the OTP (Valid International 2006).

The whole program should finally be linked with other regional and national programs and sectors dealing with food security, health and hygiene.



Graph 1: Structure of a fully evolved CTC program (Valid International 2006)

In order to evaluate the success of the nutritional rehabilitation, it is important to monitor the outcomes such as cure rates and weight gain. Internationally accepted outcome indicators for a nutritional rehabilitation program are given for example by the Sphere Project (2004). According to these guidelines, the proportion of children who died should be less than 10%, the recovery rate more than 75%, the default rate less than 15% and the mean weight gain should be more than 8 g per kg bodyweight per day. Nonetheless, the guidelines also suggest that these indicators are not adjusted for areas with high HIV prevalence and they also need to be interpreted with regard to the severity of malnutrition treated in the program.

2.2 Paediatric HIV/AIDS

Worldwide, approximately two million children aged below 15 years of age are estimated to live with HIV infection, up to 90% of them in sub-Saharan Africa. While the incidence of new infections in children peaked already from 2000 to 2003, total numbers of infected children are still rising (UNAIDS 2008).

Without preventive interventions the overall transmission risk of HIV from mother to child is estimated to be 30-40%. The virus can be passed on to the child in utero, during delivery, or through breastfeeding. The maternal health status and viral load determine to a great extent the risk of transmitting the virus to the infant. Yet, by following the preventing mother-to-child transmission (PMTCT) guidelines, this risk can be reduced substantially (Eddleston et al. 2008). Early diagnosis of the HIV infection in the mother is therefore essential in order to counsel her about the possibilities of safe delivery, ART for mother and child, and also the different options for feeding the baby after delivery.

In spite of this knowledge, in 2007 only 33% of all pregnant women known to be infected with HIV in low- and middle income countries received ART to prevent the transmission to the child, and only 18% of pregnant women were tested for HIV (Unite for Children 2008).

Once in the bloodstream, the virus attaches to T-lymphocytes with CD4 antigen, enters them and then starts replicating with the help of different viral enzymes. The viral DNA is thus inserted into the chromosomal DNA of the host cell so that billions of new virus particles can be produced every day. The immune system of the host is able to destroy circulating viruses and can in this way control the infection and keep the number of viruses in the blood at a more or less constant number. But once the virus has integrated itself into the DNA of the host, it is impossible to eliminate it completely from the body of the host. Over years in this state of immune activation, the body loses its capacity to replace killed cells because of the extremely high cell turnover and consequently, the number of CD4 T-lymphocytes declines to a level where symptoms of immune suppression arise and AIDS becomes evident in form of the typical opportunistic infections (Gill and Beeching 2004). In adults, the full CD4 cell count is used as parameter for immune competence and disease progression of HIV. Because the full cell count in children is much more variable and depends on age, the CD4 percentage (CD4%) is used instead as measurement for children below five years of age. The CD4% can be obtained

either by flow cytometry or by calculation (absolute CD4 count / (WBC count x percentage lymphocytes)) (Callens et al. 2008).
Once the immune system is not able to control the virus anymore, antiretroviral therapy (ARV therapy = ART) can be used to inhibit the replication cycle of the virus. Two major categories of ARV drugs are differentiated according to their point of action in the replication cycle: NNRTIs and NRTI/NtRTIs inhibit the viral enzyme “reverse transcriptase” while the PIs inhibit the viral enzyme “protease”. At least three different ARVs should be given at once to make sure that the viral replication is totally inhibited and therefore the emergence of resistance can be avoided. Treatment according to this guideline is referred to as highly active antiretroviral therapy or briefly “HAART” (Eddleston et al. 2008). In the further discussion the term ART is used instead of HAART for reasons of simplification, but the drugs used for this research are all categorised as HAART.

While the asymptomatic phase in adults often continues for around 10 years, the progression of the disease in children is usually much faster and consequently they experience much higher morbidity and mortality rates than adults (Dunn et al. 2008). In perinatally infected children without ART, three categories of progression can be differentiated: approximately 25-30% of children are so-called rapid progressors who develop AIDS and die within the first year of life; others (50-60%), develop symptoms early in life, but survive with a slow downhill course of disease until the age of three to five years; a few children (5-25%), who are categorised as long-term survivors, show symptoms of immune suppression only later in life and survive beyond the age of eight years (Tindyebwa et al. 2006). All together around 80% of all children infected perinatally with HIV die before the age of five years, unless treated with ARVs (Cook and Zumla 2003). A more recent study in rural Uganda shows that even 50% of HIV infected children die before reaching the age of 24 months without ART (Brahmbhatt et al. 2006). But in spite of this generally fast progression of HIV in children and the obvious need for timely initiation of ART, access to the drugs is still insufficient for children and far behind when compared to services for adults (Prendergast et al. 2008). In 2008, the median age when children started ART was five and nine years, which is far too late, given the high mortality rate in the younger age groups (Unite for Children 2008).

In addition to the already mentioned MDGs, there are specific goals for improving ART coverage. The initiative “Unite for Children, Unite against AIDS” defined its goal as reaching 80% of all children requiring ART by the year 2010. But in order to reach this goal a lot of additional efforts are required (Unite for Children 2008).

The insufficiency of services for children is caused mainly by the difficulty of diagnosing HIV infection in infants with an age of less than 18 months. Maternal antibodies (IgG) can persist up to this age in non-infected infants and can therefore cause false positive results when they are tested with the commonly used antibody tests (Phillips et al. 2008). At the same time, clinical diagnosis of HIV infection often lacks specificity especially in severely malnourished children who may present with nutritional AIDS and similar symptoms without being HIV infected (Bachou et al. 2006). Therefore a PCR is needed in order to confirm the diagnosis so that treatment with ARVs can be initiated before the age of 18 months. But the PCR is still not available in most treatment centres and is also much more expensive and time consuming than the commonly used HIV ELISA rapid tests (Cook and Zumla 2003).

A further problem in providing services for HIV infected children is the lack of good and widely available paediatric drug formulations as well as poor knowledge and policies (De Baets et al. 2007), leading to concerns about possibly poor adherence resulting in the risk of the emergence of drug resistant virus strains (Biadgilign et al. 2008). Consequently, children are usually treated with ARVs only in high level referral health facilities which are often difficult to access for the rural community because of long distances and insufficient transport facilities.

Brambhatt et al. (2006) were able to show the effect of HIV infection in children on the mortality rate: 540 compared to 128 per 1000 live births was the difference in mortality that he found in his study for HIV-positive versus HIV-negative children until the age of two years, calculated from data in different developing countries. One of the most sensitive indicators for the progression of HIV in infants is failure to thrive (De Baets et al. 2007). Often HIV infection causes an already low birth weight in newborn infants. This is followed by alterations in the gastrointestinal tract as well as frequent infections, side effects of drugs, and changes in the metabolic and endocrine functions, which all

together are most likely to contribute to further growth failure (Eddleston et al. 2008). As a consequence, children with HIV infection and weight loss may have an increased need for energy intake of 50 to 100% over the requirements for healthy uninfected children and malnutrition may occur in these children, even if the breast milk intake seems to be adequate. Hence they are much more prone to become malnourished than their non-infected counterparts even if they are living under similar conditions (WHO 2003). In addition to the increased risk of developing malnutrition, they are also often observed to respond poorly to nutritional rehabilitation as long as they are not on ART (Cook and Zumla 2003). The typical form of malnutrition in HIV-infected children is marasmus, while relatively few HIV-positive children develop kwashiorkor. If HIV positive children appear to have nutritional oedema they are very often observed to have rather high CD4% (Kekitiinwa et al. 2008).

With these findings, the importance of interaction between HIV and malnutrition is already evident. As the disease progresses, the negative effect of HIV and malnutrition on the immune system results in further infections and loss of appetite with the consequence that both conditions together form a clinical state where recovery and treatment of complications becomes extremely difficult, increasing the risk of death within a short period of time (Schaible et al. 2007). Therefore it is essential to diagnose HIV infection as early as possible and also to incorporate the control of the nutritional status into the treatment protocols of pre-ARV and ARV clinics, so that the development of severe malnutrition can be prevented (De Baets et al. 2007).

Furthermore, several recent studies, like that of Chiappini (2006), Violary et al. (2008) and Goetghebuer et al. (2009), were able to show that early ART tremendously reduces mortality, morbidity and progression of HIV in infected infants. These encouraging results indicate that immune reconstitution is a key factor in the treatment of HIV infected children. Referring to this and other studies, the WHO updated their guidelines recently and now recommends treating all children with HIV infection below 12 months of age, and all children between 12 months and 5 years who show signs of severe infection or have a CD4% of less than 20% (WHO 2008b). Nevertheless, it is not clear how these findings are to be interpreted with regard to children who suffer not only from HIV infection but also from severe malnutrition. There are fears that malnutrition

in patients who are started on ART might increase drug toxicity and the occurrence of serious adverse events (Subbaraman et al. 2007). According to the clinical staging following WHO criteria, a child is eligible to start ART in case of severe malnutrition if it is not responding to nutritional therapy, and furthermore the WHO recommends first treating and stabilizing acute conditions before initiating ART (WHO 2008b). But experience shows that initiation might already be too late once these children present in a state of severe malnutrition. Even stabilisation of this condition sometimes appears to be difficult without ART and many of these children die before they meet the official criteria for initiation of treatment. Thus the mortality remains very high among this group compared to non-infected children. Also, the terms “stabilisation” and “not responding to nutritional therapy” used in the WHO guidelines are not very specific and their interpretation may therefore vary widely between the decision making clinicians. Therefore further studies are urgently needed to gain more information in order to develop better and evidence based guidelines (WHO 2004, Heikens et al. 2008).

In their meta-analysis, Fergusson and Tomkins (2008) found, for example, a difference in mortality of 30.4% in HIV-positive versus 8.4% in HIV-negative children admitted to feeding programs with severe acute malnutrition. Recent studies in Malawi and Zambia even reported case fatality rates in HIV-infected children with severe malnutrition of 40% and higher, in an admission population of 50% HIV infected children to NRUs (Heikens et al. 2008). Other studies in Malawi showed that severe wasting is significantly associated with mortality three to six month after starting ART in children, but again it is not clear if and how much nutritional support could improve the outcome (Bong et al. 2007). These numbers again point out the urgent need to do further research and to find and discuss other possible solutions in order to improve the treatment and thus the duration and quality of life for children infected with HIV (Fergusson and Tomkins 2008b, WHO 2005b).

2.3 The situation in Malawi

The Republic of Malawi is a small landlocked country in south-east Africa with an overall population of around 14 million people. It is one of the least developed countries in the world and is, at the same time, densely populated

with 46% of the population being below 15 years of age. Most of the population lives in rural areas, depending widely on agriculture (CIA 2009). In 2003, the life expectancy for both sexes in Malawi was 41 years and the under-five mortality rate was 175 per 1.000 live births. HIV/AIDS was with 34% the most common cause of death for all ages in 2002, followed by 12% for lower respiratory tract infections (WHO 2006c). Even for causes of death in the Malawian under-five population, HIV/AIDS was held responsible for 14% of all deaths in 2000 to 2003 and might have increased today because of the rising prevalence of HIV infection in children. During this time period only pneumonia and diarrhoeal diseases were more important causes of death in the under-five population than HIV/AIDS (WHO 2009). In spite of these apparently rather discouraging numbers, Malawi has made clear progress in child survival over the last years: In the Multiple Indicator Cluster Survey (MICS) from 2006, the under-five mortality rate had reduced to 118 (138 in Zomba District) per 1000 live births which indicates a great improvement. However, the statistics of the MICS have to be interpreted with care since they are made from data of retrospective questionnaires (Phillips et al. 2008).

According to WHO (2006c) statistics, 25.4% of all children below five years of age in Malawi are considered to be underweight and 49% to be of stunted growth. In the MICS (NSO and UNICEF 2007) from 2006 the percentage of underweight children was found to be 20.5% (17.7% in Zomba District) and those of stunted growth 46% (51.5% in Zomba District). These high numbers can be assumed to contribute considerably to the high rate of the under-five mortality in the country.

Also HIV infection is considered to be a persisting problem in Malawi. The overall prevalence in adults (15 to 59 years) is currently estimated to be around 13% and the disease is still causing around 14% of deaths in the under-five population according to WHO (2006c). In the Malawi Health Survey from 2004 the overall percentage was found to be 12% among adults, 13% in women and 10% in men, but with significant differences within the regional areas of the country. While approximately 6-8% of the adult population in the central and northern region were infected, the percentage of infected people in the southern region went up to 17.6% and even up to 17.8% in Zomba District (NSO and ORC-Macro 2005). The National AIDS Commission of Malawi estimated that

about 790,000 adults and children in the country where living with HIV/AIDS in 2005, resulting in 85,000 deaths annually (MOH 2006). Also the prevalence of HIV in NRUs in Malawi depends very much on the region in the country. With an average uptake of HIV testing of 92% the prevalence varied from 23% in the north to 37% in the south with again higher percentages in cities than in rural areas and also varying within the seasons (Thurstans et al. 2008).

A national AIDS control program is in place since 1998. In June 2005 the second national HIV/AIDS action framework (NAF) 2005-2009 was published. The overall goal of this framework is "to prevent the spread of HIV infection among Malawians, provide access to treatment for people living with HIV/AIDS and mitigate the health, socio-economic and psychosocial impact of HIV/AIDS on individuals, families, communities and the nation" (National AIDS Commission 2005). Even though the provision of ART for paediatric cases is not explicitly mentioned, the framework emphasises equitable access for all people living with HIV/AIDS as well as nutritional support and prevention of mother to childhood transmission as objectives for the period 2005 to 2009. The framework for the coming five years is yet to be published (National AIDS Commission 2005). Overall there is immense progress in the delivery of ART in Malawi: while in 2004 only nine public health facilities delivered ART with 3,000 to 4,000 patients in treatment, already by the end of 2005, the number had increased to 60 health facilities and more than 37,000 patients, and the target for 2010 is to have 120 public and 80 private health facilities providing ART with 245,000 patients started on ART, of which 21,875 should be children (MOH 2006).

In Zomba district the HIV program is run by Dignitas International, an international NGO, in cooperation with the local and national government. The program is currently working on expanding decentralisation of services. Most of the health centres in the district are already distributing ARVs and some started with enrolment of new patients for initiation. The health personnel in the health centres is trained and supported by an outreach team which visits every site at least once in a month.

So-called "master-cards" contain all important information regarding ART and the clinical progress of each patient. Copies of these cards are given to the headquarters of Dignitas International in Zomba where it is entered into a digital

database. This system includes all patients who attend ARV clinics in health centres of Zomba district. If a CD4 count or percentage is required, patients have to be referred to ZCH. PCR is also taken in ZCH for confirming a positive HIV rapid test in children below 18 months of age, but has to be brought for processing to the laboratory in Blantyre, which is the next larger city from Zomba. All children are treated according to the above mentioned new WHO guidelines (WHO 2008c). First line treatment in Malawi is Triomune (Stavudine + Lamivudine + Nevirapine) for adults and Triomune Baby/Junior for children. Alternative first line treatment is available in case of toxicity or interactions with other drugs and second line in case of treatment failure with the first line regimen (MOH 2006). All patients who are not yet started on ART receive preventive therapy with cotrimoxazole.

With around 500 beds, ZCH is one of the largest hospitals in Malawi and acts as tertiary referral level health facility. Part of the hospital is the Nutritional Rehabilitation Unit (NRU), where severely malnourished children are admitted for stabilisation and which is also a referral centre for the district wide CTC program, which was established in 2007. Eight health centres were selected by the district health office (DHO) to function as OTP and SFP centres. There is a local production site for the RUTF, locally called “Chiponde” (same as Plumpy-nut^{TM}), in Blantyre, which supplies all participating centres. The fortified soya-maize porridge for the SFP program is locally called “Likuni Phala” and is also produced in the region.

The NRU in ZCH currently has a total 800 to 900 admissions per year. According to the CTC guidelines, only children with complicated malnutrition are admitted to the NRU while other children are admitted directly to the OTP in case of severe uncomplicated or to SFP in case of moderate uncomplicated malnutrition. Depending on the address of their home villages, patients for OTP and SFP are enrolled either in ZCH or in one of the eight participating health centres. Criteria are followed as described above according to the guidelines for the CTC approach. The NRU is staffed with four nurses and two health attendants as well as one clinical officer and one paediatrician as supervisor. Ward rounds are done on daily basis by the clinical officer and once a week by the paediatrician. An intensive care unit is available with oxygen supply and electric heaters to keep the

children warm. All children admitted to the NRU receive vitamin A and folic acid on admission as well as a broad spectrum antibiotic and further treatment according to WHO guidelines for the in-patient management of severe childhood malnutrition (2000). Every Thursday the so-called “chiponde-clinic” is conducted where children come for follow-up visits and receive their two weeks ration of chiponde or likuni phala as described above. During this visit the weight, height and MUAC are taken, and children are clinically reviewed and classes are held for the guardians.

As observed in other southern Malawian NRUs, and also in ZCH, the HIV prevalence is around 35 to 40%, which obviously influences significantly the mortality rates during the nutritional rehabilitation program.

