Early infant diagnosis cascade in Chiure district hospital, Mozambique: an analysis in order to improve early initiation of anti-retroviral therapy in HIV positive children.

Hope for the future

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Mozambique and the Netherlands

Master International Health 2010-2016

KIT (ROYAL TROPICAL INSTITUTE)

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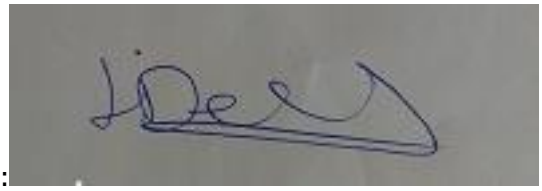
Declaration:

Where other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.

The thesis: Early infant diagnosis cascade in Chiure district Hospital, Mozambique is my own work.

Signature: 

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Abstract

Background: Mozambique is still at the 7th highest place in the world of country with the highest number of new HIV infected children. Important is HIV testing for the HIV exposed infant at 4-6 weeks post-partum and to start ART in the first year of life and thus reduce the risk of mortality.

Methods: A retrospective analysis of routine district health information data. Data were collected from the PCR registration book of the Chiure district hospital between April 2012 and January 2015. Beside that a literature review using the conceptual framework of McLeroy has been done to analysis the different barriers and motivators of the caregivers of using the early infant diagnosis cascade.

Results: There is a loss to follow up (LTFU) of 13% for testing HIV exposed children and a LTFU of 41% for starting ART in the HIV positive children. The median total delay from collecting the sample until starting ART in HIV positive children is 120 days. Main barriers to test and start ART in HIV positive children are lack of father involvement, distance, stigma and the use of traditional healers.

Conclusion: To improve the early initiation of ART in HIV positive children a holistic approach is needed; used could be a HIV infant track system and point of care testing. Beside that it is important is to empower the women with peer groups activities, a family center approach could improve the father involvement and a linkage is needed between traditional healers and the health system.

Word count: 249

List of acronyms

AIDS	Acquired Immunodeficiency Syndrome
ANC	Antenatal clinic
ART	Anti-retroviral therapy
ARV	Anti-retroviral
CHER	Children with HIV Early Antiretroviral Therapy
DBS	Dry blood sample
EID	Early infant diagnosis
HIV	Human Immunodeficiency virus
HITS	HIV infant track system
HC	Health center
IQR	Interquartile range
MOH	Ministry of Health
NGO	Non-Governmental organization
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother to Child Transmission
USAID	United States Agency for International Development
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organization

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Introduction

Mozambique is a beautiful country, however the Human Immunodeficiency Virus (HIV) prevalence of 10,5 % is the eight highest in the world. Since 5 years I am working in Northern Mozambique with the non-governmental organization (NGO) Solidarmed and I have a special interest in HIV positive children. New health guidelines have been implemented in the last years for HIV positive children in Mozambique, more paediatric anti-retroviral (ARV) medication is available on district level, more health staff has been trained in paediatric HIV care. But unfortunately, too often very sick children have been admitted at the paediatric ward and HIV rapid test were showing that they were HIV positive. The tragic is that often these children are already older than 1 year, they are severely malnourished and they have different opportunistic infections. Regularly I am wondering how we could `catch` these children at an earlier age? Therefore, for this thesis, I like to analyse the HIV early infant diagnosis cascade of the hospital where I work, Chiure district hospital, and better understand the actual situation in order to develop recommendations with my colleagues of the national health system. I hope that in the coming years we can improve together the health care of HIV positive infants in Chiure district.

1. Background

1.1 HIV infections in children

The burden of HIV is high in sub-Saharan Africa. The UNAIDS factsheet of 2014 is showing the following numbers; in 2013 24.7 million people were living with HIV in Sub-Sahara Africa, there were 210.000 new HIV infections among children and 1.1 million people died of acquired immune deficiency syndrome (AIDS) related diseases in sub-Saharan Africa[2].

Of all people living with HIV, the group of the infants and young children is the most vulnerable one and this group has a high risk of poor outcomes from HIV infection. The World Health Organisation (WHO) guideline for HIV treatment is reporting that up to 52% of the HIV positive children die before the age of two years in the absence of any intervention[3].

In 2013 new guidelines were implemented worldwide for the treatment of HIV in children. The WHO guideline is describing that an early start of anti-retroviral therapy (ART) in children would reduce the morbidity and mortality in children[3]. Literature is demonstrating good evidence for this strategy for children under de age of 2 years[4,5].

The new guidelines were implemented in many countries; in July 2013 they were also implemented in Mozambique. The key priorities of the Ministry of Health (MOH) is paediatric ART, the estimation was that in 2014 the children aged 0-14 years living with HIV was about 183,631 in Mozambique, 121,983 children were eligible for ART[6].

1.2 Prevention of Mother to Child Transmission cascade of care

Over 90% of new HIV infections among infants and young children occur through Mother to Child transmission, therefore elimination of HIV infections among children can be achieved

through the Prevention of Mother to Child Transmission (PMTCT). The current WHO guidelines (since 2013) recommend the following interventions:

- Testing of all pregnant women for HIV
- Providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage (Option B+)

The new guidelines are aiming for a global target of reducing the number of new childhood HIV infections by 90%[7].

A good working PMTCT cascade of care stimulates the HIV positive pregnant women to start with lifelong ART, to start with prophylactics for the HIV exposed infant post-partum, to test their child for HIV at a young age and to start early with ART in their HIV infected child (the last two steps are part of the early infant diagnosis cascade).

The Ministry of Health of Mozambique developed different registration books to register all the HIV infected pregnant women at the antenatal clinic (ANC) and there is an infant HIV testing registration book for the PCR HIV test[8].

1.3 Early infant diagnosis

The current WHO guidelines recommend HIV testing of all HIV exposed infants at 4-6 weeks post-partum, this is called early infant diagnosis (EID). HIV testing in an infant cannot be done with a HIV rapid test, because of possibilities of measuring the maternal HIV antibodies; therefore the best HIV test in infants is the polymerase chain reaction (PCR) DNA test[7].The PCR DNA test is conducted through a dry blood sample (DBS) and in Mozambique these samples can be send to 3 national central laboratories (in Maputo, Beira and Nampula).

These are the (inter) national guidelines regarding HIV testing in children:

- Infants < 9 months need to be tested with a PCR DNA test
- Infants from 9 - 18 months can first be diagnosed with a HIV rapid test, however a positive test result needs to be confirmed with a PCR DNA test
- Children > 18 months can be tested with the standard HIV rapid tests[8]

1.4 Chiure district situated in North Mozambique

As mentioned in the Introduction, this thesis will focus on the early infant diagnosis cascade in Chiure hospital, North Mozambique.

In the last two decades Mozambique had a remarkable economic growth progress with an average annual growth rate of 7%. This growth has not translated into significant poverty reduction as poverty fell only 4% between 2003 and 2009[8] and still 60% of the total population is living under 1.25 USD/day[10].

The district Chiure is situated in the Northern Province Cabo Delgado (see map 1), it has a surface are of 5439 km2. The distance from the capital to this province is far, around 2500 km, and the infrastructure system in Mozambique is still in development. Events like the rain

season, flooding, political situations are often influencing the supply chain to the North in a negative way and on a regular base there is a shortage of medical supplies. The population in the district is around 248.800 inhabitants of which 80% are living in rural areas. The estimated number of infants (age<1 year) is 9187 and the children (1 - 14 years) is 34.393 (estimated in 2013). The main occupation is substance farming, poverty, including poor nutrition, lack of access to water and sanitation, frequent illnesses and low education characterise the daily life of an average inhabitant of this district. The HIV prevalence in the population is 9% in 2015 and the average life expectancy is 51 years. There are not accurate calculations of child mortality in the district. The district health system contains 1 district hospital and 10 health centres (HC); HIV care is provided in 6 HCs (in 2015) and HIV testing and counselling is conducted in all the HCs[11].

Map 1 – Location of Chiure district in North Mozambique[1]

Problem statement, justification, objective and methodology

2.1 Problem statement and justification

In 2011 the global plan towards the elimination of new HIV infections among children was launched at the United Nations General Assembly High Level meeting on AIDS. Twenty-two countries were selected with the highest prevalence of HIV positive pregnant women for these countries special programs were developed to decrease the transmission of HIV to children[12]. Mozambique was included in the global plan towards elimination of HIV infection among children. The 2015 progression report shows that Mozambique has a decline of more than 69% of new HIV infections in children since 2009. In 2009 the mother child transmission rate was 26% in 2014 that was 12%. In 2009 only 36% of HIV pregnant women were receiving prophylactic or ARV during pregnancy, in 2014 that increased to 91%. Areas that need continuous attention are 1) retaining women in care and treatment during the breastfeeding period and 2) pediatric diagnosis, as only 43% of HIV exposed infants received early infant diagnoses and 37% of children (age 0-14 years) living with HIV received antiretroviral therapy[6].

One of the factors that helped in improving these indicators is the implementation of the new international guideline in 2013 of Option B+, which means, lifelong triple anti-retroviral therapy for all pregnant and lactating women living with HIV.

Despite these improvements, in 2014 Mozambique was still at the 7th highest place in the world of country with the highest number of new HIV infected children, which shows that in the coming years there is still need for improvements[6].

The South African CHER study (Children with HIV Early Antiretroviral Therapy) study, is illustrating that if children are starting with ART before 12 weeks the early mortality will be reduced with 75%[13,14]. Therefore it is important for these new HIV infected children to start early with anti-retroviral therapy (ART).

Guidelines issued by the WHO in 2013 are recommending starting pediatric ART in all children under the age of 5 years regardless their clinical and immunological status in order to `simplify pediatric treatment and facilitate a significant expansion of ART coverage for young children` [2].

Last year a small cohort quantitative study has been conducted in Chiure district (in combination with neighboring district Ancuabe) to analyze the effect of the implementation of this new 2013 guideline by looking at the age of starting ARV and the mortality rate of HIV positive children. Figure 1 is showing that in the last 6 years the number of all HIV positive children under 5 years that started with ART has increased, especially after July 2013 when the new guidelines were implemented in these 2 districts.