Because of constantly high mortality rates and poor weight-gain in HIV positive children who were enrolled in the nutrition program, the paediatrician in ZCH began initiating ART gradually earlier after admission. Before mid-year 2008, children were usually started on ART only after recovering from severe malnutrition with a weight gain reaching a weight-for-height of at least 80% SD and most of the time only after proof of low CD4 counts. Today children with proven HIV infection are started on ART immediately after surviving the acute stabilisation phase in the NRU as soon as they show no fever or acute diarrhoea and irrespective of their W/H SD-score. The new approach of early initiation seemed of particular importance for patients who showed stagnant weight despite prolonged therapeutic feeding. According to the new WHO guidelines, as described above all children below 12 months of age are now started on ART, while those above 12 months are staged clinically and according to their CD4% (WHO 2008c).

The need to analyse the outcome of the children who commenced ART early versus those who started after having reached 80% of W/H SD, became obvious. This last statement already defines the hypothesis and objective of this study.

2.4 Hypothesis and objectives

Early initiation of ART is of benefit for children with severe malnutrition and HIV infection. It can significantly reduce their mortality and contribute to faster weight gain and consequently recovery from severe acute malnutrition.

Objectives

- To prove that early ART is of benefit for children with severe malnutrition
- To gain more knowledge in order to improve the treatment
- To show that early ART can reduce the mortality rate and increase the weight gain of children with HIV and severe malnutrition, especially for those with poor response to therapeutic feeding

3. Research methods

The study was conducted as a retrospective cohort study in ZCH in Malawi as described above. Ethical clearance to conduct the research was given beforehand by the hospital administration and by involved hospital staff. This was sufficient because the research relied basically on existing hospital records. During the data collection it turned out that the health centres needed to be involved for further information and therefore agreement from the DHO was requested and given. All data were made anonymous in order to maintain privacy for the patients involved. Because of time and resource limitations it was not possible to conduct a prospective cohort study with randomly assigned treatment groups, which would have been the optimal study design with regard to the study hypothesis. Instead this research is based on the collection and analysis of data available from hospital records and information from various health centres in the district.

3.1 Sample size calculation

After formulation of the research question and extensive literature review, the sample size required for achieving statistically significant results had to be determined. Therefore a calculation was done with EpiInfo™ 3.5.1. Mortality was chosen as main outcome for the data analysis since it was considered to give the most significant result. The calculation was set up with a confidence interval of 95% at a power of 80% and a ratio of unexposed (late ART initiation, defined as W/H SD-score of >80% at day of ART initiation) to exposed (early ART initiation, defined as W/H SD-score of <=80% at day of ART initiation) of 1:1. According to the statistics of the NRU in ZCH, HIV infected children with

severe acute malnutrition had an average mortality of around 40%. Since (to the author's knowledge) no directly comparable studies had been published at the time of planning of this work, the mortality had to be estimated by considering other studies like that of Violary at al. (2008) and Chiappini et al. (2006) which deal with mortality rates mainly in not malnourished children after commencing ART. The expected reduction in mortality was consequently estimated to be at least 25% for the group with early initiation of ART compared to the 40% for late or no initiation. With these numbers the calculated sample size required for statistically significant results was 165 children for each cohort.

3.2 Data collection and analysis

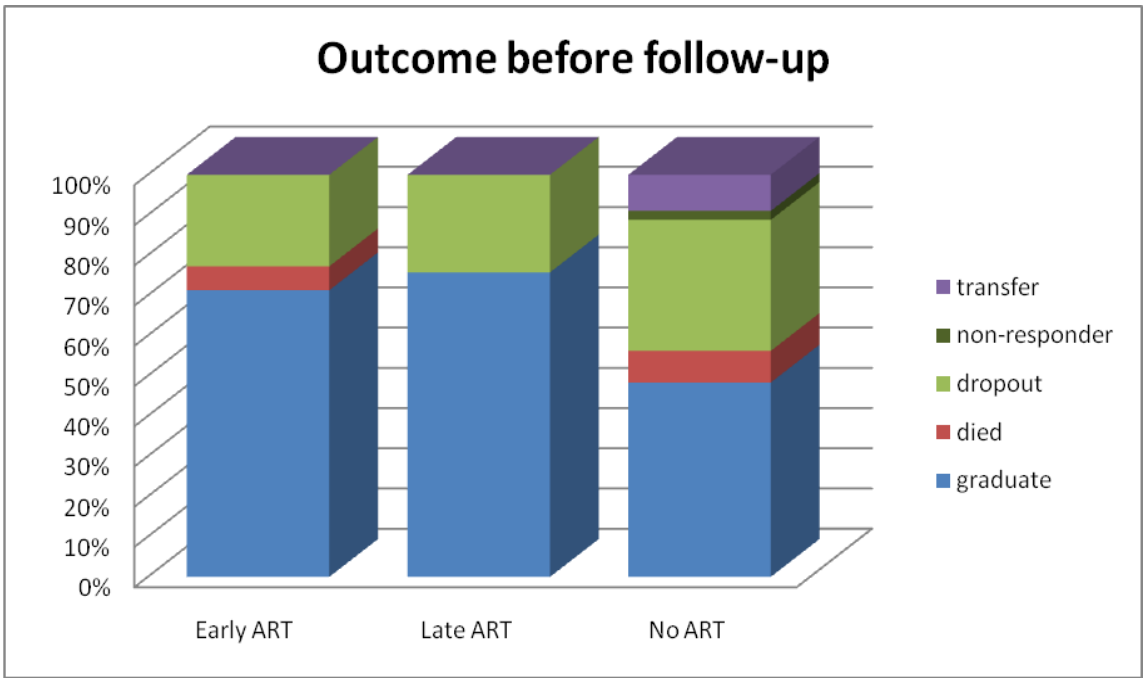
The next step was to gather information about admission numbers and the prevalence of HIV infection in order to fix the time period required to reach the calculated sample size: With around 900 admissions per year and a reported HIV prevalence of 30 to 35%, hospital admissions from a period of around 14 to 15 months was estimated to be necessary to be included and analyzed. Since the duration of enrolment in feeding programs is usually around two to three months the last possible month to be included was March 2009. Accordingly the time period was set at December 2007 to March 2009. Then a structured questionnaire was developed with EpiData 3.1 (see graph 14 in annexes, page 72). Key questions were: age, sex, presence and grade of oedema, weight and height on admission and discharge, start of ART, CD4 count/percentage as well as the way of exit from the program. The exit was determined as normal discharge, died, absconded, transfer and non-responder.

In the process of identifying all HIV positive admissions, all non-infected children admitted to the NRU during the observation period were also entered into the database as control group. Old hospital admission files as well as documentation books from the OTP and SFP were reviewed for the HIV positive patients and the data entered into the database.

Because information in the nutrition files was very often insufficient regarding the date and weight of ART start and adherence to treatment, the database of the ARV clinic also had to be searched. All names were looked up in order to be sure that no information was missed about children who started ART, and also to gain more information especially about the W/H SD score at time of initiation,

occurrence of opportunistic infections, and CD4 counts/percentages. Unfortunately the departments of the ARV clinic and NRU did not use common identification numbers. This made it necessary to identify children by name and age which made the process much more complicated. Then CD4 counts and percentages had to be traced in the hospital lab, because they were not recorded regularly in the ART and nutrition files.

First attempts at analysis showed that the number of dropouts was, with around 20%, very high and might have caused a huge bias in the interpretation.



Graph 2: High numbers of dropouts in the CTC program made follow-up visits necessary

It was therefore necessary to follow up as many of these children as possible in the district. Thus, with the consent of the DHO, visits to the health centres were conducted. Few children could be followed up in the registers of the OTP or SFP run by health centres in the district, but most children had to be followed up at home by the health surveillance assistants responsible for the respective villages. During these home visits weight, height and MUAC were taken by the health surveillance assistants and the guardian was told to come back for the paediatric HIV clinic in ZCH in case the child was not yet initiated on ART. If children dropped out of the feeding program because of death, their outcome was changed accordingly in the database from dropout to death. If children died after being absent from the OTP for more than three consequent distributions (according to the CTC manual from Valid International (2006) their outcome was

left at dropout, because not receiving RUTF could have made a significant difference in the outcome and the aim of this research was to investigate ART while children were enrolled in a therapeutic feeding program. In the beginning, 37 children from the study cohort were lost to follow-up, but 28 of them could be traced later on. The remaining nine children were, except for one which was allocated to the early initiation group, all part of the non ART group.

Because an unexpectedly high number of children did not start ART during nutritional rehabilitation the cohort was differentiated in four instead of in three groups as planned for the sample size calculation. Then the outcome and weight gain in these cohorts were compared: HIV positive children with early initiation of ART, late initiation and no initiation of ART and finally HIV negative children. Two different definitions were used to define early and late initiation: the first definition was based on the W/H SD-score at start of ART initiation (early <=80% compared to late >80%) and the second definition was based on the point of time (days after admission to NRU) of ART initiation (early = within 30 days versus late = more than 30 days). In order to make the groups comparable, only children with severe wasting at time of admission to the NRU were included in the study (defined by W/H SD of <= 70% and/or MUAC of <=110 mm). Consequently children with kwashiorkor and a SD-score of more than 70% were excluded since the criteria for early and late initiation as well as the indicator of weight gain would not have been applicable, and also the aetiology of malnutrition might be different for this group. The limits for age were set at 6 to 60 months to make the cohort more homogeneous.

The endpoint of data collection for each child was discharge from the feeding program. The outcome was differentiated into cured, death, dropout and non-responder.

The analysis was done with multinominal logistic regression for the outcome (way of exit from the program) and with logistic regression for the weight gain (calculated in g per kg bodyweight and day) as well as with multivariate regression in order to determine statistically significant differences between the described groups under stratification for possible confounders like age, sex, oedema and occurrence of opportunistic infections. Time-to-event methods according to Kaplan-Meier were used to plot and analyze survival estimations.

3.3 Problems encountered

When the first data analysis was run, several problems came up: First of all, a very high early mortality rate was observed in the group of HIV positive children without ART. Most of these children died within few days after admission to the NRU. If included into the study cohort they would have caused the mortality of the non-ARV group to be very high compared to the early and late ART groups, but the result would be due to a selection bias since ART initiated in the NRU would most certainly have made no difference in the outcome of this group. These children had therefore to be excluded from the study. Accordingly, the case definition was narrowed down to children who were discharged from the NRU into the CTC program as stable. The next problem that became evident was a group of children who started ART before admission to NRU, who also had a very high mortality rate. Many of these children had already been on ARVs for months or even years. The development of severe malnutrition after such a long time on ARVs could be interpreted as treatment failure. And even though there was available information about their W/H SD-score on initiation, this group might again have caused a selection bias of children who did not respond to ART. So the case definition had to be narrowed even further to initiation during or after admission to the NRU, excluding those who started ART before admission. A further problem involved a smaller group of children who were reported to have started ART, but the initiation time and / or weight on initiation was not recorded so that it was impossible to allocate them to one of the groups. For further details see flow chart (graph 16) in annexes on page 73.

Main outcomes for the data analysis were weight development and mortality rate. Confounders that needed to be considered were age and sex of all participating children, the presence and grade of oedema, and the status of malnutrition at admission to NRU. Also considered was the CD4 count/percentage and the prevalence of other diseases such as opportunistic infections.
Unfortunately, the information available about the statistics from the NRU in ZCH at the time of planning the research was insufficient. Otherwise some of the problems encountered later on could have been foreseen which would have resulted in some changes such as an extension of the observation period. However, because of the time limitation it was impossible to go further back to include patients from before December 2007. But if more detailed statistics

would have been available beforehand, a possibility might have been to concentrate on HIV positive children alone instead of also entering the basic data for all HIV negative children which was interesting, but not directly related to the study question.

3.4 Study limitations and explanatory power

The main limitation of this study is due to the small number of observations. The calculated sample size required in order to reach significant results could not be reached following the necessity to exclude many children as described above. Larger cohorts and preferably a prospective study design could provide much more reliable results, but was not feasible because of restrictions in time and resources. A further limitation may be introduced by the not randomly assigned allocation of children into the four different study cohorts. Even though most children were seen by a paediatrician to initiate the ART, other medical staff (mainly clinical officers) were involved in the treatment and decision making process, so that the reasons for, and time of, ARV initiation and treatment of related conditions may differ slightly from child to child over the time. This is expected to have caused another selection bias and may thus further reduce the explanatory power of this research.

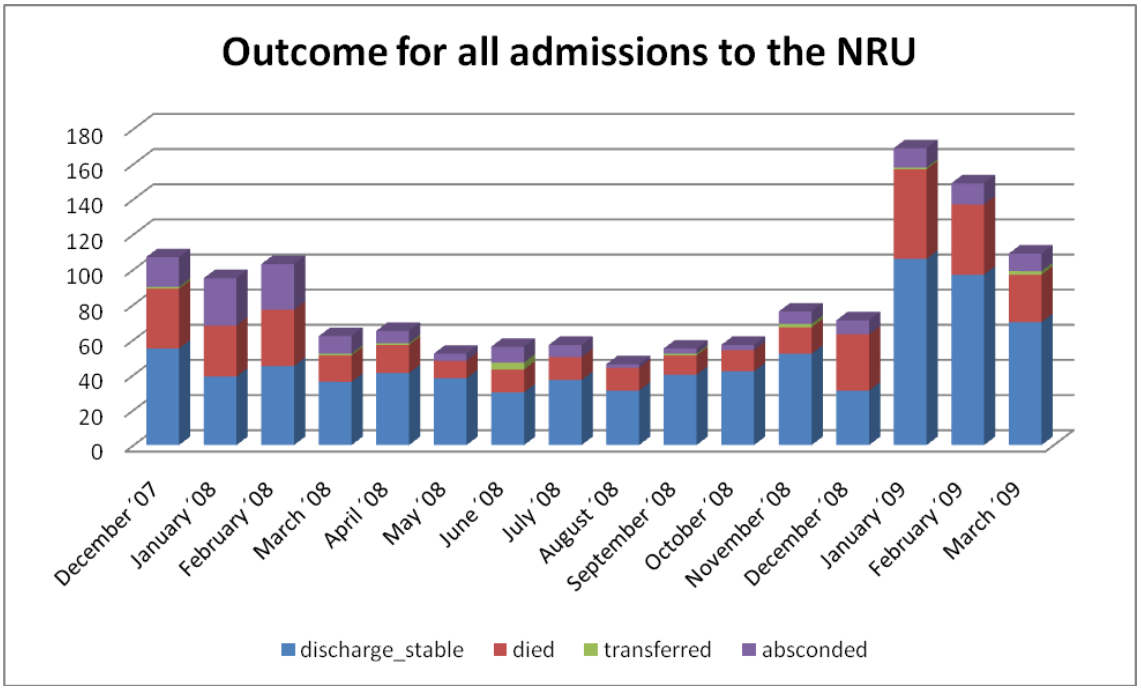
In spite of these clear limitations, this study can still be expected to make a contribution to the knowledge about optimal treatment for HIV infected severely malnourished children. Even though some of the results cannot reach statistical significance they still show a direction and therefore provide a good basis to design and conduct further possibly prospective and controlled trials.

4. Results

4.1 General Statistics of the NRU

1329 children were admitted to the NRU during the study period from December 2007 to end of March 2009. Graph 3 shows the admissions numbers split up by month and manner of exit from the program. A clear peak in the number of admissions can be noticed in January and February in 2007/8 and more clearly in

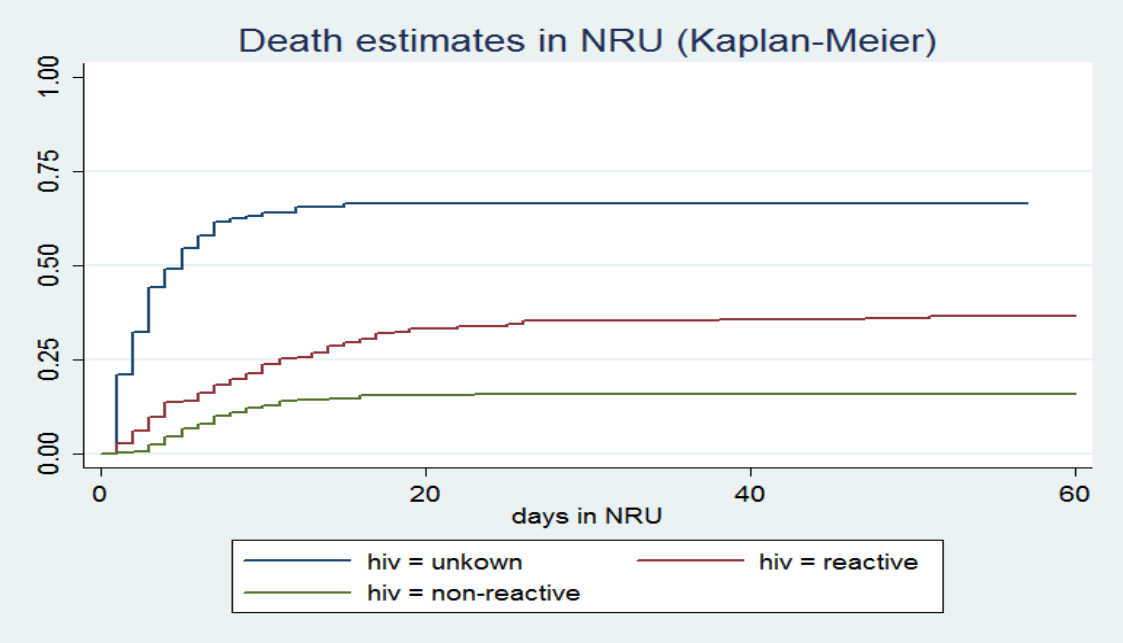
2008/9. The overall outcome was differentiated into discharge as stable, death, absconded and transferred. 59% of all admissions were discharged into the CTC program as stable, 27% died in the NRU, 12% absconded and 1% was transferred out (mostly to the general paediatric ward in ZCH). The proportion of deaths compared to those with discharge as stable was in some months (May and September to November) less than in the other months, but without statistical significance if adjusted for oedema and W/H SD-score on admission ($p>0.05$). Also the proportion of absconders and transfers showed no statistically significant difference within the time of observation.



Graph 3: Admissions to NRU over the study period by month and way of exit

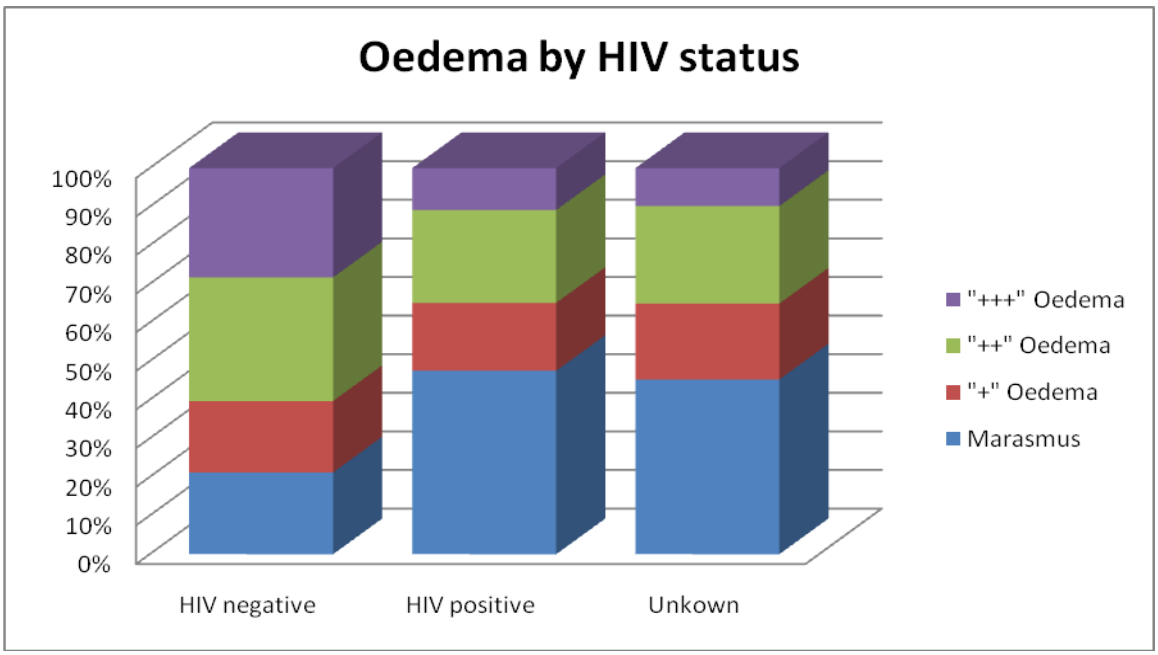
79% of all admissions were tested for HIV infection: 32.7% of all tested children were found to be HIV positive and 67.3% negative. The majority of the 21% not tested children either died or absconded within the first days after admission to the NRU. If all admissions are split up by outcome, still 5% of children who were discharged from the NRU as stable remained as not tested.

The overall mortality rate in HIV negative children in the NRU (in-patient stabilisation phase) during the study period was 13% compared to 34% for those tested reactive (RRR 3.5, $p<0.001$) and 51% for those not tested for HIV (RRR 20.1, $p<0.001$). For more details see graph 4. There was no difference in age and sex between HIV positive and negative children, but children with unknown status had significantly younger age.



Graph 4: Mortality estimates for the NRU in-patient time by HIV status

33% of all admissions were classified as marasmus (W/H SD-score <=80% without oedema), 12% as marasmic-kwashiorkor (W/H SD-score <=80 with oedema) and 55% as kwashiorkor (SD-score >80% with oedema). Oedema was differentiated into “+” = only pedal oedema, “++” = oedema in feet and legs or arms and “+++” = generalized body oedema. HIV positive children and children with unknown status had significantly less oedema than HIV negative children ($p<0.001$). The proportions of oedema in children with unknown status were more or less identical with those tested reactive (see also graph 5).



Graph 5: Differences in occurrence of oedema by HIV status

Also the W/H SD-score on admission was significantly lower in HIV positive and not tested children, even if only children with marasmus were considered. The mean of MUAC on admission to the NRU was 105 mm in HIV positive, 106 mm in not tested children and 118 mm in HIV negative children (p=0.005).

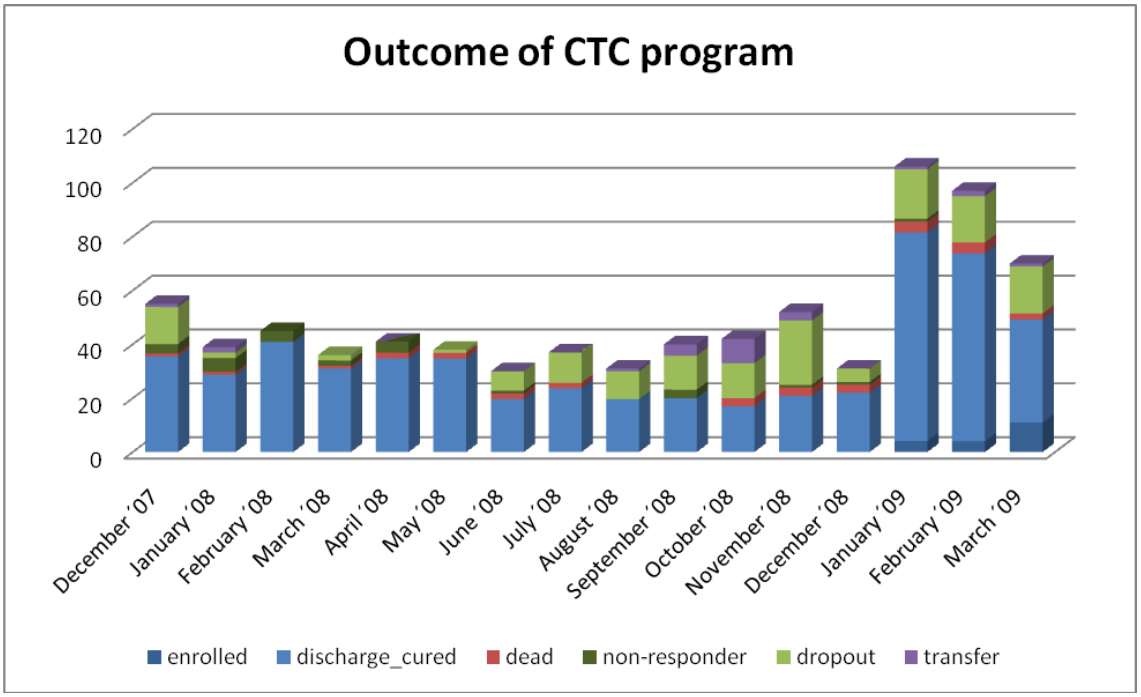
The proportion of deaths compared to those discharged as stable in HIV negative admissions to the NRU was clearly increased for children with "+++" oedema compared to those with no oedema (RRR 2.7, p=0.002), and less clearly for those with "+" and "++" oedema (RRR 1.4-1.2, p>0.05). For HIV positive children "+" and "++" oedema seemed to have a protective effect (RRR 0.65-0.68, p=0.35 and 0.5) but with no statistical significance. Also "+++" oedema had no effect of higher mortality compared to marasmus in HIV infected children (RRR 1.1, p=0.98). For more details see graph 17 in annexes on page 74.

4.2 Outcomes of OTP and SFP

All 59% (790) of children who were discharged from the NRU as stable started with the CTC program. 21.6% (171 children) were lost to follow-up while enrolled in the CTC. 96 of these 171 patients dropped out already after receiving the first ration of RUTF at time of discharge from the hospital.

14.7% (24) of children who absconded from NRU appeared later again to start CTC but nearly half of them (n=9) absconded again from the CTC program. The average percentage of transfers to the health centres was only 3%.

The overall outcome of the CTC program for all children who were discharged as stable from NRU is shown in graph 6:



Graph 6: CTC admissions by months and way of exit

HIV positive children are again at much higher risk of death compared to non reactive children while being enrolled in the CTC program (RRR 6.1, p<0.001). The percentage of children who were lost to follow-up is 24% in HIV positive and 18% in HIV negative children, which is, however, not a statistically significant difference.

The mean weight gain was higher in HIV positive children 5.3 vs. 4.7 g/kg/day and it remained higher if only marasmic children without ART were taken into consideration (6.1 vs. 5.1 g/kg/day). Children with kwashiorkor gained less than those with marasmus (4.8 vs. 6.0 g/kg/day).

4.3 ART for severely malnourished children

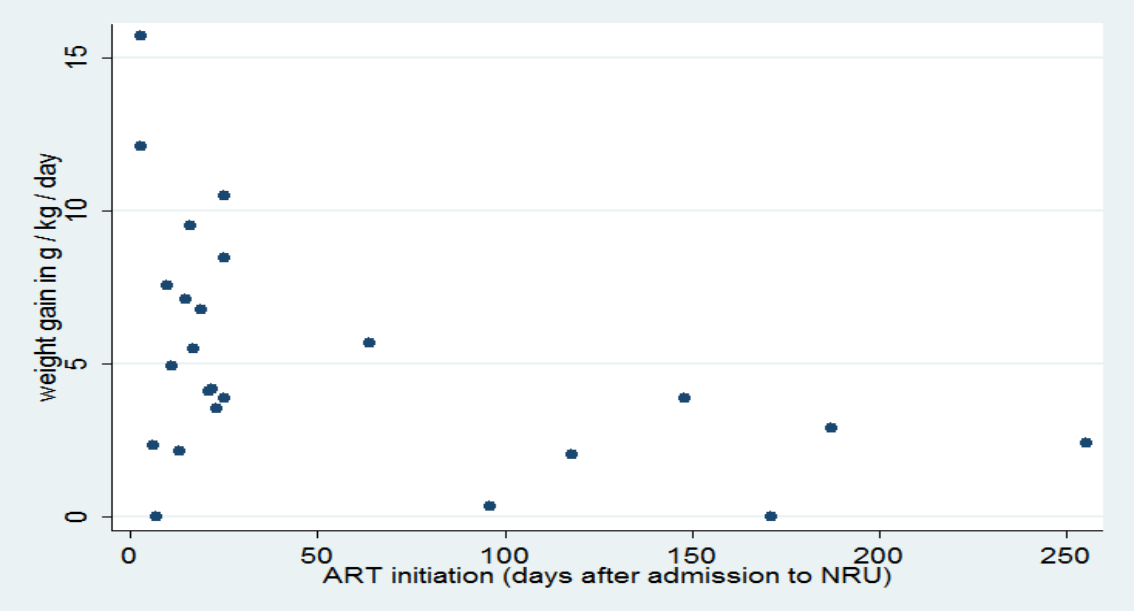
24% (82) of all HIV positive children were started on ART, of which 18.3% (15) were reported to have started ART, but either the date of initiation or the weight at this point of time was not known. Another 22% (18) were initiated before admission to NRU, while 7.3% (6) started ART after completing the CTC program. The remaining 52.4% (43 children) started ART during enrolment in the feeding program.

The 18 patients who started ART before admission to NRU had a significantly higher risk of death than those with initiation during enrolment (RRR 6.6, p<0.05). The time of initiation for these children was very different, varying from 22 to 1180

days before admission to NRU with a mean of 238 days. Only three of them were readmissions who had started ARVs while being on feeding program. Nine (50%) children from this group were admitted with severe oedema ("++" and "+++") compared to 34% in the other HIV positive children, but also this finding was without statistic significance (p=0.22).

14% (6) of those who started ART during enrolment died while being admitted in NRU with a mean of 12 days after initiation. Four of them would have been eligible for the study enrolment with early initiation of ART, but they died within three weeks after initiation.

The weight gain was calculated in gram per kg bodyweight and day. There was significant difference within the group of children on ART if analysed with multivariate regression after adjusting for age, sex, oedema and W/H SD-score at minimum weight (p=0.02):



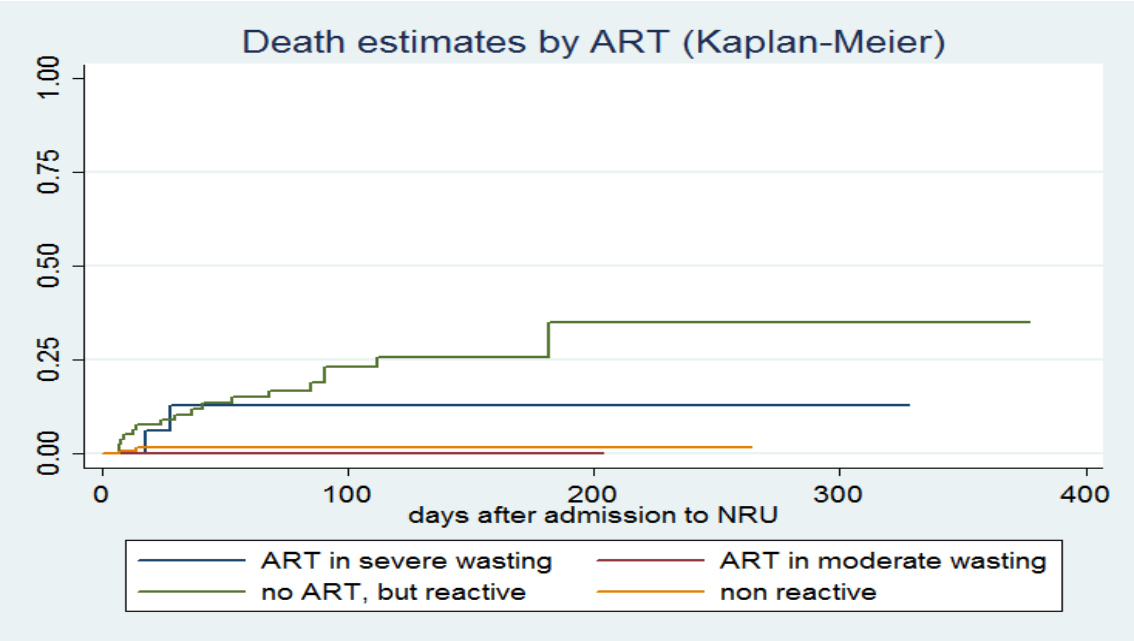
Graph 7: Average weight gain by time of ART initiation

The mean weight gain for the four different cohort groups was 6.0 g/kg/day for the early initiation, 5.5 g/kg/day for the late initiation, 5.7 g/kg/day for the no ART group and 5.1 g/kg/day for the non-reactive comparison group, if only marasmic children were taken into account. But these differences were again not statistically significant (p=0.12).

The number of children eligible for being enrolled in the study cohort was 115 according to the above described criteria (age between 6-60 months, severe

marasmus on admission to NRU, no ART before admission to NRU and discharged from NRU into the CTC program).