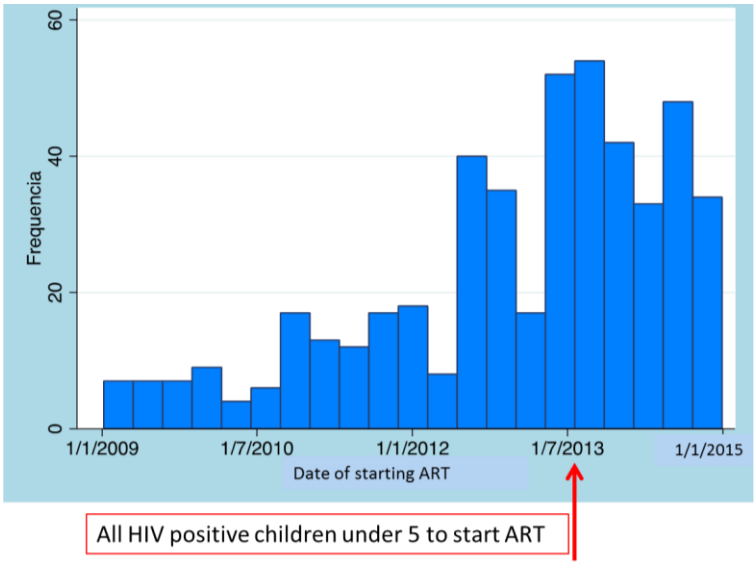


Figure 1: All HIV positive children under 5 years that started with ART from 2009 till 2015 in Chiure and Ancuabe district

The study further shows that the percentage of HIV positive children on ART that died has decreased significantly in the last two years from 16.6 to 7.4% and the baseline CD4 count (at initiation of ART) increased from 549 to 828 µmol/l and with a reduced clinical stage at initiation. This indicates that children are now starting with ART when they are still in a better clinical condition[15]. A Cochrane review of 2014 showed strong evidence that start of ART in HIV positive children before the age of 1 year will reduce morbidity and mortality[16].

The data of the quantitative study for Chiure and Ancuabe district has been further analyzed to verify the age of children starting with ART in Chiure district. See Figure 2 for the results.

Figure 2 - Age of starting ART Before and after July 2013 in Chiure district

After July 2013 more HIV positive children started with ART within the first year of life, however there are still 107 HIV positive children that started with ART after that first year.

You would expect that if the continuum of care along the PMTCT program is maintained, mothers will come early to the hospital with their HIV exposed children, the PCR HIV testing will be done in the first months of life and ART could be started before the age of 1 year old. However the data is showing that still 48% of the HIV positive children are starting ART when they are older. The median age before June 2013 and after June 2013 remained unchanged at 1.8 year[15].

A Literature review of 2013 is showing that in different countries there is a high loss to follow-up (LTFU) of HIV exposed infants along the PMTCT cascade and, according to the authors of the review, improved retention is needed in order to improve early start of ART in HIV

infected children and decrease mortality[17]. Maybe the LTFU along the PMTCT cascade is one of the factors that in Chiure the children are starting later with ART. Although mortality rates in Chiure district have been significantly decreased, an earlier start of ART may further improve the situation of HIV infected children in Chiure district.

This thesis will quantify the LTFU in Chiure along the early infant diagnosis cascade (part of the PMTCT), investigate the underlying factors for the LTFU and provide recommendations to decrease the LTFU and help improve the situation of HIV infected children.

Figure 3 shows the early infant diagnosis cascade with questions about the actual cascade in Chiure district. The red questions are about 'what' the actual situation in Chiure is, required to quantify the LTFU; the blue questions are about the 'why' or the factors behind the 'what'. Possible factors may include fear for disclosure to the family disbelief in the test, long waiting time in the health facility or the habit of first going to the traditional healer[18]. Figure 3 provides the basis for formulating the main objectives for this study. This is further described in the next section.

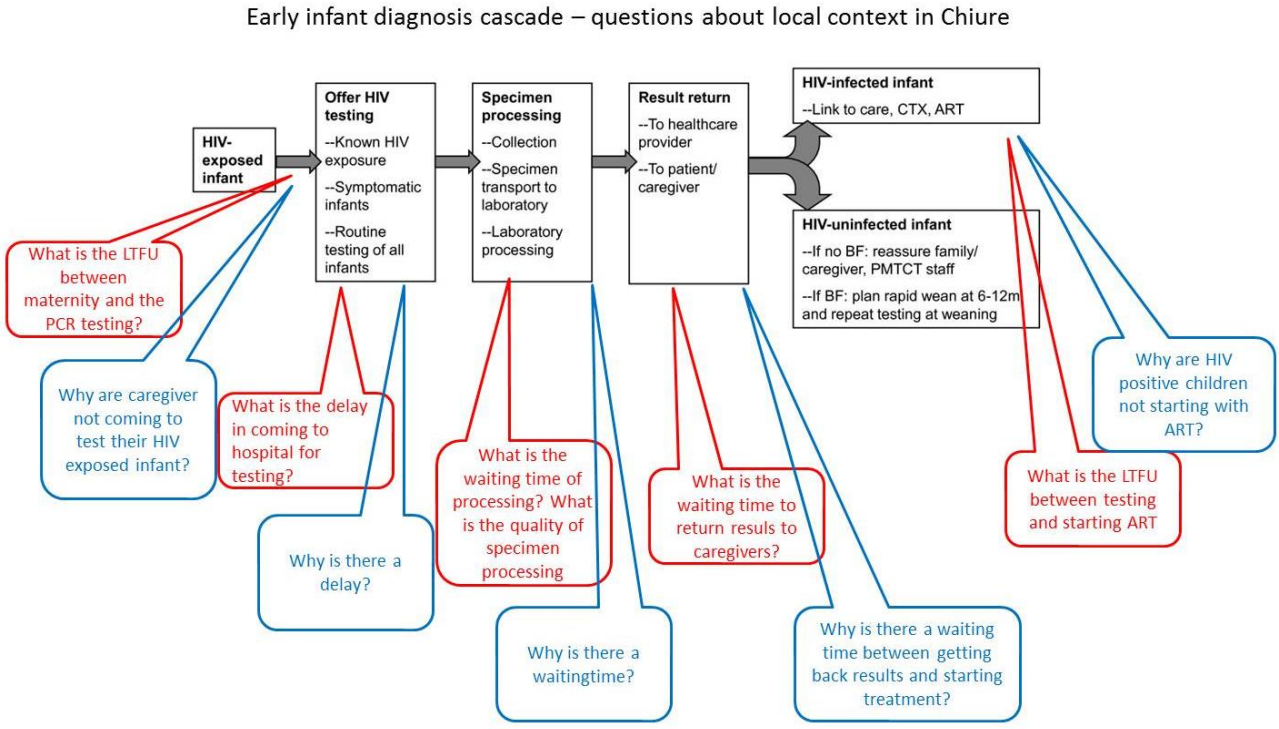


Figure 3 - The flowchart of Ciaranello et al[19] 2011 (grey) with added questions about `what` the actual situation in Chiure district is (red) and `why` questions about the actual situation (blue).

2.2 Objective

Overall objective

To explore the loss to follow-up and delay of HIV positive children in Chiure district hospital (Mozambique) along the early infant diagnosis cascade that could result in a later (after 1 year) start of ART and to identify reasons for this delay in order to write recommendations for the local health authorities to improve the HIV care for children in North Mozambique.

Specific objectives

1. To describe the existing structure of early infant diagnosis cascade and HIV care for HIV positive children in Chiure district hospital, to quantify the uptake of these services and to quantify patient and health provider delay of these services from 2012-2015 (Chapter 3).
2. To explore the factors described in the literature that possible could influence the uptake of care for the HIV exposed and HIV positive children in Chiure district in their first year of life (Chapter 4).
3. To identify evidence based interventions in the literature to improve the HIV early infant diagnosis cascade and the early start of ART in HIV positive children (Chapter 5).
4. To formulate recommendations for the local and national health authorities to improve the pediatric HIV care with the aim to improve early start of ART in HIV positive children

2.3 Methodology

2.3.1 Analytical framework

In the literature there are different conceptual or analytical frameworks provided that help to describe the different contextual factors that are influencing a process like the early infant diagnosis cascade and start of ART in HIV positive children. For this thesis the conceptual socioecological framework of McLeroy[20] et al will be used. This conceptual framework is specifically developed to analyse social and ecological factors that influence health processes. The conceptual framework is presented in Figure 4.

The conceptual framework has been applied to this thesis in the following way. First it is important to investigate the existing situation in order to understand where the problem areas are. This will be done through data analysis of the available data, which is described in Chapter 3. The next step is to understand the factors behind the problem areas. The conceptual framework will assist in addressing the possible factors at all different levels. The factors described Figure 4 are factors mentioned in the article of Schacht[18] et al e Ciaranello[19]. On the basis of available literature an analysis will be made of the factors behind the problem areas to understand the most critical and relevant factors for the late start of ART in Chiure. This is described in Chapter 4. The interventions should address the most critical and relevant factors. Through a literature study possible evidence based interventions that will address these factors will be listed in Chapter 5.

The links between the different chapters in this thesis and the conceptual framework is illustrated in Figure 4. The arrows indicate the “flow” of this thesis.