The power of this study was too small to gain sufficient evidence about mortality outcomes in the four different cohorts, but still an indication of direction as demonstrated in the following graph may be deducted from the findings:

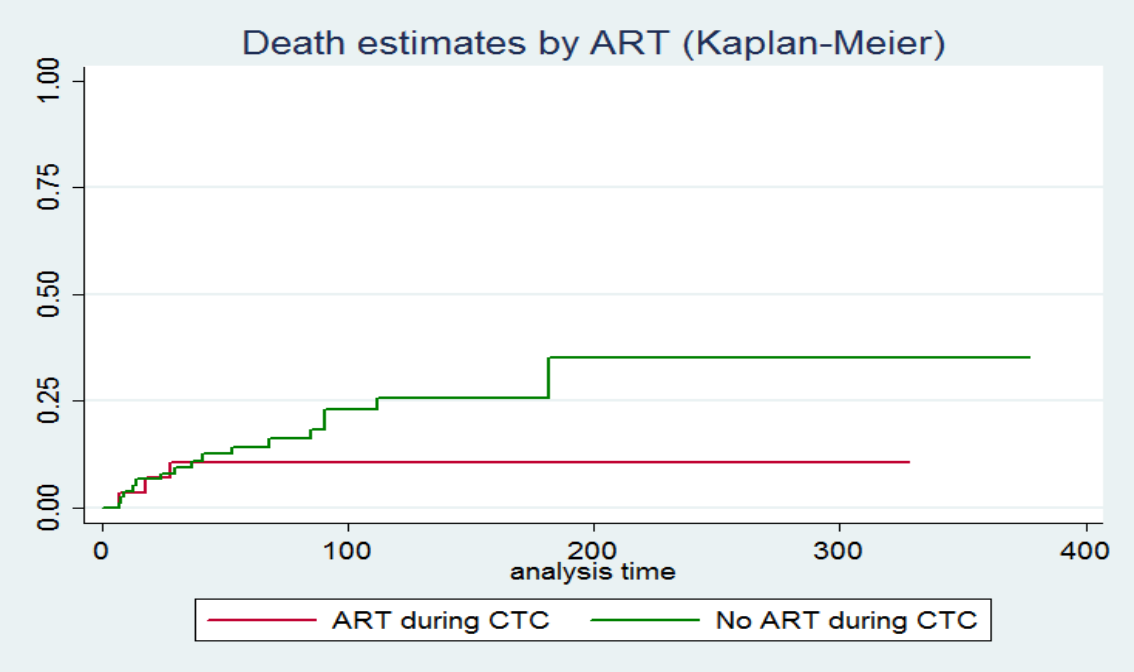


Graph 8: Death estimates for the four study cohorts by W/H defined ART initiation

If early and late ART initiation was defined by the W/H SD-score, the lowest mortality rate was found in the group of late ART initiation, but this might be biased because this cohort consisted out of only 10 children (as described above). The highest mortality rate was found in the group without ART (n=85), while the rate for children with early initiation (n=20) was higher in the beginning, but it was overtaken later on by the non-ART group.

If early and late initiation was defined by the day of ART initiation (30 days) instead of using the W/H SD-score, the graph appeared to be nearly identical with the previous (see graph 18 in annexes on page 74). The only difference was a slightly less rapid increase in the beginning for the group of early initiation, but this difference was negligible.

However, the overall picture became clearer if cohorts 1 and 2 were merged, so that the only differentiation was whether ART was started during enrolment in feeding program or not:

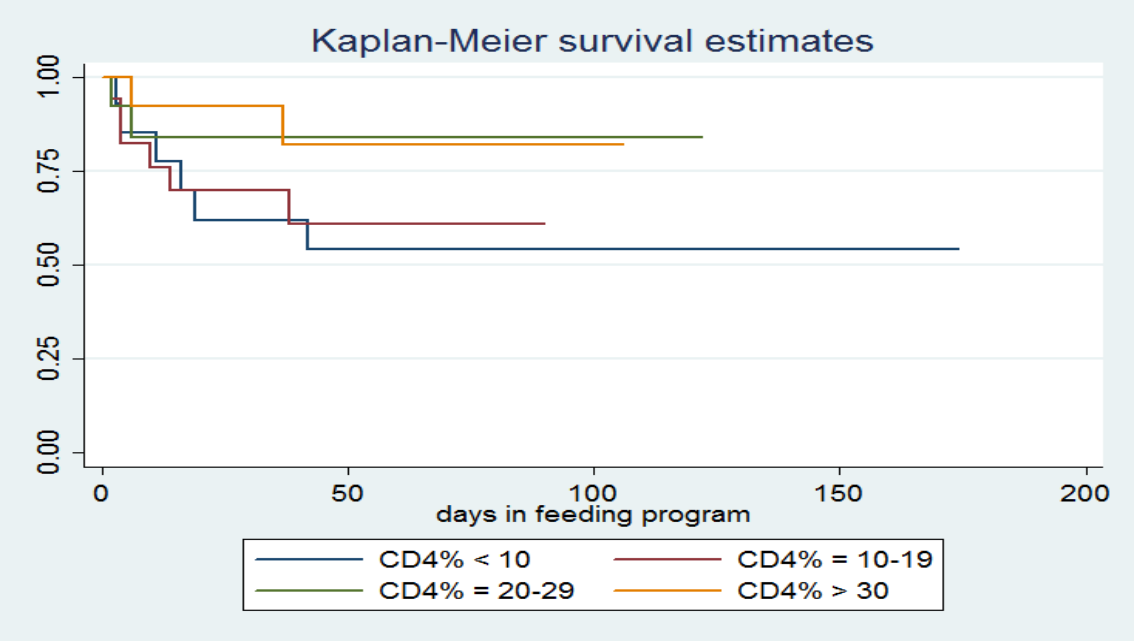


Graph 9: Death estimates with and without ART during feeding program (only children with known initiation time, adjusted)

After adjusting for age, sex, W/H SD-score, oedema and opportunistic infections this difference was clearly significant if all children with ART initiation were included (RRR 6.1, p= 0.027) and still significant if those with unknown initiation time and those who started after completing the CTC program were excluded (RRR 5.9, p= 0.041).

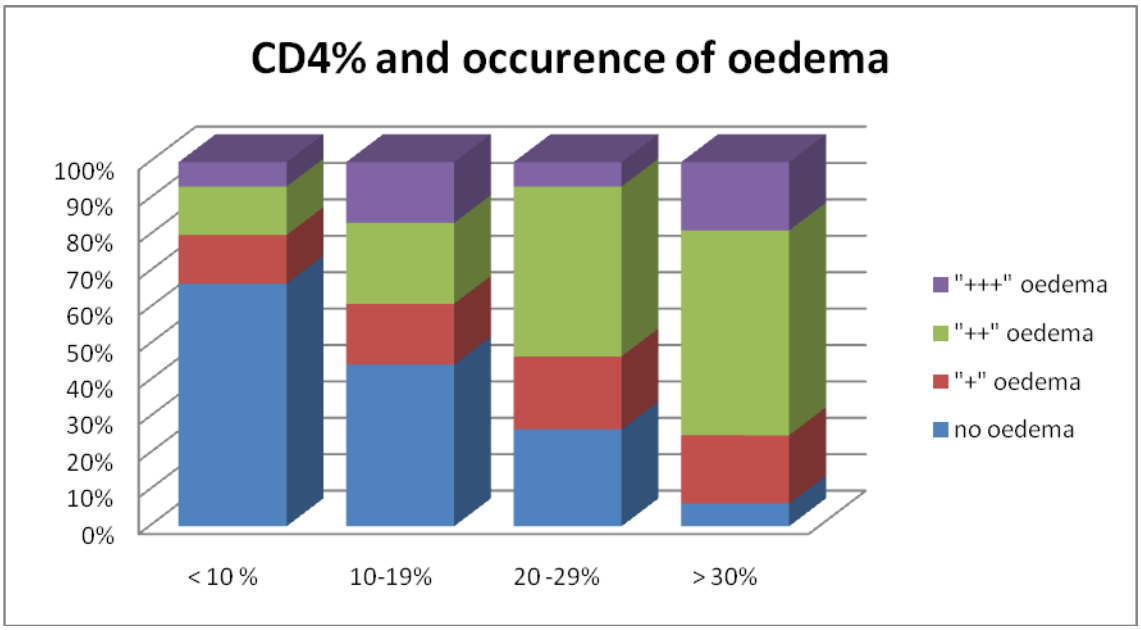
4.4 Predictors for Risk of Death

Analyzing the correlation between CD4 counts and mortality, the full cell count appeared to be a rather poor predictor for risk of death in severely malnourished children: considering all children 6 to 60 months of age the RRR was 0.9995 with a p-value of 0.055 if stratified after age, sex and oedema (129 observations).
The CD4% was only slightly more predictive, but this may be biased by the small number of observations (n=58): RRR 0.965, p=0.198. If the CD4% was categorised with a threshold of 20% the result became clearer: the RRR was 0.42 with a p-value of 0.32 for children with a CD4% more than 20% compared to those with a CD4% of less than 20%.



Graph 10: Survival estimates by CD4%

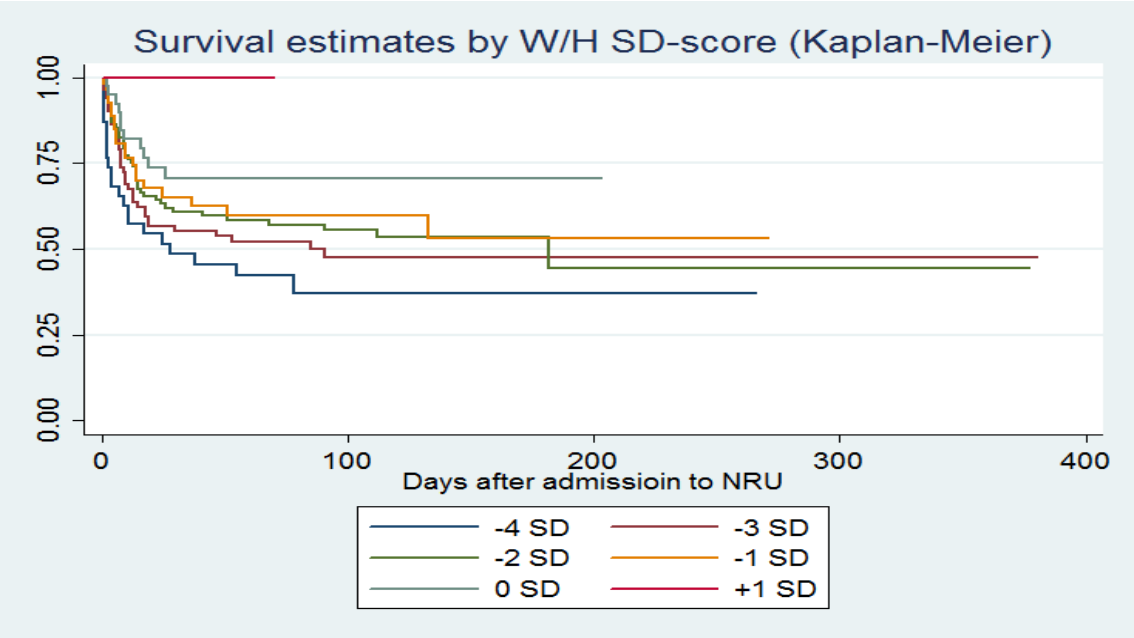
In contrast to the rather weak correlation between CD4% and mortality a statistically significant correlation between the CD4% and the occurrence of oedema could be observed (p=0.01):



Graph 11: Correlation between CD4 percentage and occurrence of oedema

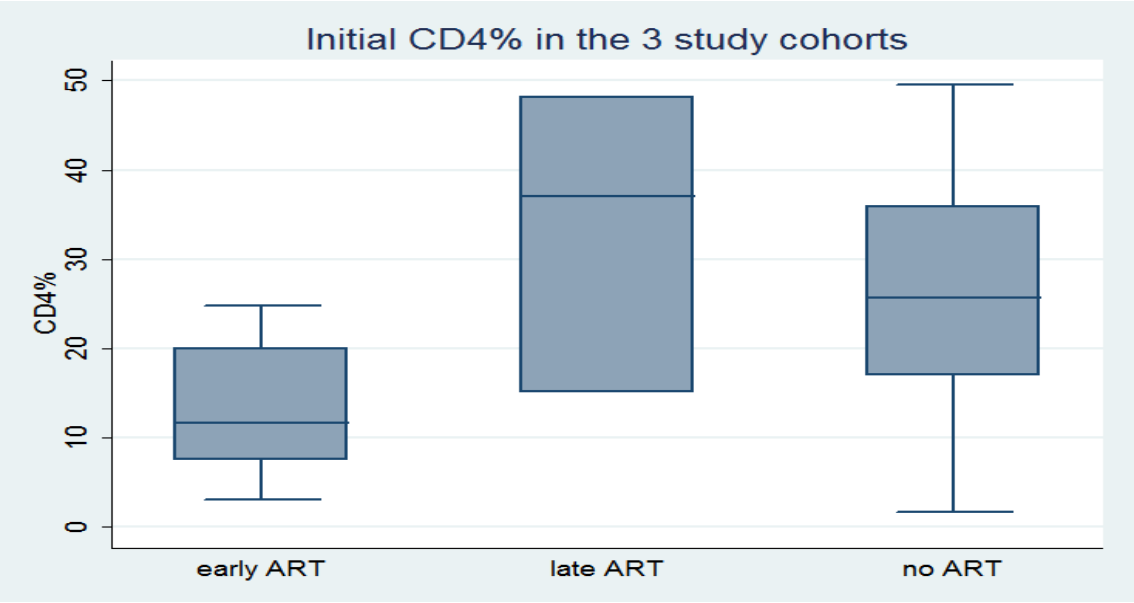
For the mortality in HIV positive children the best predictor in this study cohort was the occurrence of opportunistic infections (RRR 2.7, p= 0.006), followed by the W/H SD-score calculated with the minimum weight after oedema had resolved

(RRR 0.69, p= 0.014) and the MUAC (RRR 0.77, p= 0.02). Children with a SD-score of -4 or a MUAC of <110 mm had the highest mortality rates.



Graph 12: Survival estimates in HIV positive children by W/H SD-score on admission

The initial CD4% was taken only from 23 out of the study cohort of 115 patients. Therefore the following graph has to be interpreted with care. In the early ART group (8 observations) the CD4% was less than in the late (3 observations, p=0.038) and non ART (12 observations, p=0.09) groups.



Graph 13: Initial CD4% in the three study cohorts

5. Discussion

This study tries to find evidence for the development of guidelines regarding the optimal timing of ART initiation in HIV positive children presenting with severe wasting in a referral NRU. Retrospectively, data for 1329 children were entered into a digital database in order to extract information about differences in outcomes for different treatment schemes (early, late and no ART) in HIV positive children as well as for HIV positive, compared to HIV negative children. Many studies have shown that the mortality of HIV infected children is generally very high without ART, especially once they present with severe malnutrition. Also the recovery rate, defined by reaching at least 85% of the W/H SD-score, was frequently observed to be significantly lower than in non infected children. Up to now, there are no specific and evidence based guidelines available about the optimal timing for commencing ART in this patient group and thus many clinicians tend to wait for complete nutritional recovery. The question is whether the mortality rate and the rate of nutritional recovery can be improved by starting ART early during the enrolment in therapeutic feeding programs.

5.1 Differences in HIV positive versus HIV negative children

The frequency of HIV infection in the overall study population of 1329 children was 33% among all tested children in the NRU in ZCH, slightly less than the 37% Thurstans et al. (2008) found in their study which was also conducted in the southern region of Malawi. But since 20% of all children admitted to the NRU during the study period were not tested, this finding might not truly reflect the actual percentage of HIV positive children in the NRU in ZCH. Looking at the pattern of oedema, the average MUAC and the SD-score in the group with unknown HIV status at time of admission, it appears to be nearly identical with the patterns of those who were tested reactive (and thus significantly different from the non-reactive group). Furthermore, if the extremely high mortality rate in this group is considered, it can be assumed that most of them actually were HIV positive. Therefore the frequency of HIV in the NRU in ZCH during the observation period might have been in reality as high as 40 to 45%.

If the overall outcome of the NRU is compared to WHO or Sphere standards, the mortality rates turn out to be rather high. But these numbers need to be

interpreted in the light of the high prevalence of HIV infection as well as the frequent occurrence of severe nutritional oedema, which also result in increased case fatality rates (Cook and Zumla 2003). Accordingly, the overall mortality in a NRU is determined to a large extent by the prevalence of complicated malnutrition (Heikens 2007). At the same time the existing international standards are mainly based on experiences in situations of disaster and food insecurity and in presence of international organisations offering treatment with a high level of human and financial resources (Fergusson and Tomkins 2008b). In emergency situations with food insecurity, malnutrition tends to be more often uncomplicated while a referral NRU like that in ZCH mainly accumulates children with complicated malnutrition that cannot be handled by the outpatient program and smaller NRUs. Fergusson and Tomkins (2008b) found similar problems while evaluating their statistics and conclude that there is a need for development of new standards for quality of care for children presenting with complicated SAM which should be different from existing standards. Following this argumentation, a better indicator for comparison with the international standards might be the outcome for only non-HIV infected children. The mortality rate of this group was 14% in our study cohort and once only non-infected children without oedema were taken into consideration the mortality reduced to 9% which would be just within the given international standards of less than 10% (Sphere Project 2004).

This interpretation is supported by the findings of another study from the same region (southern Malawi) which reported similar mortality rates (Sadler et al. 2008). The authors of this study explained the high mortality rates also with the high prevalence of HIV infection in this area, with late presentation of children with severe malnutrition and consequently high early mortality rates and, in addition, with lack of trained staff in their NRU.

Nevertheless, the observed mortality rates in the NRU in ZCH remain high, even for non HIV-infected children, and it is advisable to carefully analyze options to further improve treatment outcomes, possibly by identifying patients most at risk of death early enough in order to manage close observation and immediate intervention if necessary, as suggested by Maitland et al. (2006). This might be especially helpful in settings of limited human resources as experienced in ZCH.

Looking at the outcomes of the outpatient program, the number of children transferred out to continue with OTP or SFP in health centres nearby to their home villages appeared to be strikingly low and at the same time the number of dropouts to be extremely high. Instead of being transferred, guardians were expected to come back to ZCH sometimes from far distances to collect the RUTF ration for their child. This problem can very well explain the extremely high dropout rate in the CTC program. During discussion with the hospital staff about this concern, it was mentioned that there is a problem with supply of RUTF in the health centres and also that too few health centres are involved in the CTC program. Further analysis is urgently needed to find out about the underlying reasons for not transferring patients for OTP and SFP to primary care health facilities. This is essential to tackle the problem of the high dropout rate and also to reduce the extremely high workload for the staff in the NRU of ZCH.

As expected and shown in many other studies (e.g. Fergusson and Tomkins 2008b), the mortality rate of HIV infected children was also significantly higher in this study cohort compared to children without HIV infection. In the same way the higher frequency of marasmus in HIV positive children combined with lower occurrence of oedematous malnutrition was also already reported in several other studies like the study of Bachou et al. (2006) in Uganda. But rather new (to the authors knowledge) and interesting are the observed mortality rates in the subgroups differentiated by their grade of oedema: HIV positive children were at highest risk of death when they had no oedema which is the exact opposite of what was observed in HIV negative children who presented with increased risk of death corresponding to the severity of oedema (for further details see graph 17 in annexes on page 74). Thus it seems that the causes of death in HIV positive children differ from causes in their HIV negative counterparts and consequently the risk of mortality can probably not be assessed in the same way. Possible explanations for this finding could be an involvement of the immune system in the development of nutritional oedema which will be further discussed in chapter 5.4 (page 52 et seq.).

5.2 ART for severely malnourished children

5.2.1 Mortality

Graph 19 on page 35 indicates clearly the overall benefit of ART for severely malnourished children. Comparing the outcome of all children on ART with those not on ART, the relative risk of death was greatly increased for the second group (RRR 5.9, p=0.041). This is even more impressive if the relatively short observation period, limited to the enrolment in the community-based feeding program after discharge from the NRU, is considered. This emphasises clearly the importance for commencing ART during the time of enrolment in feeding programs.

In order to answer the question about the optimal timing for initiating ART within the time of enrolment, the group of children on ART needed to be split up into subgroups, as described above, so that differences in their outcomes could be analysed. For this reason the two definitions of early and late treatment were made: one regarding the time and the second one regarding the W/H SD-score at start of ART. Both definitions resulted in rather similar death estimations according to Kaplan-Meier. If the definition of W/H SD was used, the mortality in the early treatment group (initiation at <=-2 SD) seemed to be slightly higher than in the second definition with early and late defined by the time when ART was initiated (number of days after admission to the NRU). In both definitions a relatively high early mortality was observed within the first weeks after commencing ART, which slightly overtook the mortality in the non ART group after around 30 days, but after approximately 50 days the lines crossed again and only a few deaths were observed in the early ART group afterwards. Since it takes some weeks until the effects of the drugs are noticeable in terms of rising CD4% and possibly lower mortality, the curve for the early initiation group might be explained as follows: For the first 50 days after admission the curve for the early initiation group resembled the one for the non ART group. Considering the mean initiation time of 15 days in the early treatment group, 50 days might be exactly the time when the ARVs begin to show effects on the immune system and this was the time when the mortality went down compared to the non ART group. Nevertheless, the difference between the early and late ART group seemed striking: While several early deaths were observed in the early ART group, there was no death at all in the late ART group. Even though this curve has to be interpreted with caution because of the small cohort of only

10 children, this finding seems to highlight the late treatment rather than the early treatment option. Important to know in order to draw conclusions from this observation would be the exact causes of death in the early ART group which was unfortunately not properly reported in the files.

Similar observations regarding to high early mortality rates after commencing ART were also made in other studies with HIV positive adults: Marazzi et al. (2008) e.g. showed that severe malnutrition (BMI < 18) in adults caused much higher early mortality rates in patients after starting ART especially over the first months compared to patients with a BMI > 18. Thus they recommend commencing ART in adults once the BMI drops to 18 and below even if the CD4 cell count is still high. Unfortunately there are no data available about mortality rates in a comparable malnourished population without ART. Hence also here it cannot be determined if this early mortality is attributable alone to the severe malnutrition in HIV or to drug interactions. Other studies in children showed an at least threefold higher risk of death in children in developing countries after starting HAART compared to children in developed countries which was explained not only with later diagnosis, but also with more frequent and higher levels of malnutrition and infections in developing countries (Kekitiinwa et al. 2008). Like Marazzi at al. also these authors conclude the urgent need for earlier diagnosis and start of treatment as well as nutritional support for HIV infected patients in African settings.

Regarding the question about the difference in the mortality rate between the early and the late ART group, it might be valuable to further consider the CD4% as indicator for the progression of the HIV infection in children. The data analysis showed that the percentage for the early ARV group in this study population was in average significantly lower than for the groups with late and without ART initiation. Since children with low CD4% are more likely to die as shown in several other research projects (Callens et al. 2009, Bolton-Moore et al. 2007), this finding has obvious effects on the expected mortality rates in the cohort. Thus without ART the expected mortality rate for the early ART group would be higher compared to all other groups which might have biased the overall outcome of this research. Unfortunately only few percentages were taken which makes stratification impossible and reduces the explanatory power of this finding. Nevertheless, the low CD4% in the early ART group might explain at least part of the high early mortality in the early initiation group, which might have been

therefore not only attributable to the ARV initiation itself and its interactions but also to the already extremely weak immune system in children who presented with probably already full blown AIDS. On the other side, if the difference in the CD4% is considered, it is even more impressive that the overall outcome in this group by end of the study period was still better than in the non ARV group which had higher CD4%. This again argues strongly for early initiation in spite of severe malnutrition and immune suppression.

In the same way the CD4% for the analysis with two groups (ART and no ART during enrolment in feeding program) was lower for the group with ART (18.7% versus 25.2%, p=0.26) and still they presented with a significantly lower mortality rate. This interpretation strengthens again the conclusion drawn above that ART is of benefit for children with HIV infection and severe malnutrition.

Regarding this high early mortality rate after commencing ART, another theory needs to be considered: Part of the mortality may be also caused by the effects of the paediatric HIV immune reconstitution inflammatory syndrome (IRIS). As Boulware et al. (2008) described in their review, a marked early mortality appears in children commencing ART, which might be related to IRIS especially if the CD4 cell count is very low at time of initiation, and also underlying malnutrition seems to enhance the development of IRIS in these children. The most common pathogens associated with IRIS in African settings are mycobacteria, followed by herpes viruses. Unfortunately it is difficult to differentiate IRIS from other infections, but it always needs to be considered if symptoms arise shortly after commencing ART. In order to avoid the development of IRIS it is important to treat latent infections before ART is started. This proves sometimes to be difficult, especially in children with severe malnutrition because they often show no symptoms of infection. Therefore broad-spectrum antibiotics should be given in any case of severe complicated malnutrition according to the WHO guidelines. Nevertheless, even if part of the early mortality observed in our cohort is due to IRIS, it is unlikely that deferred therapy start would have resulted in a big change in the number of deaths. A deeper insight about the occurrence and diagnosis of IRIS in these children might help to optimize therapy and care.

For further interpretation it would be also interesting to compare mortality rates of our cohort with rates observed in other studies under similar conditions. Unfortunately, there are (to the authors' knowledge) few comparable studies. Bolton-Moore et al. (2007) calculated e.g. a mortality rate of 17.4 deaths per 100

child years in Zambian children within the first three months after commencing ART. But this study is not really comparable with our study population, because the mean age was 81 months versus 34 months in our study and there were only few children with severe malnutrition in the Zambian population. However, according to Bolton-Moore et al., children with low weight for age and those with younger age are at higher risk of death. Considering the much younger age of our study population, which usually causes higher mortality rates compared to older children, and the severe malnutrition as starting point for all children, it is not surprising that the mortality rate in our study was much higher than the rate observed by Bolton-Moore and his colleagues. The comparison is further limited by small observation numbers as well as different observation periods, which were often shorter than the three months in our study, even if the child was discharged as cured. But still, if calculated for the group of children who started ART during enrolment in the NRU, the cumulative patient years add up to only 6.5 years and the number of deaths during this time to 7, which means 108 deaths per 100 child years. This would be more than five times as high as in the Zambian study population.

The mortality rate in our study population with early initiation was 19% if all age groups and all children who died while being admitted in the NRU were included. Since all children with severe malnutrition can be assumed to be eligible for ART, this group is somehow comparable with the deferred treatment group in the CHER (children with HIV early antiretroviral therapy) study, which had a mortality rate of 16% (Violari et al. 2008). Even though these two studies are hardly comparable, because the children of the CHER study were much younger (median of 7.1 weeks) and also not malnourished, the outcome appears to be not much different. Nevertheless, it remains difficult to draw a conclusion from this comparison. It seems that the mortality rate was not unexpectedly high in our early ART group when compared with the outcomes of these other studies, but this is more an arbitrary than evidence based conclusion.

Nearly the same picture is seen by looking at HIV infected adults: In their study, Lawn et al. (2008) found that between 8% and 26% of HIV infected persons who started ART died within one year, most of them within the first few months of treatment. Common causes of death in this study were TB, acute sepsis, cryptococcal meningitis, malignancies and wasting syndrome. A low BMI was strongly associated with increased mortality. The authors conclude that patients

need to be diagnosed and treated earlier. Even short delays while preparing patients for ART increased the mortality (Lawn et al. 2008).

The effect of malnutrition on survival after commencing ART in adults was also examined in a study of Paton et al. (2006): The authors were able to show that moderate and severe malnutrition in adults starting ART doubled the hazard ratio for death, while this finding seemed not to be associated with impaired immune reconstitution. The overall mortality rate in adults commencing ART in Tanzania was 29.7% after 12 months, and in addition to anaemia and thrombocytopenia, severe malnutrition proved to be an independent strong predictor for the risk of death: while only 13.7% of people with normal nutritional status died, the rate was 21% for those with mild and moderate malnutrition and 46.8% in cases with severe malnutrition with most of the deaths occurring within the first three months after initiating treatment (Johannessen et al. 2008). This study shows the immense effect malnutrition has on the survival of HIV infected patients. But neither study included a comparison of malnourished patients with and without ART, so the effect of the drug itself cannot be distinguished from the effect of malnutrition. Also the potential benefit of nutritional support for these patients and the respective grade of immunosuppression and CD4 cell counts remained untouched. Still, the authors deduced from these observations that nutritional support while starting ART might improve the outcome profoundly. With similar findings in his study, Zachariah et al. (2006) even suggested that the BMI could be used in adults as screening tool for individuals at high risk for early death.

Considering the results of these studies in adults and the severe malnutrition and young age of our study population, the mortality rate of 23% for all age groups and 20% for those between 6 and 60 months after starting ART until reaching the target weight, appears again to be acceptable (including those who died directly in the NRU). Unfortunately, there was no follow-up information after one year, but if only the time during enrolment in the feeding program is considered, it seems that the children of our study cohort are doing even better than severely malnourished adults who did not receive any nutritional support at start of ART. Therefore the conclusion of the other authors can be highlighted again: Nutritional support is essential for survival of malnourished individuals who start ART, whether adults or children. It might be not sufficient to just wait for the ART induced weight gain because then preventable deaths may occur.

5.2.2 Weight gain

In line with the study of Fergusson et al. (2008a) the weight gain in the HIV infected study cohort was higher than in the non infected cohort if calculated in g per kg bodyweight and day (5.3 versus 4.7). This is true for marasmic children as well as for children with kwashiorkor and remains the same after adjusting for age, sex and W/H SD-score on admission. Although these findings are statistically insignificant in both studies, it is a very interesting point because most people would expect HIV positive children to gain less weight as a result of frequent infections, alterations in the gastrointestinal tract and loss of appetite. If this finding could be validated by further studies, it would highlight the great importance of nutritional support for HIV positive children.

Nevertheless, in contrast to the findings of Fergusson et al. (2008a), our study population showed a higher weight gain in children with CD4% of less than 20%, even though this result is not statistically significant. A possible explanation for the difference might be enhanced by further splitting up the cohort into four instead of two subgroups: children with a CD4% of 10-19% gained significantly faster than those with a lower and also those with a higher percentage (9.1 versus 3.5-4.6 g/kg/day). The lowest weight gain in our study cohort was observed in children with a CD4% of less than 10%. In the article of Fergusson et al. the mortality rate for children with a CD4% of less than 10% was not reported, but differences in the proportion of children below 20% and 10% might possibly have caused the discrepancy in the observations. In addition, this result needs to be interpreted while considering the occurrence of oedema which was clearly depending on the CD4%: the higher the CD4% the more severe oedema appeared and, as shown in the general statistics, children with kwashiorkor usually show a less rapid weight gain than marasmic children. Consequently it would be plausible that children with lower CD4% would gain weight more rapidly because a bigger proportion of them might be marasmic while those with higher CD4% more frequently have kwashiorkor and are therefore expected to gain less weight. A further point that should be considered is the percentage of children who commenced ART which was higher in the group with a CD4% of less than 20% (48% versus 35%). Actually children on ART were expected to gain weight faster which could possibly have caused a bias in this result but, in our cohort, children on ART did not gain weight

significantly faster than those without ART (as further discussed in the following paragraph) and thus the outcome remained the same after adjusting for ART.

In order to answer the question about the optimal timing of ART during enrolment in the nutritional rehabilitation program, the average weight gain, (discharge weight minus minimum weight) again calculated in g per kg bodyweight and day, was plotted against the number of days between admission to the NRU and ART initiation (see graph 7, page 33). This visualisation clearly shows the benefit of commencing ART early during enrolment in a therapeutic feeding program: the average weight gain was significantly higher if ARVs were started early during the enrolment and increasingly slower with later initiation. Therefore children who started ART early recovered faster from severe malnutrition compared to those who started towards the end of the therapeutic feeding program. The role of ART in improving the nutritional status is increasingly recognised (Heikens et al. 2008) and several studies like that of Kabue et al. (2008) were able to show the positive impact of ART on weight development in children. In contrast to these apparently clear and obvious findings, the average weight gain of HIV infected children without ART was observed to be even slightly higher when compared to those with ART in our study population (4.9 versus 5.2 g/kg/day, p=0.6). This difference is far from being statistically significant, but still it is unexpected and difficult to explain. On the contrary, most clinicians report rapid weight gains after commencing ART. One hypothesis to explain this phenomenon could be that ART impairs the weight gain for a short period of time after starting treatment, possibly because of the initial side effects of the drugs, but accelerates it in the long term run. This would at least fit the observations described above about the average weight gain according to time of ART initiation, because children who started early had a more rapid weight gain than those who started late and had even a slightly more rapid weight gain than the non-ART group (6.0 versus 5.5 versus 5.7 for non-ART). But this is hardly more than speculation. Detailed data and weight curves, as well as information about appetite and side effects of the drugs for the first days and weeks for children commencing ART, are needed for further investigations and conclusions which could not be found in currently published articles.

Considering the higher rates of weight gain in children who started ART early, it can be assumed that they reached their target weight faster and therefore had a shorter duration of enrolment in the feeding program, which is exactly what we could observe in our study population (p=0.017): children who started early stayed an average of 84 days, while those with late initiation stayed 160 days and those without initiation 95 days. Accordingly, the time of enrolment for HIV positive children and therefore the workload for the respective health staff could probably be reduced by starting ART early.

In a recent study about the effect of pre-existing malnutrition on growth and weight gain in HIV positive children who commenced ART (Bandyopadhyay and Bhattacharyya 2008), the study cohort without malnutrition showed higher weight gain than the cohort of children who were malnourished at the point of initiation. The authors conclude that pre-existing malnutrition might impair the nutritional response to treatment. This finding is surprising because usually, in malnourished children, a catch-up growth with very high rates of weight gain can be observed, but this might only be true if nutritional support is given which was not the case for the study population of Bandyopadhyay and Bhattacharyya. This study also stands in clear contradiction to the observations of our research where, within the group of children who started ART during nutritional rehabilitation, the fastest weight gain was found in those with severe malnutrition in terms of a W/H SD-score of -3 and -4 (6.5 and 5.9 g/kg/day), while the weight gain for the moderately and mildly wasted children was far slower: 3.6, 3.2 and 1.3 for SD-scores of -2, -1 and normal weight for height, respectively. There is no obvious explanation for these reverse findings, except, possibly, the nutritional support which could have made an important difference in the outcomes. However, it would be an interesting subject for further research projects.

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5.3 The role of the CD4%

The CD4% is widely used for determining the progression of HIV disease and the functionality of the immune system in HIV positive children, in addition to the clinical staging according to WHO criteria. Even though severe malnutrition itself often results in a reduced CD4%, a difference can be observed if severely

malnourished children are split up according to their HIV status: HIV negative children usually present with higher percentages than their HIV positive counterparts (Bachou et al. 2006). A further difference is that the immunological dysfunction caused by malnutrition alone is much broader and not mainly limited to CD4 cells as in HIV disease. Nevertheless, the immunosuppression in malnourished children can cause similar symptoms as AIDS and is therefore sometimes difficult to differentiate without immunological diagnostic. Thus this condition was named as nutritional AIDS (NAIDS). Even more problematic is the development of secondary NAIDS in an AIDS patient which is difficult to treat and often results in very high mortality rates (Beisel 1996). Since the CD4 counts were only taken in HIV infected patients in our research project, there was no information available about these described differences in our study cohort and hence the interpretation can only focus on differences within HIV infected children. Unfortunately, even for HIV infected children, the information available from the hospital laboratory was limited to the time after June 2008 and with CD4 counts being repeated usually only after six months follow-up, values were available only for very few children. For some more children, instead of measuring the CD4%, only full CD4 cell counts were done without total lymphocyte cell counts so that the percentage could not be calculated retrospectively and therefore this information is of very limited use for analysis and interpretation, especially if the wide range of age within the cohort is considered. It would have been very interesting to see how the CD4% changed after some time on ART in order to judge the immune response to ART in severely malnourished children with HIV infection, but because of the described limitations in the dataset this discussion is confined to a number of base-line CD4% taken before ART was commenced, enhanced by information and findings of other published studies.