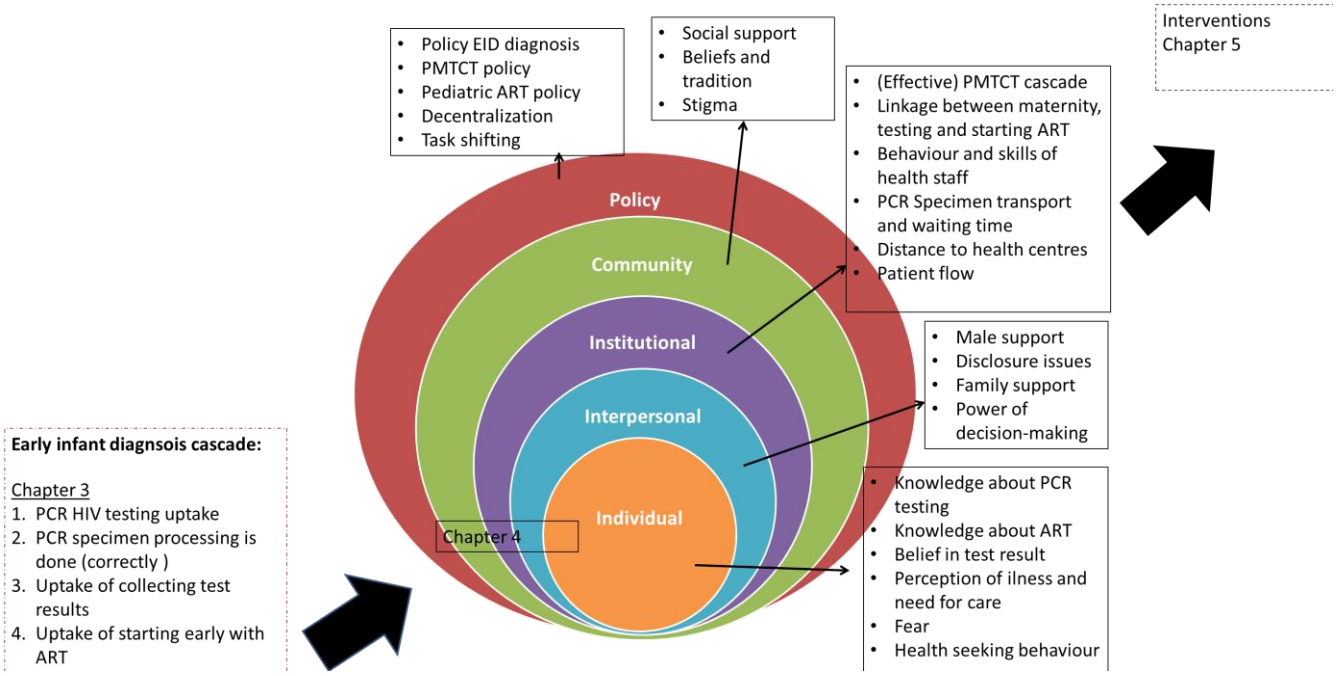


Figure 4 - The socioecological framework of McLeroy et al[20] linked to the early infant diagnosis cascade with factors described on the five levels.

2.3.2 Data analysis about the early infant diagnosis in Chiure district hospital

A retrospective analysis of two available data sources related to the early infant diagnosis cascade in Chiure district hospital has been conducted:

Data source 1: routine district health information system. This data is collected on a monthly base by the local health staff and they are put in the computer based national health information system. This data includes: number of institutional birth, number of institutional birth in HIV positive women, number of HIV exposed children that did a PCR test, number of PCR test with positive test result, number of HIV positive children that started with ART. This data is used to calculate the percentage of loss to follow up along the early infant diagnosis cascade.

Data source 2: the PCR registration book of the Chiure district hospital between April 2012 and December 2015. 885 registered HIV exposed infants <18 months of age are included in the analysis. Main outcomes will be median age of testing the HIV exposed children and the delay (in days) that each step of the cascade incurred. Children with a positive PCR test result registered in the PCR registration books were cross checked in the HIV database to see if the children opened a HIV patient file yes or not.

Table 1: overview of the columns in the PCR registration book

Number	*Name*	*Date of collecting DBS*	*Age in months*	*Date of sending the DBS*	*Date of getting back test result*	*Test result:* positive negative undefined	*Date of giving back test result to caregiver*	*Date of start ART*

The following components are analysed with the data of the PCR registration books (see table 1):

- ➔ Waiting time of
  - sending DBS to laboratory
  - getting back test result to health facility
  - for giving back test result to caregiver
  - Total waiting from collecting DBS till starting ART
- ➔ Age of collecting DBS in
  - all children
  - children with positive test result
- ➔ Percentage of test result
  - Positive
  - Undefined
- ➔ Percentage of unfilled registration fields
- ➔ Percentage of double testing in same child

In the analysis, continuous variables were described using medians and interquartile ranges (IQR). Excel was used to calculate the waiting times. SPSS version 23 was used to compare the data: Wilcoxon rank-sum was used to compare medians, the Chi-square test was used for the bivariate analysis. The total waiting time could be used to calculate the age of starting ART in the children with a positive PCR.

Only the PCR registrations books of April 2012 – December 2015 were available in Chiure district hospital therefore this analysis has been focusing on that period Information about personal identifiers was only used to verify if the infants had repeated a DBS test and had opened a patient file. These personal identifiers were not shared with others and the information was deleted after the analysis. The use of the data has been approved by the hospital and the district health authorities. To better understand the working of the early infant diagnosis cascade in the hospital, to understand the data of the PCR registrations books and the data of the district health information system consultations in the hospital are done with the head maternity nurse and with the head of the statistics department. Own observations are used in describing some processes, the author of the thesis is now working for 5 years in North Mozambique, which is helpful in providing inside information about the health system.

2.3.3 Literature study

Search strategy

A literature review (qualitative and quantitative evidence) of published and unpublished documents on early initiation of ART in HIV positive children was conducted. For general information about the health indicators and the health situation in Mozambique the following websites were accessed: WHO / USAIDS / Unicef / Worldbank / Solidarmed project reports.

After that an online search was conduct in Pubmed with as focus describing the underlying factors of starting or not starting ART in HIV infected children and the possible interventions to improve this.

The following search terms were used:

- Child OR Infant OR New born OR baby
- Early diagnosis OR EID
- Early initiation of antiretroviral therapy OR antiretroviral therapy
- HIV OR AIDS OR HIV infected OR HIV exposed
- Prevention of mother-to-child HIV transmission OR PMTCT OR postpartum
- Retention OR Loss to follow-up OR LTFU OR continuum of care
- Barriers OR motivators
- Qualitative research OR qualitative
- Health Policy OR policy
- Community OR Stigma OR Peer
- Institutional OR family centred OR integrated health services
- Male involvement OR partner involvement OR father involvement
- Disclosure OR Fear
- Intervention OR evidence-based practice
- Mozambique OR sub Saharan Africa

For every search a combination of 3 or more search terms was used. A few studies were found because they were linked to the other articles with the hyperlink `similar articles in Pubmed`.

Selection process

Publications were excluded if they did not address 3 or more terms (like mentioned above) and the following filters were used: free full text, English / Portuguese. These filters were used to select the articles that could be read and analysed. There was not a specific time frame used as filter, however some older articles from 2006-2012 were less relevant because in the last decade new guidelines have been implemented in the HIV care for HIV infected children.

Table 2 The results of the various stages of the research process (see Annex 1 for more detailed information).

First search (with filters)	Selection criteria – relevant	Excluded due to repetition	No access to full article	Included in study
289	98	19	15	64

2.3.4 Limitation of the study

Data of health information system

The study will focus on HIV exposed infants and HIV positive children that were born in the district hospital and that are entering the early infant diagnosis cascade. This is a strong limitation because it doesn't include all HIV exposed children born in the district.

The quality of the registrations books is poor to moderate especially in 2015 when not all tables in the registration books were filled-in completely.

The data about the earlier steps in the PMTCT cascade (number of women tested, number of women on ART) of the national health system is not accurate enough to use for further analysis (there is duplication of numbers in the collected data).

Literature

Different new guidelines have been implemented recently on international level for HIV exposed and HIV infected children (in 2011 and more recently in 2013), so the time frame is too short to find publications about the effectiveness.

Chapter 3 - HIV care in Chiure district hospital for HIV exposed and HIV positive children

3.1 Early infant diagnosis cascade in Chiure

This chapter will describe the current situation of HIV care in Chiure district hospital for HIV exposed and HIV infected children. Like mentioned in the Section 2.3, data from the district health system and data from the PCR registration books are used to analyse the loss to follow up and the delay in starting ART in HIV positive children.

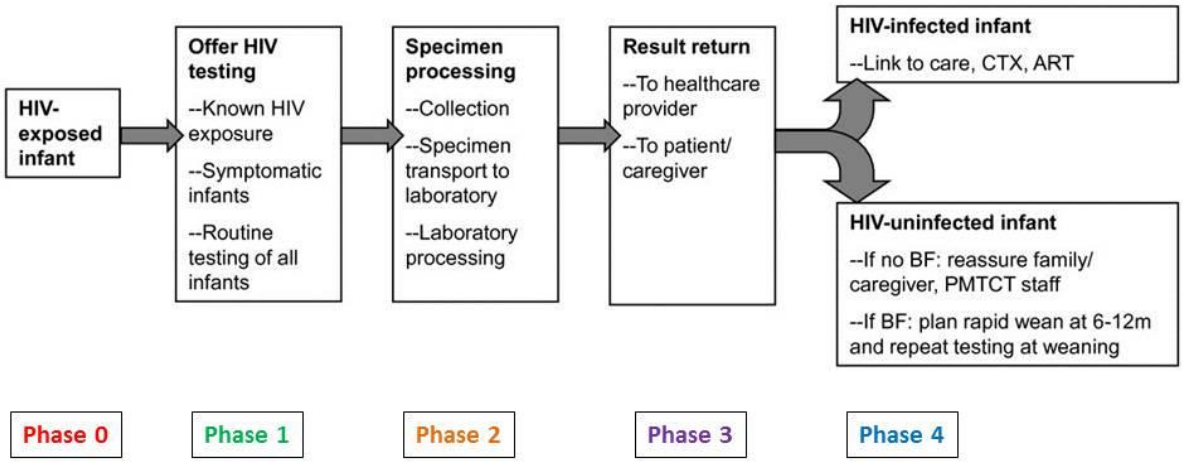


Figure 5: Five different phases in the early infant diagnosis cascade[19]

Five different phases can be distinguished in the early infant diagnosis cascade (see Figure 5). The start of the early infant diagnosis cascade, phase 0, is at the maternity ward; the HIV infected woman that is coming to the health facility for her delivery will receive more information about the follow-up of the HIV exposed child and it will start with prophylactic medication for her child[7].

After discharge the mother and child need to come back to the out-patient clinic between 4 and 6 weeks after the delivery[7] (phase 1). There is a special consultation room for the children at risk, this room is located in the maternity block with antenatal and postnatal care, and the consults are conducted by a maternity nurse.

During the first consultation post-delivery, the nurse will collect the PCR DNA HIV dry blood sample (DBS). The DBS will be send to the district laboratory and from there it will be transported to the provincial laboratory and subsequently to a countrywide laboratory (Phase 2). The PCR tests are repeated in the same child when the DBS samples are not of good quality, when results are missing or when the PCR test is positive it needs to be confirmed with a second test[7].