As already mentioned above, the mean CD4% has generally shown to be significantly lower in HIV infected than in non-infected children. For example, Fergusson et Tomkins (2008b) calculated a mean of 13% versus 33% for HIV positive versus HIV negative children admitted to feeding programs with severe malnutrition. Within the subgroup of HIV infected children the CD4% was significantly lower in those with marasmus than in those with oedematous

malnutrition (Hughes et al. 2009), which corresponds exactly with the 14% versus 26% (n=32 versus 41, p=0.001) in our observations.

It has already been briefly discussed that the CD4% influenced mortality as well as the rate of weight gain in our study cohort. The mortality rate for children with a CD4% of less than 20% was higher than for children with a CD4% of more than 20% (RRR 0.3, P=0.113). Several other studies reported similar and even more significant results. For example, Chinkhumba et al. (2008) found a difference in the mortality rate of 40% versus 15% in ART naïve children without serious medical complications using the same CD4% threshold of 20%. These results strengthen the explanatory power of our findings even though they are not statistically significant. However, it is quite interesting that in our study cohort the grade of wasting (W/H SD-score) was clearly the stronger predictor for the risk of death than the CD4% (RRR 0.98 versus 0.63, p=0.56 versus <0.005, univariate analysis). Since wasting appeared as an independent risk factor it can be assumed that part of the high mortality rate is attributable to the severity of malnutrition and not only to advanced immunosuppression. This finding could be interpreted in line with the above mentioned problem of secondary NAIDS in AIDS patients. At the same time, this finding questions the value of the CD4% in deciding about ART eligibility in severely malnourished patients. If the grade of wasting is a better indicator for the risk of death, it might be also better for deciding about ART eligibility in these children than the CD4%. This assumption may be supported by the findings of the recently closed DART trial where Mugenyi et al. (2009) where able to show that, within the first two years after starting ART, clinical driven monitoring in HIV infected adults leads to similar results as routine laboratory driven monitoring. In contrast to this finding, many other studies emphasise the high value of the CD4%: according to the observations of De Baets et al. (2007) the CD4% was found to be the strongest prognostic value for disease progression. Also Callens et al. (2008) suggest that age specific CD4% thresholds should be used for determining ART eligibility in children even though they found the agreement between clinical and immunological criteria to be poor. In addition, some authors argue that the CD4% correlates directly with the grade of malnutrition in HIV positive children (which matches with our findings) and leads to a further depletion of CD4 cells in this population, so that most of the HIV positive children with severe malnutrition can be expected to be eligible for commencing

ART after completing nutritional rehabilitation (Agarwal et al. 2007). In accordance with this, Hughes et al. (2009) found that the CD4% of uninfected children with severe malnutrition remained more or less the same before and after nutritional therapy, while it dropped clearly in those infected with HIV. They also found that the percentage of children with severe immunosuppression (defined by CD4% <15) in their HIV positive population increased from 46% to 85% during nutritional recovery. At point of discharge from the hospital, all children who initially presented with severe marasmus and HIV infection showed severe immunosuppression and were therefore eligible for commencing ART. Hughes at al. concluded that all children with severe malnutrition in HIV infection should be started on ART. This emphasises again the importance of seizing the opportunity to start ART already during enrolment in therapeutic feeding programs. Once patients are discharged they may be much less likely to come back for initiation and may even disappear in the community without making use of the opportunity of ART for their children, until it may be too late for initiation.

Another important subject that should be addressed in a discussion about CD4% is that of opportunistic infections. Generally the occurrence of opportunistic infections is expected to correlate with low CD4%. 20% (68) of all HIV positive children in our research were reported to have at least one opportunistic infection during enrolment in the feeding program of which 79% (54) were identified as PTB. Looking at the risk of contracting an opportunistic infection, it was, as expected, significantly increased for those with CD4% below 20% when adjusted for age, sex and W/H SD-score (p=0.041). The mean CD4% for those with opportunistic infection was 16% versus 23% for those without opportunistic infections. If the threshold was increased to 25% a difference was still observed, but it was not significant anymore, while the difference increased slightly if the threshold was reduced to 15%. Only 4% of children with CD4% of more than 20% had contracted an opportunistic infection is spite of severe malnutrition, while it was 35% in those with a CD4% of less than 20%. This finding supports the recommended threshold of 20% by the WHO (2008c) as indicator for severe immunosuppression. In addition to an increased risk of contracting opportunistic infections, children with a low CD4% are also more likely to develop IRIS and drug related toxicities which was not

recorded in this dataset but might also have influenced the overall outcome as discussed in chapter 4.2.1 (Subbaraman et al. 2007).

Another interesting observation reported by one study is that severely malnourished children without HIV infection had better chances of survival even if their CD4% was at a level similar to HIV negative children (Chinkhumba et al. 2008). Even though this observation was based on very few patients (only few non-infected patients have such low CD4 levels), this might indicate that there is more involved in the high mortality rate than simply the CD4% as measure for immune suppression, and therefore the CD4% alone might be insufficient to decide ART eligibility. Again the hypothesis about secondary NAIDS as aggravator in AIDS patients may be part of the explanation.

5.4 Nutritional oedema

As shown above nutritional oedema significantly influences the outcome of non-HIV infected children in terms of higher mortality rates, while their interaction with HIV seems to be rather complex. The correlation between the occurrence of oedema and the CD4% in HIV positive children has been observed and reported already before by other authors. But still it remains difficult to bring it in line with the aetiology of kwashiorkor.

The mentioned theory about the involvement of the immune system in the occurrence of nutritional oedema can be further supported by also analyzing the respective CD4% in the subgroups. Bachou et al. (2006) were for example able to show that children with kwashiorkor have generally higher CD4 counts than marasmic children. In line with this report, in our cohort the CD4% of HIV positive children corresponded more or less directly to the occurrence of oedema (see graph 11, page 36). Within the group of HIV positive children those with high CD4% appeared to have even significantly more oedema than those with low CD4% (RRR 2.2, p=0.005). This supports the assumption of immune system involvement in the development of nutritional oedema. It seems that HIV positive children with kwashiorkor have better immune competence than their marasmic counterparts. This can be expected to result in a better immune response to infections and therefore in fewer deaths, which might again be affected by the severity of oedema and the accordingly increased mortality rate. In HIV negative children the immune suppression caused by malnutrition

might not play such an essential role in mortality rates because it is generally not as severe as in HIV positive children (Bachou et al. 2006).
These findings and the hypothesis about immune system involvement could be interpreted in line with the theory of oxidative stress and free radicals being involved in the aetiology of nutritional oedema. Studies showed that free radicals are increasingly generated following infection and sepsis and are thus triggered by the body's response to bacterial endotoxins or even to aflatoxins ingested with food (Golden 2002). Consequently, if the immune system is very weak, the body might respond less strongly with generation of free radicals which might again lead to reduced occurrence of nutritional oedema. In the same way, HIV positive children with high CD4% might have better immunological response to their often frequently acquired infections which in turn might cause increased occurrence of oedema. This hypothesis could easily be proven by measuring free radical activity levels and CD4% in HIV positive and negative children with and without kwashiorkor. But as long as we do not know more details about the pathophysiology it is too early to change treatment guidelines like giving high doses of antioxidants for children with kwashiorkor (Golden 2002).

In the group of HIV positive children with "+++" oedema, the mean observed CD4% was less and the mortality rate higher than in the groups with "+" and "++" oedema. Unfortunately the number of observations in this group was small (eight children) and therefore this finding far from being statistically significant, but a possible explanation might be that the severity and effects of nutritional oedema overlaid the immunosuppression in this group. However, it would be interesting to study this issue, especially because it might give us further hints about the aetiology of nutritional oedema.

Of further interest is that only 6% of HIV positive children with CD4% above 30% were admitted with marasmus (n=16), while it was 67% for those with a CD4% below 10% (n=15) and 21% for HIV negative children. Bachou et al. (2006) found a mean CD4% of 33% for the 192 HIV negative children in his study. If this percentage is transferred to our findings it seems that children with HIV and high CD4% are at even greater risk of developing nutritional oedema and also of developing more severe oedema than HIV negative children with

similar high CD4%. The only obvious explanation would be that the non-infected malnourished children in our cohort had lower CD4% than observed by Bachou et al. in Uganda, but this might be not very likely. Therefore it would be interesting to see if studies in other settings find similar results in order to know if the pattern of oedema generally corresponds to the CD4% or if there are other factors involved. But unfortunately (to the authors knowledge) there are currently no comparable published studies.

5.5 ART initiation before admission to the NRU

Another interesting group is that of the 18 children who started ART before admission to the NRU. Except for one child, all were admitted with severe complicated malnutrition within one year after commencing ART. The mortality rate among these children was significantly higher than the one observed for the group with initiation after admission to the NRU (50% versus 27% until discharge from the NRU and 67% versus 30% until exit from of the feeding program (p=0.002) and it was even higher, though not statistically significant, than the rate for those without ART (39% and 46%, p=0.6). 14 out of the 18 children came to the NRU with a lower W/H SD-score than they had at time of ART initiation, and 11 had even directly lost weight. The mean weight change in all 18 children between start of ART and admission to NRU was -0.9 kg and even -1.75 kg if the minimum weight was used for the calculation. Those few children who did not lose weight were admitted with severe oedema so that all except for one child ended up with lower weight compared to start of ART once the oedema had resolved. Considering this development it gives an extremely discouraging picture of ART in children. But it is impossible to judge from this limited information if the weight loss was caused by treatment failure, side effects of the drugs, food insecurity at home or a combination of these factors. It would, for example, be interesting to know the total number of paediatric admissions to the HIV program over the time period when those 18 children commenced ART, but these data were not available. Therefore it is impossible to tell what percentage of children who started on ART came back with severe malnutrition. Also remarkable is the high percentage of children admitted with “++” and “+++” oedema which was 50% compared to 34% in the rest of HIV positive children. Unfortunately only few CD4% were taken in this group and

most of them were baseline CD4% and not the respective value for time of admission to the NRU, hence the correlation between CD4% and oedema, as described before, could not be investigated in this group. Though this finding is not statistically significant it could still be interpreted in line with the above mentioned finding of immune system involvement in the occurrence of oedema. If children with oedema have a higher CD4% on average, then it would be plausible that children who started on ART appear after some time with similar patterns of oedema to those not infected with HIV, or infected, but with still high CD4%. This would argue for an adequate immune response to ART in these children instead of treatment failure, but without further information about the CD4% before and after treatment, this interpretation remains speculative and it would also not explain the high mortality in this group. Another point relating to these observations is the importance of close monitoring and nutritional support once a child is started on ART. Only four out of the 18 children were enrolled in a feeding program at start of ARV treatment while nine had a W/H SD-score of -2 and less at this time which means that they were actually eligible for enrolment in either SFP or OTP. But even children with completely normal W/H SD-score lost weight dramatically within weeks or months after starting treatment while not receiving nutritional support. Consequently it might be desirable to enrol all children starting ART for nutritional support independently of their W/H SD-score or, if this should be not feasible, at least close monitoring of weight and appetite over the first months of treatment should be part of every ART program so that intervention can be started immediately in case of any problems. According to our observations it cannot be assumed that all children commencing ART will recover from malnutrition automatically. Still the question of possible treatment failures remains unanswered. And also the high mortality rate among these children remains unexplained. Additional information like follow-up CD4 counts, viral loads and individual treatment adherence would be necessary in order to determine how many of these children came back because of treatment failure.

5.6 Mortality in HIV positive children without ART

The overall mortality rate in HIV infected children admitted to the therapeutic feeding program was very high: 34% of all HIV infected children died during the

in-patient stabilisation phase in the hospital and until end of the feeding program the mortality rate increased up to 43% for all and up to 47% for those without ART. Even if ART would have been initiated early during enrolment in the feeding program, it might have been too late for most of these children and thus would not have improved the early mortality rate much. In order to make the cohorts more comparable, only children who survived the initial stabilisation phase in the NRU were included in this study. Consequently all children who died in the NRU had to be excluded from the data analysis. But actually this group accounted for the majority of deaths and therefore it is worth discussing possible solutions to improve the outcome for these children. 56% of all deaths in this group occurred within the first week after admission, 26% during the second week and only 18% after staying more than two weeks in the NRU. The mean time of survival was 8.8 days after admission to the NRU. This early mortality indicates the advanced status of AIDS and/or malnutrition and the late presentation of these children to the hospital. The mean CD4% was 17.3% for children who died in the NRU compared to 23.6% (p=0.088) for those who were discharged as stable into the CTC program and the mean for the minimum W/H score was -2.7 SD versus -2.3 SD (p=0.043), respectively. As has been already described in the analysis of the children on ART, the W/H SD-score seems to be a stronger indicator for the risk of death than the CD4%. But in contrast to the above mentioned findings, the CD4% is nearly as significant in predicting the risk of death in those who died in the NRU. This means that the CD4% is much stronger in predicting the short term death (mortality during stabilisation phase) than it is in predicting long term death (mortality during outpatient program), while the predictive value of the W/H SD-score was nearly identical in both categories. This observation is difficult to explain. A possible reason might be that children with severe immunosuppression are at much higher risk of contracting infections in a hospital setting, infections which can easily cause death in such weak children. It would be interesting to see if the same observation can be made also in other settings. Nevertheless, the conclusion that can be drawn from the high mortality rate in this group is that, in order to save more lives, it is essential to diagnose these children earlier and to give nutritional support before they end up in a state of severe immune suppression and malnutrition which is clearly associated with a very poor prognosis.

Attending pre-ARV clinics needs to be emphasised in order to monitor the development of vertically infected infants and to ensure early treatment.

Other authors make similar recommendations. For example, Chinkhumba et al. (2008) observed that 37.7% of children in Malawi who required ART, determined by their CD4% according to WHO (2006b) criteria, died during the in-patient stabilisation phase in the NRU and nearly 70% of all children with SAM in this study were already eligible to start ART at the time of admission. Again the authors highlight that it may be too late to start ART once children arrive with severe malnutrition.

In the CHAP study in Zambia 63% of children with malnutrition at the beginning of the research project died within the observation period (maximum of 2.6 years) while not being on ART. Malnutrition and hospitalisation for respiratory or bacterial infections predicted mortality independently of immunosuppression, which suggests that they captured HIV as well as non-HIV related deaths (Walker et al. 2006). As an indicator for immunosuppression and therefore AIDS related mortality, oral candidiasis was the strongest variable. The percentage of deaths observed by Walker et al. is somewhat consistent with the observed mortality of 46% in our non-ART study cohort in a maximum of 370 days observation time, especially if assumed that at least a part of the 20% of dropouts died at home. Also malnutrition and opportunistic infections as predictors of mortality seem to be in line with the findings of our study.

Several authors, who were cited above, mention the need to start ARVs much earlier than typical, in other words before children enter the vicious cycle of malnutrition, infections and AIDS. This appears to be the only way to reach the MDGs in countries strongly affected by HIV/AIDS. The whole human development in these countries depends on improvement of interventions to prevent the further spread of HIV and to give optimal support to those already affected. As shown in this discussion, one of the most effective interventions within the framework for tackling HIV disease might be nutritional support (Colecraft 2008).

An additional reason to initiate ART prior to severe immunosuppression is the dependency of the immune system recovery on the baseline CD4 count (Newell et al. 2006). A recent study of Pensieroso et al. (2009) was able to show that early initiation of ART during the first year of life resulted in normal percentages

of memory B-cells in vertically infected children and accordingly in much better immune responses to vaccinations compared to the late treatment group who had insufficient response, in spite of being successfully treated with ART. Since successful vaccination plays a key role in reducing under-five mortality rates (Eddleston et al. 2008) this is a strong additional argument for initiation of ART in children before they reach the age of 12 months.

Furthermore children with severe immunosuppression are at higher risk of developing IRIS, as described above, and the overall associated morbidity and mortality increases greatly with severe immunosuppression (Becquet and Mofenson 2008). Consequently, the median survival in resource-poor settings is only 1.6 years for perinatally infected infants without treatment. As mentioned in the introduction, it is increasingly recognised that early initiation of ARVs for all children with under 12 months is feasible and improves greatly the outcome, even if distributed from decentralized primary health care facilities (Becquet and Mofenson 2008).

Thus the recently updated guidelines of the WHO (2008c) are based on good evidence about the benefit of early ART for infants below 12 months of age. This should set as priority in the fight against HIV/AIDS. If these guidelines could be applied worldwide and with good coverage, it would automatically reduce the impact of the difficulties in determining the right timing for the initiation of ART in HIV infected children older than 12 months.

And since prevention is always better than therapy we should, in addition to early diagnosis and treatment for all children at risk, not forget to emphasise the need for interventions that strengthen the prevention of mother to childhood transmission (Brichard and Van der Linden 2009).

5.7 Further issues for discussion

5.7.1 Is RUTF the best solution?

The question may be raised if home based therapy is the optimal form of rehabilitation for severely malnourished children with HIV infection. There is good evidence for the benefit of the use of RUTF in home-based therapeutic feeding programs in HIV negative children, but since HIV positive children are at much higher risk of developing complicated malnutrition as well as frequent infections it might be better for them to be treated as in-patients to ensure close

monitoring. On the other hand, the risk of attracting infections is higher in hospital settings. Ndekha et al. (2005) compared the outcomes of their RUTF based OTP program in southern Malawi and found a recovery rate (here defined by reaching 100% W/H SD-score) of 56% in the HIV infected compared to 84% in the non-infected group. The outcomes of our study were somewhat different from the findings of Ndekha et al.: 62% of HIV infected and 69% of non-HIV infected children who started the OTP program were discharged as cured after reaching their target weight. These results may be biased by the high dropout rates of 18 and 20% respectively, but the difference in the outcomes between HIV positive and negative children still appears to be smaller. Another possible explanation might be that the difference is caused by the definition of recovery: For our study recovery was defined as 85% W/H SD-score instead of 100% in the study of Ndekha and his colleagues. HIV infected children may be more likely to reach 85% than 100% compared to non-infected children. Thus comparability of these statistics is quite limited.

Unfortunately it is also impossible to compare these results with inpatient treatment statistics since children are admitted to the OTP only after a stabilisation phase so that deaths occurring during this time period are not included. However, considering the calculated difference in death of 30% versus 8% for HIV versus non-HIV infected children by Fergusson et al. (2008a), the observed differences in the OTP seem to be at least not worse. Therefore it can be assumed that home-based therapy is also of benefit for HIV positive children (WHO 2005a).

5.7.2 Micronutrient deficiencies

This research did not tackle the question of the role of micronutrient deficiencies which also play a vital role in the immune cell functions and can thus be expected to complicate general malnutrition. These deficiencies might also influence viral expression and replication as well as progression and mortality of HIV disease especially in malnourished children (Oguntibeju et al. 2007). Often they are difficult to diagnose, especially in resource poor settings. However, the therapeutic foods used in the NRU, OTP and SFP are all fortified with vitamins and minerals so that micronutrient deficiencies are addressed even without being diagnosed. Nevertheless, further research about the influence of micronutrient deficiencies on the clinical progress of HIV in children with severe

malnutrition would be very interesting and might improve the treatment and care by adjusting the dosage of single micronutrients.

5.7.3 Treatment adherence

Also not sufficiently addressed by this project is the question of treatment adherence. Especially in the group of children who presented with severe malnutrition some time after commencing ART, information about their adherence to the treatment would have been very important for interpretation. But insufficient adherence might have also influenced the outcomes for the other children who started ART. There is an interesting study which showed that children who had once received nutritional support were less likely to adhere to ART than those without support and, similarly, children from parents who had to pay a treatment fee were more likely to adhere compared to those who got treatment for free (Biadgilign et al. 2008). These are rather discouraging results that need further investigation. Insufficient treatment adherence will obviously have dramatic effects on the long term outcome, especially regarding the risk of emergence of virological resistance to the first-line treatment. Adherence in children is absolutely essential, considering that they need to continue with the treatment for their whole live.

5.8 Explanatory power and limitations of this research

This research is limited in its explanatory power mainly because of the retrospective study design and the small sample size. At some points sufficient data were not available to answer arising questions. Information about changes in the CD4% before and after starting ART would have been of great value for further interpretations. Also the recording of opportunistic infections was quite poor and mainly restricted to children who were enrolled in the paediatric ART clinic. Standardised recording of information for children in the pre-ART phase started in Zomba district just in May 2009. Therefore all data for this group came solely from the nutrition program which was often insufficient regarding information about HIV disease progression. Also the heterogeneity of the cohorts caused problems in interpreting the results. Furthermore, the measure of severe malnutrition as a starting criterion might be of limited use in defining the clinical state of HIV in an area with a generally high prevalence of

malnutrition because of food insecurity. In spite of these serious limitations, this study presents some interesting results and gives background information that might indicate better options for treatment of children with HIV infection and severe malnutrition. Certainly, this research provides ideas for further significant research projects.

6. Conclusions

The key point for answering the study question is the evidence provided by this dataset that starting ART during enrolment in a CTC program is strongly advisable for children with HIV infection and severe malnutrition. The difference in the observed risk of death between discharge from the NRU until end of the feeding program was significantly higher for those who did not commence ART (RRR 5.9, p=0.041). As several other studies have shown, children with HIV infection and severe malnutrition, especially if they are marasmic, are nearly always eligible of initiating ART at time of discharge from the feeding program if immunological criteria such as the CD4% are used for staging and determining ART eligibility. Since patients are generally less likely to come back to begin treatment once they are discharged from feeding program, all of them should be initiated before reaching the target weight especially while considering that initiation prior to severe immunosuppression seems to be much more beneficial for them. Furthermore, it might be advisable to give them nutritional support during the first weeks on ART, even if they are already above target weight, because some of them appeared to lose weight for a short period of time after commencing treatment without being on nutritional support. At least close observation is essential during the first weeks, and possibly months, on ART so that immediate intervention can be guaranteed if they do not respond to the treatment as expected.

The more detailed question concerning the optimal timing of ART within the therapeutic feeding program still remains not clearly answered. It seems that there is an increased mortality during the first weeks after early initiation of ART, especially in children who were still severely wasted at time of ART initiation, but it is not clear if this mortality is attributable mainly to drugs and its interactions or possibly to a higher prevalence of severe immunosuppression

and hence advanced AIDS in this study group. The conclusion that can be drawn from these results is that it might be advisable to give newly admitted children with severe wasting and HIV at least a chance to stabilise clinically and also in terms of weight. In general, the HIV infected children of our study cohort showed surprisingly good weight gains and response to nutritional therapy when compared to non-HIV infected children. And since no deaths were observed in the late ART group, it might be worth to wait for some days in order to see if a child responds to the therapeutic feeding. In case a child shows good weight gain, the initiation of ART could be deferred until it reaches a state of moderate malnutrition, but if a child does not respond within few days to nutritional support, ART should be started even in a status of severe wasting, because this is still expected to reduce the overall risk of death according to the results of this study. This recommendation can be backed up by the finding that children in the category of early initiation had a better outcome in spite of apparently more advanced status of HIV infection (i.e. lower CD4%) compared to those who did not receive treatment. Since the power of this study was not enough to prove statistically the benefit of ART for this specific group, it still may indicate better options in treatment and at the same time emphasise the need to conduct further research in this area to provide more and stronger evidence for these recommendations. A prospective cohort study about the optimal timing of ART within a CTC program is urgently needed, including randomly assigned treatment schemes as well as detailed information about CD4% and clinical staging. Otherwise it remains unclear if the high mortality within the first days and weeks after commencing ART in the early ART group was really caused by the drugs or, what might to be more likely, by the already advanced status of HIV disease in these children.

Regarding weight gain, this study showed that children with early ART recovered significantly faster from severe malnutrition than those with late initiation. This highlights the benefit of commencing ART early during enrolment in feeding programs. Nevertheless, the weight gain of children not on ART was observed to be higher than for the late initiation group, but lower than for the early initiation group. Even though this result was unexpected, it appears to be plausible in a sense that primary adverse reactions to ARVs could probably cause less weight gain in the beginning which is then overtaken by the recovery of the immune system, followed by the often reported catch-up growth.

Therefore a hypothesis may be proposed that ART slows down the weight gain for a short time after initiation, but increases the weight gain in the long term. However, this theory is just speculative and needs to be supported by further research with detailed weight curves and questions about adverse reactions and appetite after commencing ART during nutritional support.

Regarding the role of the CD4% this research showed that, even though it is generally recognised as a useful or even as the best predictor for the risk of death, the W/H SD-score was a stronger indicator in this specific group of malnourished children. Interestingly this was especially true for the long term outcome (OTP and SFP) while there was nearly no difference in predictive value for the short term mortality (in-patient stabilisation phase). The WHO threshold for the CD4% of 20% for defining severe immunosuppression proved to be valuable according to our data because the risk of death, and also of developing opportunistic infections, increased clearly once the percentage was found to be less than 20%. Again further research is needed to gain more knowledge about changes in the CD4% in severely malnourished children after commencing ART during enrolment in feeding programs compared to those who start later. This could contribute greatly to strengthen the evidence for the benefit of early ART in children with severe malnutrition.

A further interesting result was the interaction between nutritional oedema and HIV infection. Children with HIV reportedly have less kwashiorkor than their HIV negative counterparts. Thereby the occurrence of oedema is clearly related to the respective level of the CD4%: the higher the percentage, the more oedema is observed. On average, HIV positive children with a CD4% of more than 30% presented with even higher prevalence of kwashiorkor than HIV negative children. Unfortunately there were no CD4% available for the HIV negative children in our study population so the information was not sufficient to know if CD4% and oedema were closely correlated. A further point is that the mortality rates observed in HIV-positive children were in clear contrast to the rates for those who tested non-reactive once they were split up by the grade of oedema. While HIV positive children were at highest risk of death when they were marasmic, HIV negative children were more likely to die when they had severe nutritional oedema. Therefore it may be concluded that the immune system is somehow involved in the development of nutritional oedema, possibly

explainable with the theory of oxidative stress. Thus the high mortality in the marasmic group of HIV positive children was probably caused by advanced immunosuppression, but this information was not sufficient to draw conclusions regarding treatment options. Nevertheless, the interpretation could be backed up by the findings in the group of children who were admitted some time after commencing ART. This group also presented with increased occurrence of severe nutritional oedema and, even though there are no repeated CD4% available, it can be assumed that the oedema occurred during rising CD4% levels under ART. Since all these findings are based on small observational numbers it would be interesting and important to see if other studies in different settings find similar patterns of oedema, CD4% and mortality. Further research in this area could provide additional explanations about the aetiology of nutritional oedema and thus open possibilities for improving treatment outcomes in these patients.

Not directly related to the study question but still important for the work of the NRU in ZCH is the question about the high mortality rate in the NRU, the high rate of dropouts from the outpatient program and the low number of transferrals to primary health care facilities. The observed rates are not meeting the international criteria in spite of following the current treatment guidelines. This can partly be explained by the high prevalence of HIV infection and complicated malnutrition and therefore the international standards need to be adapted to areas with high HIV prevalence and complicated malnutrition. But even for non-infected children the mortality rates are high and the weight gain, especially during the outpatient program, quite poor. Thus further evaluation is needed in order to improve the services. In the same way, it is urgent that a solution is found for increasing the rate of transferrals to primary health care facilities, because otherwise the whole CTC program is ineffective.
Summarizing the rest of the discussion points it seems that RUTF is quite beneficial not only for rehabilitating HIV negative but also for HIV positive children and moreover that other, by this research not directly addressed aspects like micronutritient deficiencies and treatment adherence, need to be kept in mind and possibly addressed by further research.

Even though this study has serious limitations especially because of the small sample size, the retrospective study design and consequently the not randomly

assigned treatment schemes, the author believes that the results are strong enough to provide evidence that ART initiation is beneficial for all HIV infected children during enrolment in therapeutic feeding programs relative to reduced mortality as well as faster weight gain and hence recovery from malnutrition. The question whether ART should be initiated while children are still severely wasted or whether it would be better to wait for recovery until a state of moderate malnutrition is reached, remains somehow uncertain and needs further investigations. Nevertheless and in spite of the risk of early mortality, it seems to be a good and possible option, especially if children are not responding immediately to nutritional therapy.

In summary, the extremely high mortality rate in HIV infected children with severe malnutrition becomes evident when compared to their non-infected counterparts. To reduce this mortality rate different strategies are possible and urgently needed. One possible strategy is the early initiation of ART which is the main subject to this study. However, focussing exclusively on optimizing the timing of ART in severely malnourished children is clearly not enough to achieve a significant impact on the overall situation, because for most HIV-infected children it is already too late once they present with severe malnutrition and thus most of them die within few days after admission to the NRU, sometimes even before the HIV test can be done.

Therefore the emphasis should be placed not only on treatment, but possibly even more on prevention of new infections, for example by expanding PMTCT services as well as early diagnosis and treatment of infected infants below 12 months of age, according to the WHO guidelines as described above. If these services function well with good coverage worldwide, the problem tackled by this research would automatically reduce to very small numbers. But since there is still a long way to go until preventive measures are sufficiently in place, it is important to discuss optimal treatment, such as the right timing of ART for older children, malnourished or not. Finally, long term care and support for all these children and their families needs to be considered, in order to avoid drug toxicities and resistances and consequently to achieve good and permanent adherence to treatment.

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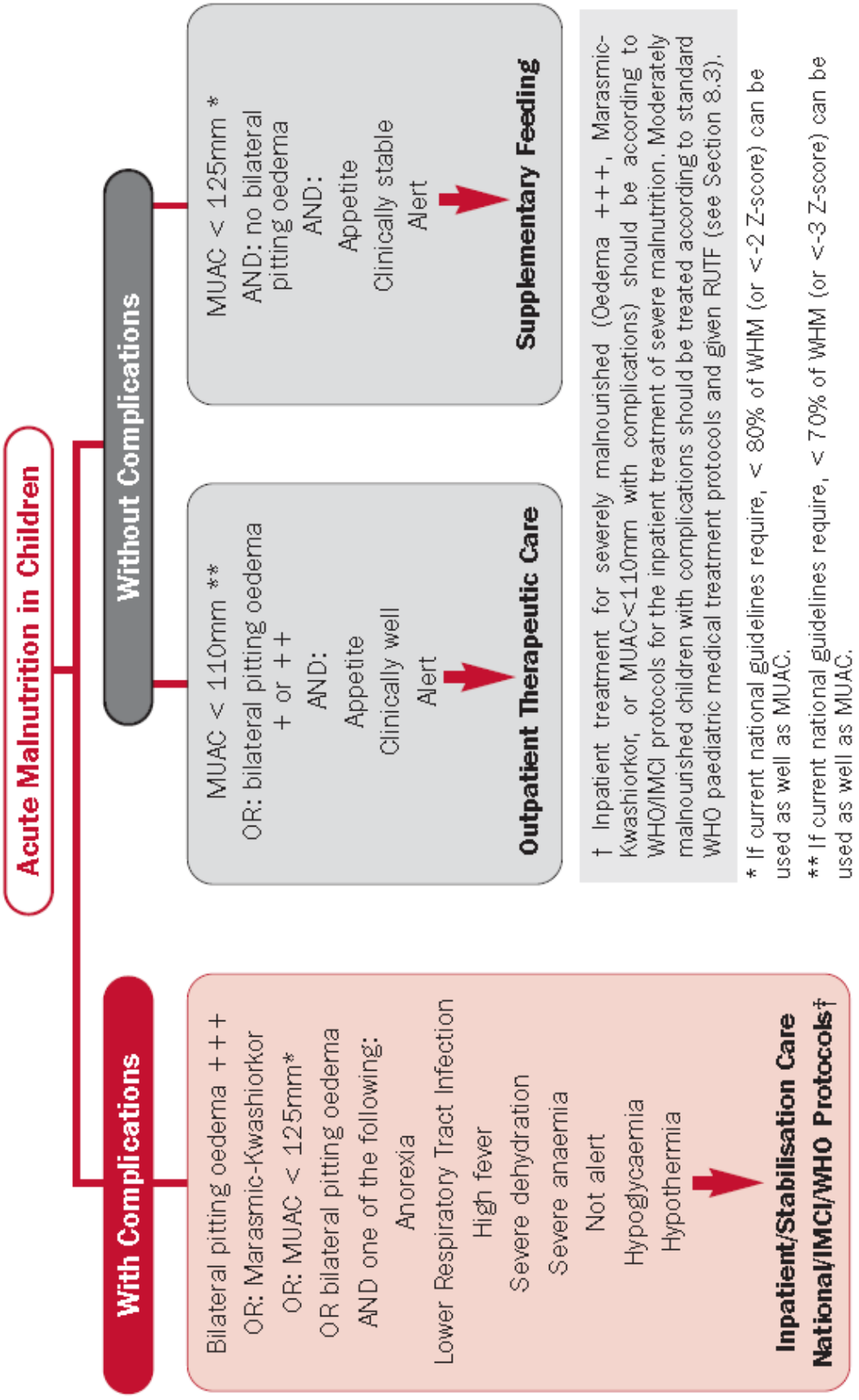
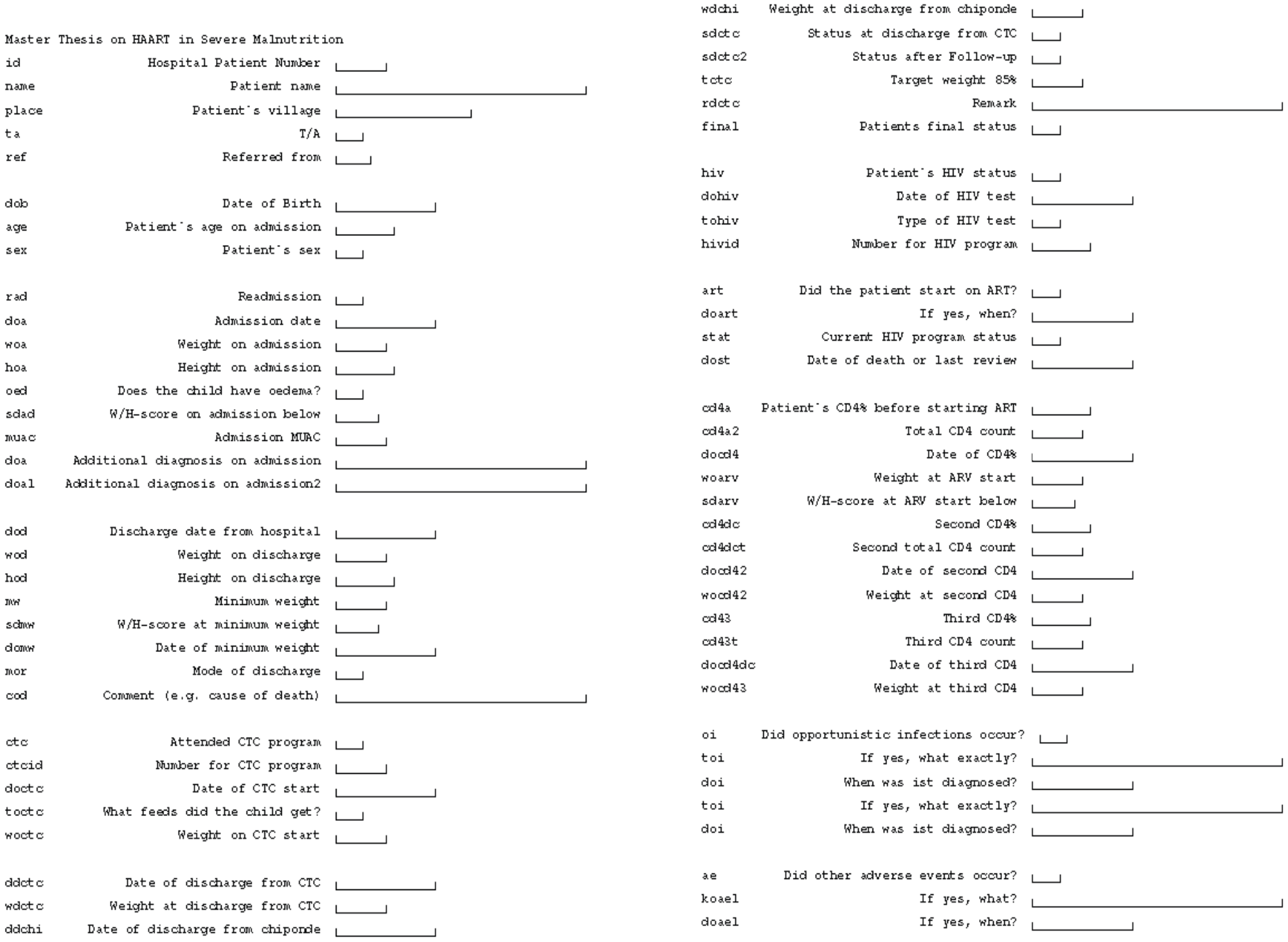
8. Annexes