The mother and child need to come back to the health clinic on a monthly base to collect test result and for their treatment; the ART treatment for mother and the prophylactic therapy for the infant will be given by the same nurse (Phase 3).

The HIV positive children (after getting back the test results) are referred to the paediatric HIV care (phase 4), in the district hospital this is done by the medical doctor in a special consultation room in another outpatient block (this started in 2015).

3.2 Data about EID cascade in Chiure district hospital

3.2.1 Data

Every quarter district health data is discussed in the district health meeting, although specific analysis of the data of the EID cascade is not done on a regular basis.

The table below demonstrate the data of the district health information system[21] about the follow up of infants from HIV positive mothers.

Table 3 – Follow up of HIV exposed infants born in Chiure district hospital from 2012-2015 based on district health information system and the PCR registration books.

	District hospital	Data				Total of the 4 years
Phase	**Indicator**	**2012**	**2013**	**2014**	**2015**	
Phase 0	Total number of children that were born alive	3235	3554	3621	3752	
	Total number of children that were born alive with an HIV infected mother	163	251	275	294	983
Phase 1	Total number of children tested with PCR (excluded 2nd test)	128	239	234	250	851
	% of exposed HIV children that did a PCR test	79%	95%	85%	85%	87%
Phase 2	Data not available in district health information system but in PCR registrations books					
Phase 3	Total number of children with positive PCR	26	27	28	29	110
	% of positive PCR of the total PCR tests	20%	11%	12%	12%	13%
Phase 4	Total number of childen with a positive PCR started on ART	15	15	17	19	66
	% of children that started with ART of the total group of children with positive PCR	58%	56%	61%	66%	60%

3.2.2 Analysis

Phase 0 - Children born alive with an HIV infected mother

Like mentioned before the early infant diagnosis cascade starts at the maternity ward of the district hospital, were the HIV exposed children are born. The number of children born alive with a HIV infected mother is increasing in the last 4 years, however the total number of children born alive too.

Phase 1 - Care for the HIV exposed infants

From Table 2 it can be observed that 87% of the children did a PCR test in the first 18 months. The total percentage of testing children improved in 2013 from 79% to 95% after that it decreased till 85% in 2014 and 2015. Looking into more detail in this dataset, it can be seen that the children tested at an age of 1 months has increased from 45% in 2012 to 65% in 2015, see Figure 6. It is noted that for the period 2012 to 2015 the median age is 1 month, with a interquartile range (IQR) 1-3.

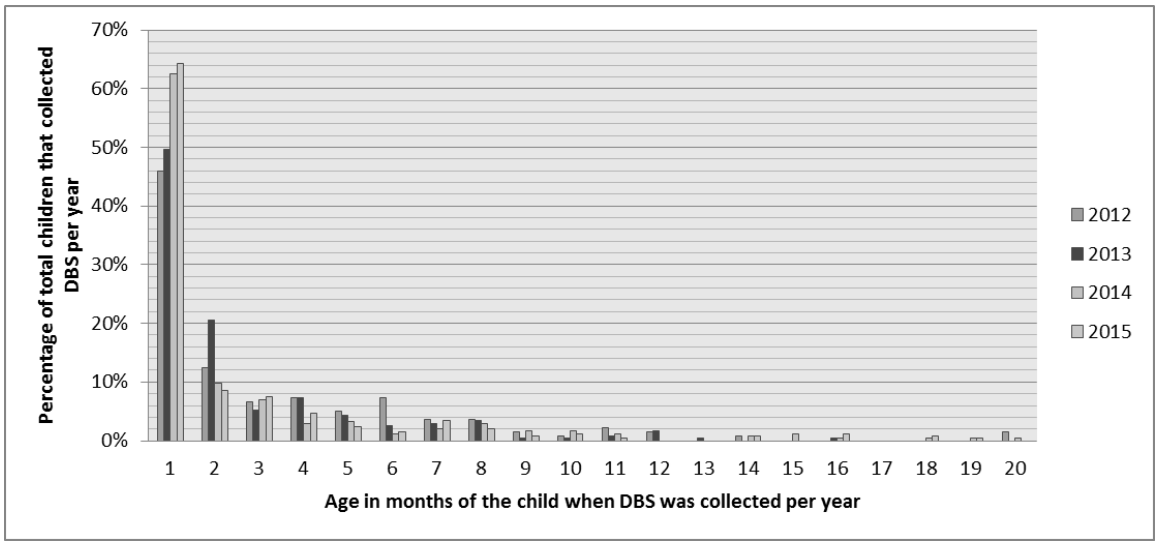


Figure 6: Percentage of children per year, grouped by month of age, of collecting their first blood sample (n=851)

The article of de Schacht et al[18] indicates that clinical illness is a motivation for parents to test their child in Mozambique. Therefore a specific analysis was done to see what the age of testing is in the HIV positive children only. Figure 7 shows the bar-graph of this analysis. The median age of collecting the first DBS for children with a *positive* PCR test was 5 months (IQR 1-10). The same analysis was carried out for children with a negative PCR test and resulted in a median age of 1 month for children This is a significance difference (p<0,001) according the Wilcoxon rank test.

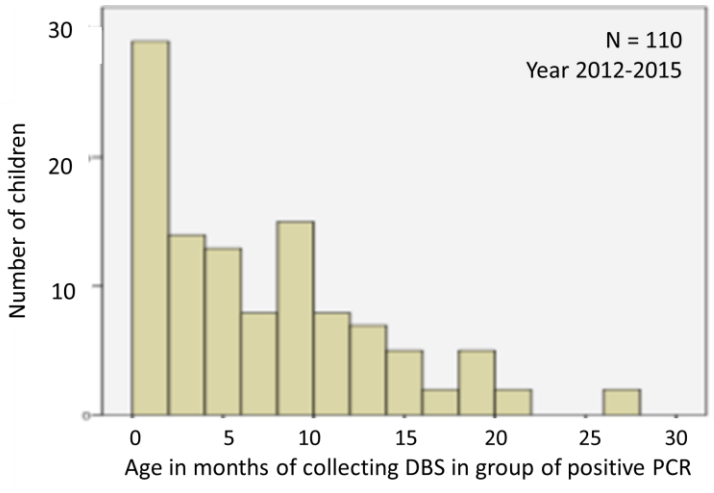


Figure 7: Age at collecting DBS for children with positive PCR test result n=110

Phase 2 - Specimen processing

As Indicated in Figure 5 there are different components in the specimen processing: 1) Specimen collection 2) Specimen transport to laboratory 3) Laboratory processing

The waiting time from collecting till sending the DBS to the central laboratory has a median of 6 days from 2012-2015 (IQR of 6 – 13), see Figure 8.

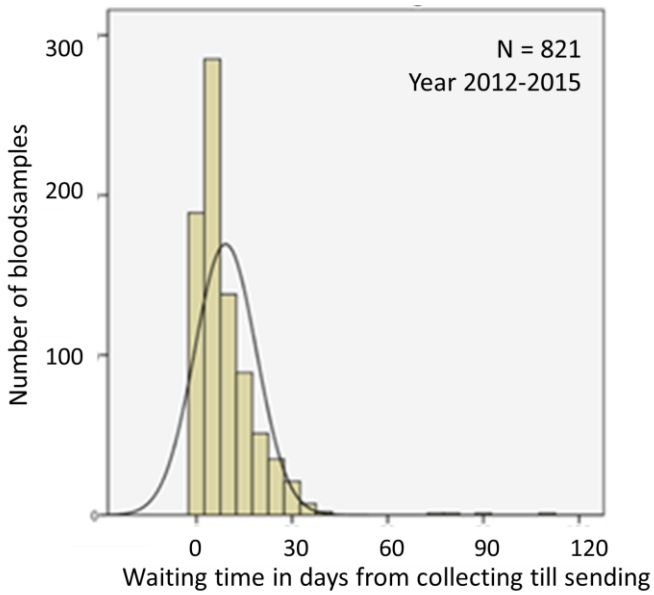


Figure 8 Waiting time from collecting till sending the DBS

The skill of the nurse to collect the PCR DBS can influence the quality of the sample. The laboratory will send back a notification to the hospital when there is a collecting error of the dry blood samples which means that the nurse needs to conduct a second collection.

Table 4 summarises the results of the PCR test including the number of collecting errors or the number of PCR tests that did not have an end result.

Year	number of children that did a test	Test result: negative	Test result: positive	number of children with test result	positive PCR of children with test result	collecting error	unknown	Total number of children without test result	% of children without test result
2012	128	92	26	118	20%	1	9	10	8%
2013	239	166	27	193	11%	18	28	46	19%
2014	234	163	28	191	12%	25	18	43	18%
2015	250	153	29	182	12%	30	38	68	27%
Total	851	574	110	684	13%	74	93	167	20%

Table 4a Overview of the PCR test results in Chiure district hospital from 2012-2015 (excluded are the 2nd test in same child). Note: in 2012 there are 4 months of data missing (January – April)

In 2012 the percentage of PCR test without result was 7%, this has increased over the last years till 27% in 2015. About 50% of "no test results" is related to a collecting error. The remaining part is due to unknown factors and may happen on laboratorial, hospital or on transport level

Year	Total number of testing samples	2nd test done in same child
2012	137	9
2013	247	8
2014	244	10
2015	257	7
	885	34

The total group of children that need a second DBS test are the 167 children without test result and the 128 children with a positive test result, which is a total group of 295 children. In reality only 6% (34) of these children conducted a second test (see table 4b).

Table 4b Number of children that conducted a 2nd test.

Phase 3 – Return of test result

Figure 9 is showing the percentage of positive test result in the group of PCR with a defined test result.

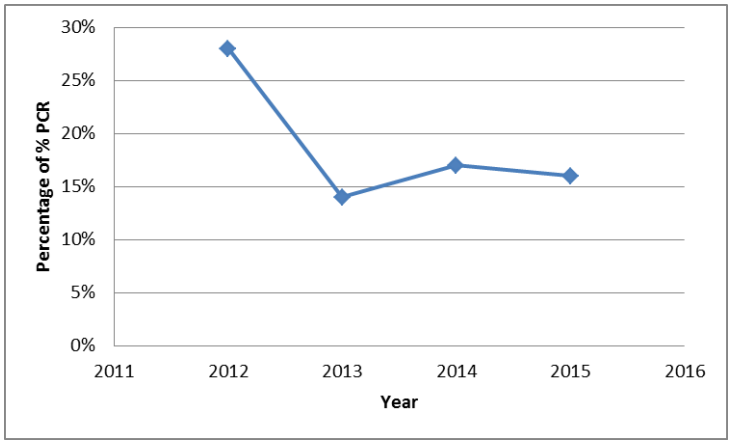


Figure 9: Percentage of children with a positive HIV PCR test result of the total group of children with a defined test result

The total PCR tests with a positive test PCR HIV test result are 20% in 2012 and 11%-12% in the years thereafter. The difference of percentage of positive PCR between 2012 and 2013-2015 is a significant difference according the Chi-square test $p<0.001$. The shift in percentage may be related to new policy (Option B+) that came into place in 2013 .

The waiting time for the return of the test results consists of two elements: the waiting time from the laboratory to the hospital in Chiure (see Figure 10) and the waiting time from the hospital in Chiure to the caregiver (see Figure 11). The median waiting time for getting back the test result to the hospital (2012-2015) was 54 days (IQR 26-84). The waiting time for giving back the test results from the hospital to the caregiver was 18 days (IQR 8-31).

In order to analyse the waiting time from the laboratory to the hospital in Chiure 748 DBS were used as 107 of the 855 PCR dry blood samples did not have a date recorded in the registration book. Related to the waiting time from the hospital to the caregiver only 177 out of the 748 samples were available for the analysis. This may be due to not recording the data by the nurse or the caregivers not coming to collect the test results. See Annex 2 for more details on the analysis carried out.

Figure 10 Waiting time of getting back test result to hospital

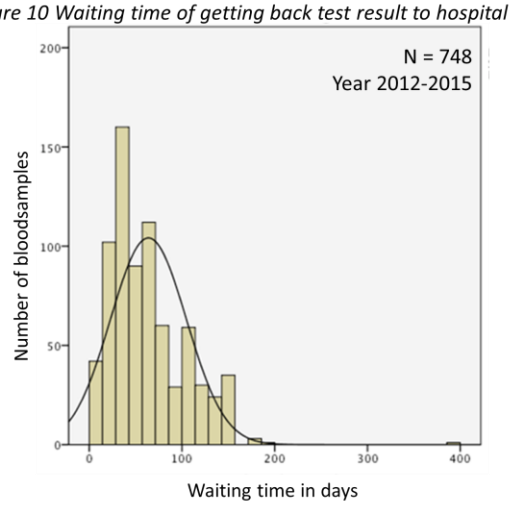
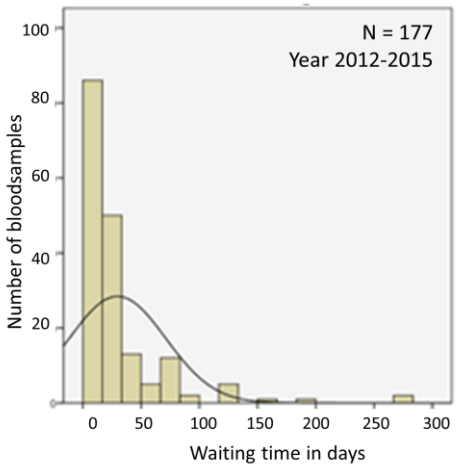


Figure 11 Waiting time of giving back test result to caregiver



Phase 4 – The HIV infected child on ART

In case the test results of the PCR tests are positive, the caregiver needs to open a HIV treatment process at another consultation room. The LTFU of children with a positive PCR that did not open a HIV treatment process was 41% in the last 4 years (table 3). Figure 12 is showing the decline in LTFU from 2012-2015. Since 2013 health volunteers are conducting active searches for children with a positive PCR that are loss to follow up. The decline in Figure 12 may indicate that it is effective, however the results of the search is not well registred.

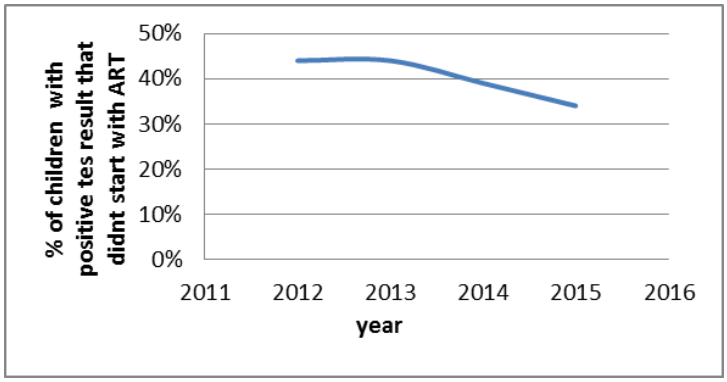


Figure 12 percentage of LTFU of HIV positive children that did not start with ART

Table 5 is showing more detailed information; the number of total positive PCR tests, the number of children that died while waiting for the test results and the number of children that started with ART before or after getting back the test results. For some children a second DBS was collected to confirm the test results, these test are excluded for calculating the percentage of LTFU or death.

	Total children with pos PCR	Died	% of children that died before start ART	startedART before PCR result	started ART after PCR result	Total number of children started ART	never started ART	% LTFU
2012	26	3	12%	4	11	15	8	19%
2013	27	0	0%	5	10	15	12	44%
2014	28	4	14%	3	14	17	7	11%
2015	29	2	7%	7	12	19	8	21%
total	110	9	8%	19	47	66	35	24%

Table 5 Number of children with a positive PCR test, number starting ART and LTFU

8% of the children with a positive PCR died before starting with ART, but probably more HIV positive children have died in the communities without being registered at the hospital.

Besides that there are 19 children (29%) that started with ART before getting back the test result. Starting ART without result can be done based on clinical symptoms, or if the HIV rapid test in children in the age group of 9-18 months shows a positive result. Children that are confirming their status with a second PCR test are excluded from this group because they always start with ART before getting back the second test result.

The group of 47 patients with a positive PCR test that started ART after getting back their test result is used to calculate the total waiting time from collecting the DBS till starting ART. The numbers are small, but Figure 13 shows the distribution with a median of 120 days and IQR of 85-162.

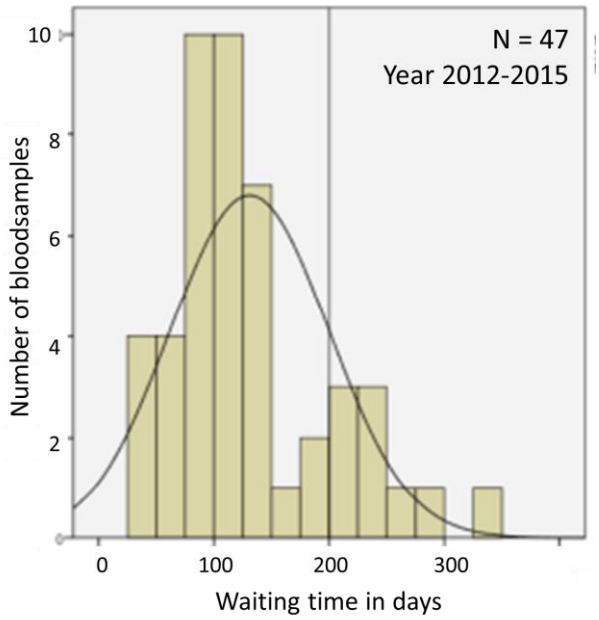


Figure 13 Total waiting time in days from collecting DBS until start of ART in the period from 2012 to 2015

Figure 14 shows the different components of the waiting time for the children with a positive PCR: 68% (62 + 6) of the total waiting time is related on health care provider and 32% (19+13) is on health care consumer level.

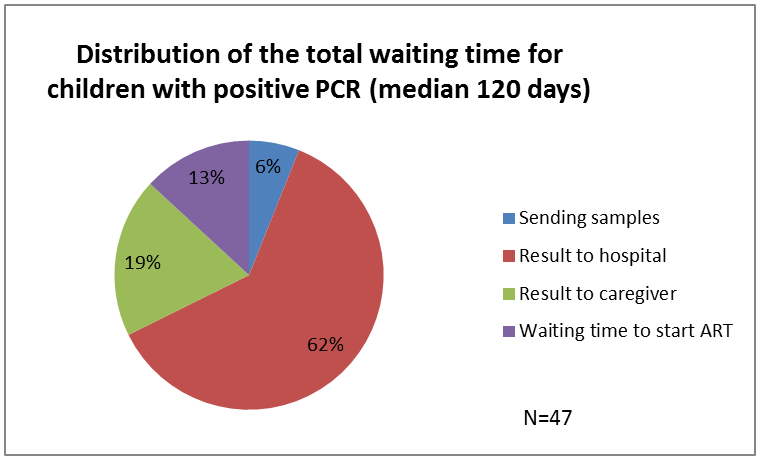


Figure 14 Distribution of the total waiting time from collecting DBS until start of ART in the period from 2012 to 2015

The last analysis conducted is to calculate the age of starting ART in the group of children with a positive PCR (, see Figure 15) The median is 8,5 months with a IQR 5-13.

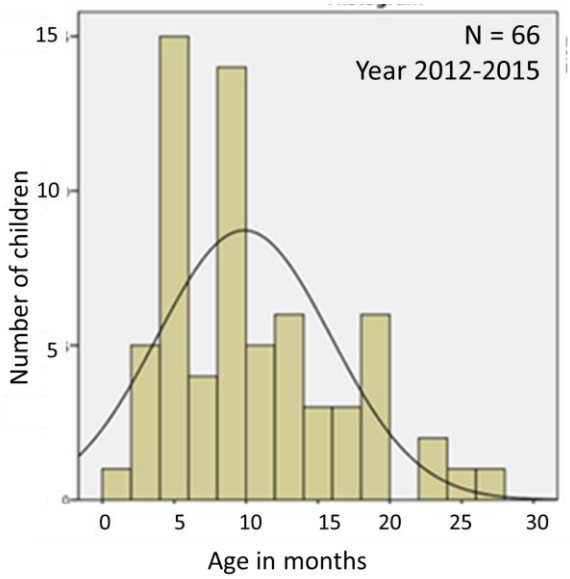


Figure 15 The median age of starting ART in HIV positive children that started with ART in Chiure hospital.