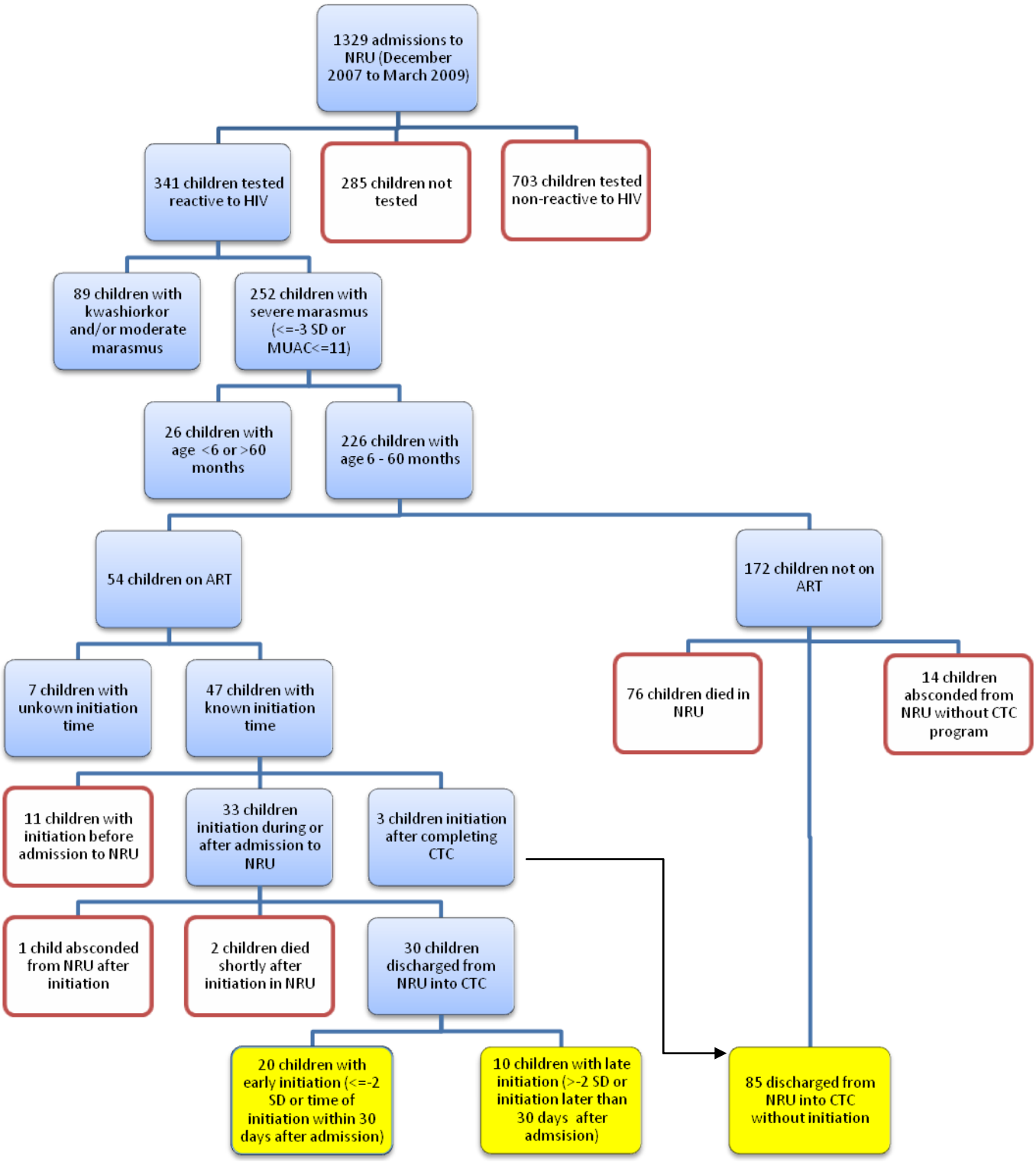


Graph 14: Admission criteria for enrolment in NRU, OTP and SFP

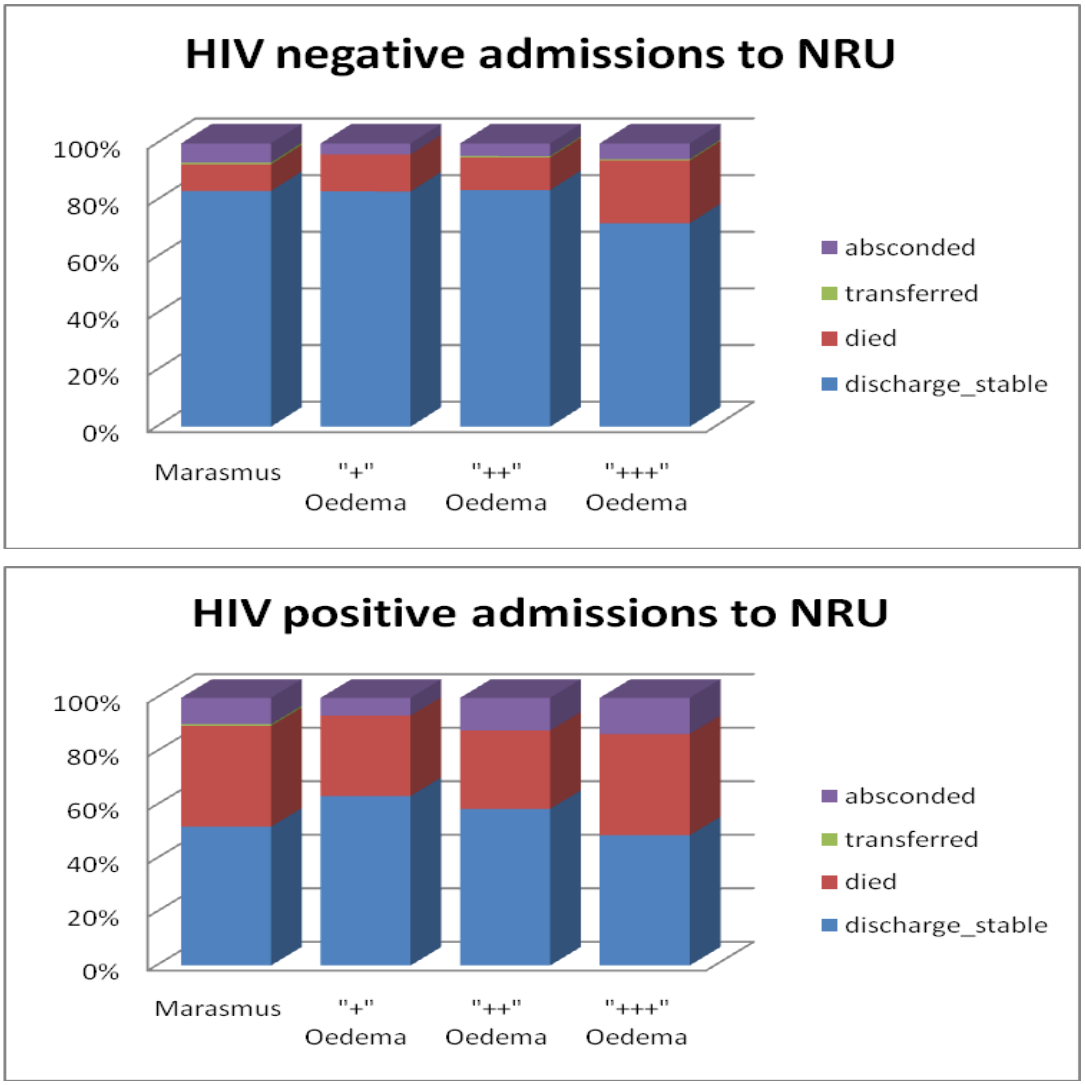


Graph 15: Study questionnaire developed with EpiData 3.1

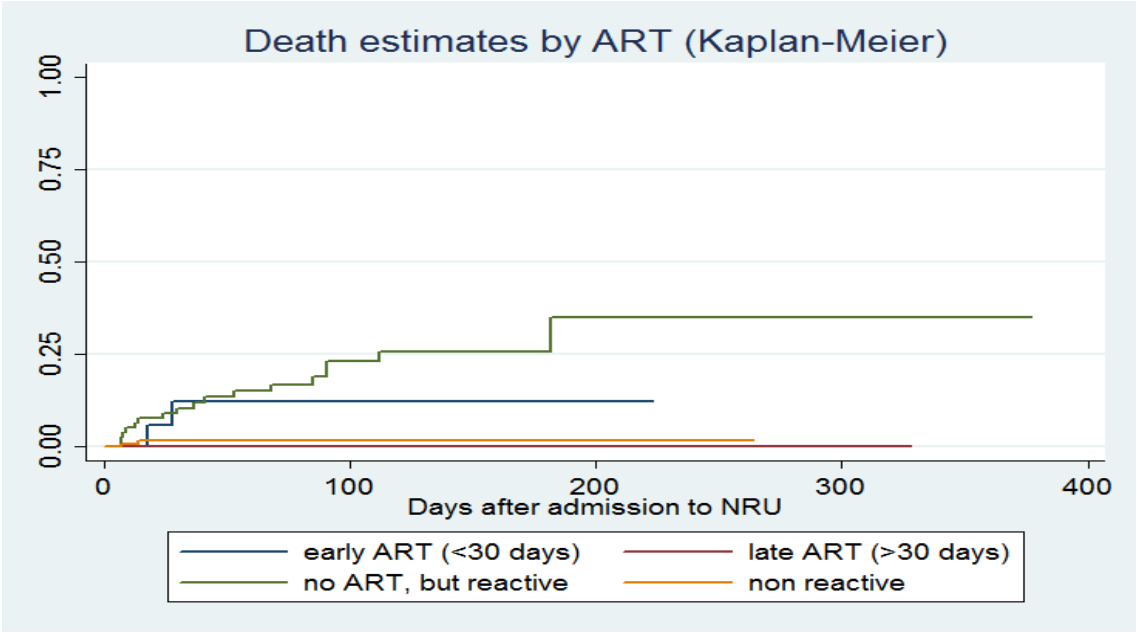
In- and Exclusioncriteria for Study Cohort



Graph 16: Flow-chart for in- and exclusion criteria for the study cohort



Graphs 17: Mortality by oedema and HIV status



Graph 18: Death estimates by ART defined by day after admission

Curriculum Vitae

Personal information

First name / Surname	**Esther Rauen**
Address	Kastanienring 18c 37520 Osterode Germany
Telephone	+49 5522 6597
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E-mail	E.Rauen@gmx.de
Website	www.madshi.net/afrika
Date of birth	05 September 1978
Gender	Female
Civil Status	Single
Nationality	German

Work experience

Dates	01 December 2007 – 29 February 2008
Occupation or position held	Dietician and Pedagogue
Nain acrivities and responsibilites	Introduction of computer software for calculating nutritional values in 5 old people´s homes, teaching and supervising kitchen and nursing staff about nutrition for geriatric patients
Name and address of employer	Tilch Verwaltungsgesellschaft gmbH, Sultmerberg 2, 37154 Northeim

Dates	01 of May 2005 - 31 August 2007
Occupation or position held	Dietician, in charge of Therapeutic Feeding Centre in Kumi, Uganda
Main activities and responsibilities	Rehabilitation of malnourished children, teaching parents, field-work, supervising local staff
Name and address of employer	German Missionary Medical Team (GMMT), Auf der Buchdahl 9, 57223 Kreuztal-Osthelden

Dates	01 October 2002 - 30 April 2005
Occupation or position held	Dietician
Main activities and responsibilities	Counselling and teaching patients in nutrition related health problems, instructing kitchen staff, preparation of special diets
Name and address of employer	Evangelisches Krankenhaus Lippstadt, Wiedenbrücker Straße 33, 59556 Lippstadt

Dates	01 September 2001 - 12 September 2002
Occupation or position held	Dietician
Main activities and responsibilities	Training individuals and groups in nutritional therapy in a rehabilitation centre
Name and address of employer	Knappschafts-Klinik Bad Driburg, Georg-Nave-Straße 28, 33014 Bad Driburg

Education and training

Dates	01 March 2008 – July 2009
Title of qualification awarded	Master of International Health
Principal subjects covered	Tropical Medicine, Public Health
Name and type of organisation providing training	Charité, Institut für Tropenmedizin, Spandauer Damm 130, 14050 Berlin

Dates	01 October 2001 - 30 June 2005
Title of qualification awarded	Bachelor of Arts
Principal subjects covered	Educational science, behavioural science
Name and type of organisation providing training	FernUniversität Hagen, 58084 Hagen

Dates	01 September 1998 - 31 August 2001
Title of qualification awarded	Dietician
Principal subjects covered	Nutritional medicine, counselling of patients, calculation and preparation of special diets
Name and type of organisation providing training	Diätassistentenschule am St. Joseph Hospital, Elmarstraße 38, 33014 Bad Driburg

Dates	01 July 1991 - 30 June 1998
Title of qualification awarded	Abitur (equivalent of english A-levels)
Principal subjects covered	Biology, mathematics, latin and politics
Name and type of organisation providing education	Tilman-Riemenschneider-Gymnasium (equivalent of english grammar school), Dörgestraße 34, 37520 Osterode am Harz

Personal skills and competences

Mother tongue	German
Other language	English – fluent French – basic
Social skills and competences	Good ability to adapt to multicultural environments, gained through my work experience abroad; team spirit
Organisational skills and competences	Leadership and sense of organisation (being in charge of the hospital ward for more than 2 years)
Computer skills and competences	Good command of Microsoft Office applications (Word, Excel and PowerPoint), EpiInfo, EpiData and Stata 10, Prodi 5
Driving licence	Category B

Date and signature

Declaration of originality of work

This thesis is the result of independent investigation. Where my work is indebted to the work of others, I have made appropriate acknowledgements.
I declare that this study has not already been accepted for any other degree nor is it currently being submitted in candidature for any other degree.

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Date and signature