Chapter 4 - Literature Analysis

In Chapter 3 the EID cascade in Chiure district has been described and it showed that the main loss to follow up is between testing and starting ART in HIV infected children and there is a total median delay of 4 months. This chapter will describe the literature that has been found and analysed in order to find answers for the LTFU and delay described in Chapter 3.

The five levels of the conceptual framework of McLeroy[20] are used as a guideline to describe the results of the literature study (see Figure 4). The literature study will start at the inner circle of the framework (Individual) and subsequently describe barriers and motivators that may play a role in the process of seeking health care for their HIV positive children at each particular level

4.1 Individual

What kind of characteristics of the caregiver, such as knowledge, attitude, skills and behaviour could influence their health seeking behaviour for their HIV exposed or HIV positive child?

4.1.1 A barrier for the caregiver

Fear The period before getting back the results of the PCR of the child can be very emotional and stressful for the mothers. Qualitative researches in different countries are showing that this fear is sometimes too strong for the mother to cope with and to make the decision to go to the hospital. Stigma from community members or personal experience of living with HIV was sometimes one of the reasons for the fear[18,22,23,24.] One example is described in a qualitative study in Malawi: *"What prevents mothers from having their babies tested is that they are scared that once they know that their babies is HIV positive they have already thrown away their 'chicken'. And they might shorten the life of that baby because they are worried most of the time.[24]"*

This fear could also influence the women in Chiure, in case they are coming to the hospital to test their child but they are not coming back for the results[25].

Test results

Literature is showing that mothers are aware of the likely outcomes of the test results. A positive test result of the child will give different emotional reactions to the caregivers, the following emotions are described; guilt, self-blame, unbelief, fear and sadness[18,26,27]. In Mozambique not everyone believes and accepts the test results; HIV mothers are having distrust of HIV testing technologies which is influencing their health seeking behaviour[19] and this could increase the LTFU of HIV positive children after testing.

Low educational level

In general a few studies are showing that a higher educational level of the women is associated with better ART adherence[28,29]. Lack of knowledge about health services and ART was associated with a poor adherence or retention[30,31]. There is a high change that if

education is influencing the ART adherence of the women herself, it will also influence the adherence of the women for her HIV exposed and HIV infected children. However, no literature has been found that confirms this assumption. The Unesco fact report demonstrates that only 22% of the children in Mozambique complete their basic education[32]. This percentage demonstrates that there is a possibility of a low educational level in the population, which could influence the adherence of HIV positive women in Mozambique and Chiure hospital.

Alternative care

De Schacht[18] is mentioning in her study that in Mozambique alternative care by traditional healers can delay, or replace HIV testing and care in the health facilities. Other studies are showing that in Mozambique 70% - 85% of the population first visit a traditional healer before they go to a regular health facility[33,34,35,36]. A women in northern Mozambique was saying: *"I have gone to traditional healers as well, but I start coming here at the hospital and if there is no improvement I take him (the child) to the traditional healer, but if their things are also not good, I end up staying hopeless at home*[18]*."*

There is limited literature about alternative treatment seeking especially under caregivers of HIV exposed and infected children.

Economic barriers

The review article of Hiarlaithe[37] is showing that in 13 of the 19 studies socio-economic barriers were mentioned as a barrier in accessing PMTCT care, the main barrier was transport costs. In Mozambique the ANC and the HIV care is for free, so health fee costs don't play a role in this context. However the distance to the health centres in Chiure district are far (will be discussed further) which makes the transport costs high or the caregiver needs to walk long distances.

4.1.2 Motivation of the caregiver

Visible illness of the children is a motivation for the caregiver to come to the health facility to test their child, this could also play a factor in Chiure. Besides hope and positive examples could influence the caregivers in Chiure to come earlier to the clinic for diagnosis and treatment[18].

4.2 Interpersonal

In this section more attention will be given to interpersonal processes and literature will be reviewed to see if family, friends or peers are causing a barrier or if they are providing support to the caregivers of HIV infected children.

4.2.1 Barriers for the caregiver

Disclosure to partner / male involvement

In the review of Hodges[38] 18 studies were highlighting the roll of a partner on ART initiation, adherence and or retention. In different countries the women often felt that they need the partners' permission to visit the health centres and start/adhere on ART. Non-disclosure is described as a main barrier to enrol in PMTCT program. Other review articles are confirming this information[37].

Only a few articles are specifically giving attention to the roll of the father / partner in the access to HIV care for HIV infected children. De Schacht[18] is demonstrating that in Mozambique women are afraid to go to the health facilities with their children because the husband will find out about their status and he will send them away. In Malawi women made their own choices regarding infant feeding, however most of them felt that other health-related decisions for the child should involve the father[39]. Fear to be send away and lack of husband support in health related decisions could also influence the adherence of HIV positive mothers and their children in Chiure hospital, which could influence delay and start of ART.

Decision makers in the family

In Mozambique the most important decision maker is the father of the child or the grandmother in absence of the man[18,40]. De Schacht is also mentioning that partners are insisting to follow instructions given by the traditional healer because they don't trust the national health system. These decisions of the father could influence the health seeking behaviour of the mother and could give a delay in HIV care for the child.

4.2.2 Motivators for the caregiver.

Positive male involvement is vital and important for the HIV infected women[41,42] and it could reduce the infant HIV infection rate[43]. However this last study did not find a correlation between male involvement and child mortality and it did not mention if partner involvement would improve EID and early initiation of ART in HIV infected children[43]

Mothers that were surrounded with a strong social network (in South Africa) were more able to manage the stress, which resulted in a hospital visit to get their child tested and more of them would come back for the test results of the PCR of their child. It is unknown if HIV positive women in Chiure that are coming to the hospital for testing their child are having a strong social network[22,44].

4.3 Institutional

4.3.1 Barriers at health facility level

PMTCT cascade

The earlier steps in the PMTCT cascade are important for a good working EID cascade. Every pregnant woman in Chiure district hospital is tested for HIV and counselling is given to women and man about father involvement. In July 2013 the new guidelines about option B+ are implemented, which means lifelong ART for HIV positive women, started during the pregnancy. A study in a neighbouring district Ancuabe (district is similar to Chiure) is demonstrating that retention of HIV positive women is poor and that there is a LTFU of 57% after one year of treatment after implementing of option B+ in 2013[45]. Beside this the percentage of institutional birth rates are still low, according to the national health data is the institutional birth rate was 48% in Chiure district[21].

Distance

Caregivers of HIV infected children in the north of Mozambique were describing the distance and lack of transport to the health facility as a barrier for seeking care[18]. Other studies in adult HIV patients in Mozambique are showing the same problem[46]. Chiure district has a surface of 5.439 km2, with 11 health centres and one district hospital. Transport means are scarce, which makes transport to the health facilities difficult.

HIV care has been more decentralized in the last 10 years, it is a gradual process and every year more health centres (HC) are providing HIV care, see table 6.

Year	Number of HC with PMTCT prophylaxis	Number of HC with HIV care and ART
2012	11	3
2013	11	4
2014	11	7
2015	11	8

Table 6 Decentralization of HIV care in Chiure district[21]

Decentralization of HIV care to all the health centres will improve access to HIV care, however it is important to realize that in Mozambique in general more than 50% of the population lives more than 8 km (2 hours walking) away from the nearest health facility[10]. This is not different for Chiure district.

Patient flow

Long waiting time to health services is a barrier for the caregivers in Mozambique to access the HIV health care for their children[18,46]. There is no data available about the actual waiting time of the patients at the district hospital. The general process is that mothers are coming

early in the morning around 7h30 and they need to wait until it is their time. Usually the last mother is leaving the health facility around 14 h, which is a waiting time of more than 6 hours.

The waiting time could be caused by the fact that Mozambique has a strong shortage of health staff (see table 7) and there is no appointment system.

	Chiure '12	**Chiure '13**	**Chiure '14**	**Chiure '15**
Medical doctors	2	2	4	6
Superior technicians	2	7	4	16
Medium technicians	35	59	75	85
Basic technicians	57	62	68	54
Elementary technicians	5	6	6	6
Total clinical staff	102	136	157	167

Table 7 Number of health staff in Chiure district[21]

The minimum internationally acceptable health worker density (doctors, nurses and midwifes) is 230/100,000[47], in Chiure district this density was much lower; in 2015 it was 67/100.000.

Waiting time for test results

One citation of the qualitative research of Schacht about the situation in North Mozambique[18]:

"… They did blood tests of the child and said the blood will be taken to Pemba… three months passed, we always asked and they said the result has not returned yet… the fourth time they told me that my child does not have the disease, only that I have to go to the doctor; I went but I was told that the doctor does not work today and I should come back on Monday… I came back, but they did not work and they told me to come the next Monday. I came on Monday. They said to come back the next Monday…and I gave up to going to the hospital …"

Like mentioned before, the data of the HIV PCR registrations books were analyzed for this thesis to verify what the waiting time is of getting back the test results. The median waiting time from collecting DBS till getting back results in the hospital is 60 days.

That the long waiting time at the health facilities is increasing the LTFU is described by a few studies. Besides that, having appointments on different dates, times, or locations for a mother and her child can add to this time burden and increase the LTFU[48]. In Chiure the EID of the infant is at the same location as the ART consultation for the lactating mother. A child that needs to start with ART will move to a different location together with the treatment

consultation for the mother. Maybe this change of location could increase stigma for the caregiver and could result in LTFU.

Skills and attitude of health staff

The skill of the nurse to collect the PCR dry blood samples can influence the waiting time for the caregivers to get back the results. If there is a collecting error of the dry blood samples, the caregiver needs to wait longer, which can influence their health-seeking behaviour. As discussed in Chapter 3 in 2015 27% of the PCR test did not have an end result, due to a collecting error. The head nurse of Chiure hospital mentioned that in the last years there is high turnover of nurses that are coming to work in the hospital. Young nurses are arriving in the district and experienced nurses are going to the larger cities.

Next to the technical skills of the health staff, the attitude of the nurses is important. Lack of confidentiality and poor communication and treatment from the health workers to the care givers could influence the retention of HIV patients[34,46,49].

4.3.2 Motivators on health facility level

Studies are showing that in case the follow up of HIV exposed children is integrated in the maternal and child health clinics, the retention is higher than if the HIV exposed children need to go to specific HIV clinics[50,51,52] (like in Chiure district). It is noted however that a study in Tete, Mozambique showed that the effect of an integrated EID cascade in the maternal health could be overshadowed by structural health system limitations as staff absence and irregular supply[53].

4.4 Community

This subchapter will focus on the factors on community level that are playing a role for the care-givers to visit the health facilities for early infant diagnosis (EID) and initiation of anti-retroviral therapy for their HIV positive child.

4.4.1 Barriers in the community

The study of De Schacht is showing that in Mozambique on community level two factors were influencing the decisions of the care givers: lack of social support and fear of disclosure to those in the community[18].

Stigma

A qualitative study in Malawi (of 2012) concluded that there is a lack of knowledge about EID in the community which can increase the stigma which will influence the decision of the mother/caregiver to go to the health facility for testing. People in the community think that if a child needs to be tested, it has HIV and it will die, so it is better not to know or not to put effort in an HIV exposed child. An example from the article: *people tell her that "why not get rid of him, he is a child, he will keep you busy."* This lack of knowledge about EID and ART

makes that mothers do not want to share their concerns about their child with other community members and they may not visit a health center due to lack of social suppor[24].

This is also described in a similar study in Kenya and in the review of Nayar et al; there is an indirect effects of stigma that positive HIV children (under an age of 5 year) may experience because of stigmatizing attitudes and actions of adult care takers and community members[54, 55]. The review is describing the situation in different sub-Saharan African countries; which makes it likely that this is could be a factor in Chiure district, Mozambique.

Cultural and beliefs in the communities

As mentioned in other paragraphs, there is a strong parallel alternative health system with traditional healers in Mozambique. Often there is no linkage between the traditional and conventional health system[34].

In the communities in Northern Mozambique there is a widespread belief that HIV is a fatal disease[56]. A general belief like this can have a strong impact on the social support for caregivers of HIV positive children in a community. This can cause a delay in finding health care for their children and in starting ART.

4.4.2 Motivators in the community

Social support groups in the communities are important and could stimulate care givers to go to the health facilities with their sick child[18].

A motivator of the community could be traditional healers that are motivated to work together with the conventional health system and that want to refer HIV patients to the HIV care of the hospitals. A study in 2012 in Zambezia province (Mozambique) is showing that 4 of the 5 traditional healers are willing to engage with the national health system[57]. In Chiure district there are meetings for linking traditional healers to the health system, however they are not specifically focused on HIV in children (according to the HIV district program coordinator).

4.5 Policy

In Mozambique the health policies are mostly made on national level by the ministry of health and they are gradually distributed to the rest of the health system. The majority of the HIV/AIDS health policies in Mozambique are based on international recommendations like the WHO guidelines.

The Pediatric Working Group, an Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children published their recommendations with the WHO in 2013.

The main recommendations were:

- Decentralize diagnosis, treatment and care for HIV children and scale up of EID
- Task shifting to nurses

- Empower all treatment sites to manage children in a family centred approach
- Improve pediatric retention by: improving quality of service and linkage between testing and treatment
- Strengthen community mobilization[58]

Below a short explanation about these recommendations and more detailed information about the local context.

4.5.1 Decentralization

As described in Paragraph 4.3, decentralization in Mozambique is a gradual process. Every year more health centers are starting with HIV care.

Next to this EID through the dry blood sample (DBS) is decentralized to all the health centres. Transport is still needed to another province to analyse the DBS, but the government wants to distribute more PCR DNA HIV testing machines in the future to the other provinces including Cabo Delgado.

Although decentralization is resulting in better access it does not mean that it results in better and optimal care[59]. For successful decentralization of HIV care sufficient and continuous support to all the HIV health facilities is needed.

4.5.3 Task shifting

In 2008 the WHO launched a global recommendation and guideline on task shifting, meaning moving tasks to less specialized health workers. This method will lead to increase number of health workers that are able to give HIV care and to improve access to HIV care[60].

The review of Penazotto [2014] is suggesting that task shifting of paediatric HIV care can result in outcomes comparable to routine physician care[61]. Since 2015 the policy in the province of Cabo Delgado regarding task shifting in paediatric HIV care, is that in the peripheral health centres the non-physicians are trained to deliver paediatric HIV care (according the local health authorities). In the larger health centres and hospitals, it is the responsibility of the physician this in order to retain the quality of care for the more complicated transferred cased.

4.5.4 Family centre approach

Another recommendation by the task group is the family-centred HIV care approach.

This method could help to improve access to HIV care because of partner involvement, it could help in a better disclosure of the HIV testing to the partners and starting ART of other family members. Until now there is not enough evidence, but the literature that describes that the family-centred model shows promising results[62,63].

In Mozambique the family centred approach is not yet integrated in the national health system. A study of Myer et al is analysing the co-enrolment of family members in HIV care in 5 different countries and shows that in Mozambique this enrolment is only 1%[64].

4.5.4 Linkage between testing and treatment

The data of Chiure district presented and analysed in Chapter 3 is showing that the majority of the mothers are coming to test their child with a PCR test at the age of 1 or 2 months, which means that the linkage between maternity and testing is strong. However the linkage from testing to treatment remains weak. In Mozambique there are no specific policies that are focussing on this linkage.

4.5.5 Community mobilisation

A national policy is to use community ART groups to improve access to health care and increase patient retention[65]. There are no special family groups for HIV infected children. Evidence suggests that community mobilization could decrease the stigmatization (mentioned earlier) which could improve the knowledge about PCR testing and early start of ART in children.

Chapter 5 – successful interventions

Three main problems are described in Chapter 3, related to the EID cascade of Chiure hospital:

- LTFU of 13% before testing
- Problems on institutional level: delayed waiting time of getting back test result (60 days) and collecting errors (19%)
- LTFU of 41% for starting ART in HIV positive children.

In Chapter 4 different barriers and motivators are described that are influencing the EID cascade on the five levels of the socioecological framework of McLeroy[20].

In this chapter more attention will be given to interventions that address the problems of Chapter 3 and the barriers of Chapter 4. Literature has been reviewed that focus on interventions in the following three areas: improve the uptake of EID, improve the quality of services, improve the early ART initiation (see Figure 15).

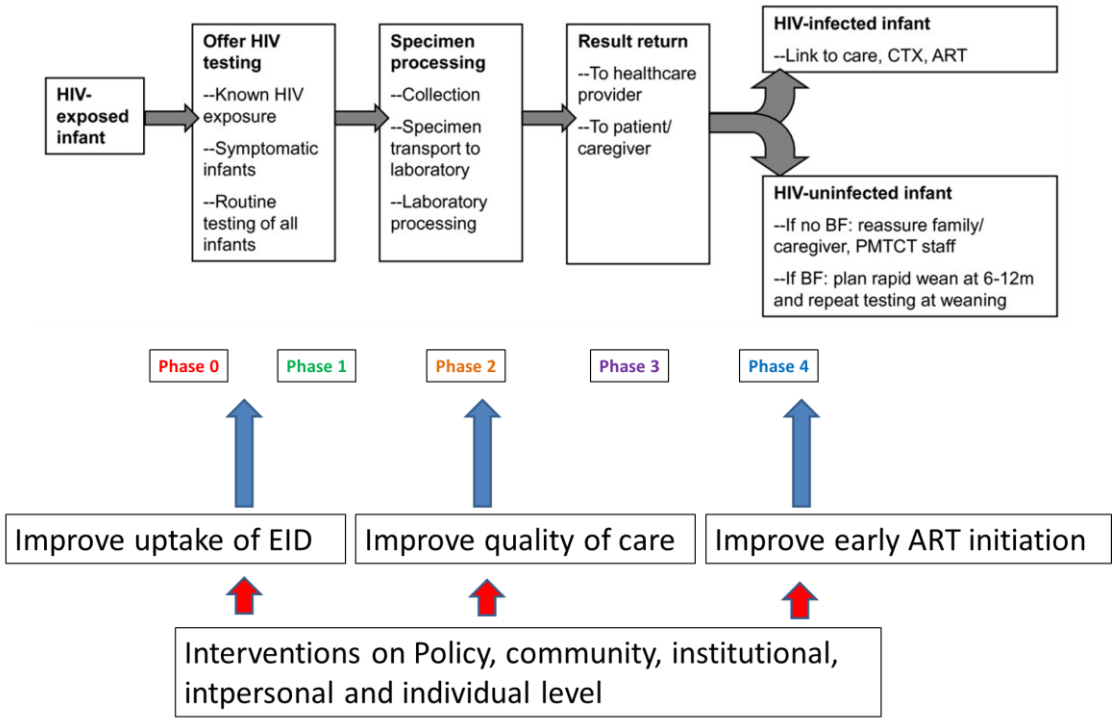


Figure 15 EID cascade[19] and the three areas of improvement for the Chiure district Hospital

5.1 Improve the uptake of early infant diagnosis

5.1.1 Individual

The review of Ambia and Mandala (2016) showed that 11 of the 19 analyzed articles are demonstrating a significant benefit in the uptake of EID after implementation of the intervention with peer mentoring (in Sub Saharan Africa). The intervention with peer

mentoring was described in 4 studies of which two of these studies reported an increased number of early infant HIV testing[66]. The main benefits of the peer group programs were empowerment of the women, improved knowledge and increased disclosure among participants. All of these factors can help the women to cope with the stigma that is in the communities and it can empower them to make their own choices regarding HIV testing and starting ART for their children[67].

Mother peer groups have been implemented in Chiure district however my own observation is that the peer groups do not continue to exist when the responsible nurse for these groups is leaving due to the high turnover of nurses on district level.

5.1.2 Interpersonal

There is lack of evidence about the effectiveness of male or father involvement with children affected by HIV. Interventions about male involvement at ANC could perhaps also influence the involvement of fathers postnatal with the HIV exposed and infected children.

A review about male involvement in ANC of 2013 is showing that 5 studies (in Sub Saharan Africa) are demonstrating that an invitation letter from the health centers to the men in the community was popular and it appeared to be an important facilitator to improve male involvement in ANC care[68].

Promotion and acceptance of father involvement at the maternity ward could have positive effect. One study in Uganda is showing that fathers that accompanied their wife to the delivery room were more involved with the health of their wives and their future babies[68].

It is also important to recognize that a high male attendance at the PMTCT services does not mean directly that the men are also engaged. A study in rural South Africa is showing that special psychoeducational programs are needed to engage the men[69].

5.1.3 Institutional

Five studies in the review of Ambia, were evaluating the effect of text messages or phone calls to the caregiver to give a reminder (between 6-10 weeks post-delivery), the pooled effect of these studies showed a statically significant increase in uptake of early infant HIV testing[66].

Currently there is a larger randomized control trial running in Kenya that is analyzing if a HIV infant track system (HITS) will work to improve the retention of HIV exposed and HIV infected children. In this system the health care providers, the laboratory and the HIV infected mothers are better linked to each other with a web-based tool. The HITS is sending messages to the HIV infected mothers and the first results are showing that with a good working HITS 98% percentage of the mothers are returning to the health facilities[70].

5.1.4 Community

Seven studies analyzed the effect of home visiting, six reported a statically significant difference in uptake. However the author of the review is describing that the studies were very heterogeneous which made it impossible to do a meta-analysis[66].

One study in Mozambique is showing that a new type of community health agent namely; “male Champions”, are effective in the engagement of men in ANC services. The counselling is done between man and man and the focus is to change the community norms around engagement in partner pregnancies[71].

There was no specific literature found that focused on interventions with involving traditional healers and HIV exposed/positive children.

5.1.5 Policy

Integrated health care is not a new and innovative topic. Chamla et al describes 4 methods how early HIV testing could be integrated in child survival platforms[72,73]: HIV testing integrated with 1) immunization and 2) nutrition programs, 3) testing in the clinics and wards and 4) HIV testing in community-based programmes. The first three methods have been implemented in the last 2 years in Chiure district hospital however there is no specific data available to analyse the effectiveness and my own observation is that the integrated testing in the immunization program is not working that well as there is often no counsellor available.

5.2 Improved quality of EID health care services

HITSystem in Kenya also reduce the complete turn-around time for the communication cycle of test result (from collection to mother notification), it reduced significantly from 8.1 weeks to 3.4 weeks[70].

The point-of-care PCR HIV testing for infants could be the solution for the future, according to larger health organization as World Health organization, USAID. The point-of-care CDV machines are increasing the retention in adults[74]. The machines are simple, affordable and it could help in a better linkage between HIV diagnosis and care by reducing waiting time and collecting errors. At the moment different global stakeholders are working to getter to implement a project that will catalyze the introduction of point-of-care PCR HIV testing into African countries[75,76,77].

5.3 Increase early initiation of ART in HIV positive children

In the review of Ambia[66] only two studies are describing a statistically significant decrease of the age for ART initiation among HIV positive infants. With the HITS; the time for ART initiation among HIV positive infants was reduced from 38 to 7 median days[70]. In Malawi the community health workers helped to decrease the median age of starting ART of of 9.1 months to 4.9 months[78].

Discussion

It is important for a HIV positive child to start before the first year of life with ART in order to reduce the risk of mortality. The early infant diagnosis cascade is helpful in diagnosing the HIV exposed infants at an early stage and to refer the HIV positive children at a young age to the pediatric ART clinic. Chapter 3 described the early infant diagnosis cascade in Chiure district hospital with the uptake and waiting time of the services. In Chapter 4 the different factors were explored that could explain the LTFU or delay in the EID cascade. Chapter 5 discussed the evidence based interventions that could improve the uptake and health care services of the EID cascade in Chiure district hospital in order to start earlier with ART (< 1 year) in HIV positive children.

Age of collecting DBS

The data demonstrates that the majority of the mothers (87%) are coming to the clinic to test their child at the age of 1 month. This is much better than other studies in Mozambique and Sub-Saharan African countries are demonstrating[21,79,80,81]. A reason for this could be that the PCR testing is well integrated in the maternal health clinic. Therefore women are easy transferred to the right place. Besides this, the women can combine the testing of her child with the routine visit post-delivery / vaccination and therefore the barrier given by stigma and male involvement can be reduced. There is 13% loss to follow up in this stage. Possible reasons described in Chapter 4 are fear for testing, transport problems, non-male involvement and lack of knowledge.

In the group of HIV positive children the median age for collecting DBS is significant higher (5 months), it is difficult to say what the exact reasons are for this. A few thoughts; women who have been less adherent to their ART are also likely to not adhere to their appointments with children, who are more likely to be HIV positive because of the intermittent PMTCT[82] and as children are at continual risk of contracting HIV whilst breastfeeding it could be that there is HIV transmission during the breastfeeding phase. A child could first be LTFU in the EID cascade but if it develops clinical symptoms it could motivate the caregiver to come to the clinic or the child has been transferred by another clinical department through the integrated pediatric HIV approach[72,73].

Delays and errors in collecting and processing DBS

The waiting time between collecting and getting back the test results to the hospital was 60 days (median) in the last 4 years. This waiting time of 2 months is probably due to overload of the three central laboratories in Mozambique and logistic delays because of the means of transport and the distance (500 km). Besides the waiting time there is also an increase in undefined test results during the last 4 years from 7% to 26%. According to the head nurse in the hospital this could be due to the high turnover of the nurses. The increased undefined test results could also take place on laboratorial level, however there is no specific information about this available. Both factors; the waiting time and collecting errors could negative influence the adherence of the caregivers.

Of the group that required a second test, only 17% of the children got tested twice in the four years. That children are not tested twice could be because the children are not coming back to collect their test result or because the nurse doesn't have enough skills or knowledge to

test the children twice. That these children are not tested for a second time can delay the decision making that a HIV positive child needs to start with ART.

Linkage of HIV positive infants to ART services

In the last 4 years there has been a high LTFU of 41% (8% died) between testing and starting ART in HIV positive infants. This is consistent with existing literature[79,80,21] .
For the 59% that do start with ART; the median delay from the caregiver side is 60 days between getting back the test results and starting ART. The delay and LTFU is a multifactorial process that is caused by different factors. Factors mentioned in Chapter 4 include fear or disbelief in the test results, lack of social support from husband, family or community, the strong tradition in the community to go to the traditional healer, lack of transport and lack of knowledge. Factors described that could motivate the caregiver to come, even when it is delayed are: clinical symptoms, positive examples in the community and male or family support.

The data of the PCR books is showing that the 66 HIV positive children (2012-2015) that started with ART had a median age of 10 months when they opened their patient file at the pediatric HIV clinic. So with this group of children alone we cannot explain why there are 48% of children starting with ART after the age of 1 year and therefore we need to look broader than the EID cascade.

Linkage of the HIV pregnant women to the health facility

It is Important to take into consideration that the data used for this analysis is focused on children that have been born in the hospital and that are coming to the hospital in their first months of life to be tested for HIV. However there is still a group of HIV exposed children that have been born outside the hospital, the institutional birth rate was 48% in 2015 in Chiure district and besides that the LTFU of HIV positive pregnant women is high along the PMTCT cascade (see Paragraph 4.3.1). These children will enter the health system at a later age and from the age of 18 months they will be tested with a HIV rapid test. These children are not necessarily included in the analysis of the PCR registrations books, but they can influence the data about the age of starting ART in HIV positive children. Therefore it is important to start the early infant diagnosis cascade with a good working PMTCT cascade. It is difficult to describe or predict which types of pregnant women are coming to the hospital for their delivery in North Mozambique, due to lack of research. Other ways of finding these home born HIV exposed children are needed. A way forward could be by integrating HIV testing in the vaccination program or testing in the communities done by community health workers or traditional birth attendants.

A holistic approach to improve the quality of pediatric HIV care

The data discussed above is useful to describe were interventions and improvement of quality is needed in the district hospital to improve the early initiation of ART in HIV infected children. Improvement in DBS collecting and processing is needed to avoid the high percentage of undefined test. This improvement on institutional level can influence the adherence of the caregivers and it could improve the belief in the test results on individual level with as result an earlier diagnosis and an earlier start of ART in HIV positive children.

The data about the median number of 60 days in between processing the DBS and getting the results back to the hospital could show the importance of good logistics on institutional level and the process of decentralization of advanced laboratories on policy level. In the future it could be very helpful to implement a point-of-care PCR HIV testing machine to reduce the problems mentioned above.

A good working HIV infant tracking system could improve the communication between laboratory, health workers and caregivers (like used in a Kenya)[70]. A web based system would be beautiful, however when this is not feasible yet, a good infant tracking system could already be started by using the existing registration books. A better coordination, analysis and linkage between the different registration books are needed on a regular basis. After the results arrive at the hospital, action needs to be taken by sending messages to the caregiver, or the community health workers need to conduct a home visit to counsel the caregiver about the HIV test results and the importance of early initiation of ART.

The high LTFU and delay between testing and starting ART means that more counselling, attention and guidance to the caregivers is required to improve their knowledge and motivation about pediatric ART and to reduce their fear for HIV.
It is Important to get the fathers involved. Simple methods that could work are; sending invitation letters to the fathers, working with role models of fathers that will give counselling in the communities and the use of a family based HIV center. Beside that it is important to empower the women by educating and supporting them to make their own decision regarding their exposed children. Peer groups could give a significant improvement of adherence, but specific evaluation needs to be done on district level to see how the peer groups could stay sustainable with the high turnover of nurses.

It is also important to link the traditional healers to the health facilities because there is strong culture of using traditional healers in the community. As mentioned in Chapter 4 one study in Mozambique showed that 80% of the traditional healers are open for collaboration but more research is required to evaluate the effect of this collaboration on PCR uptake and early initiation of ART in HIV infected children.

The information presented in this thesis is showing that a holistic approach is needed to improve the early initiation of ART in HIV positive children with interventions on the 5 levels of the conceptual framework of McLeroy[20]. The local and provincial health authorities could use this thesis to implement new interventions in these areas.

Limitations

There is no specific knowledge about the processing of the DBS on laboratorial level, therefore it is difficult to differentiate if the collecting error are taking place on hospital or laboratorial level.

There is a lack of information about the 41% of LTFU of HIV positive children that did not start with ART and the active searching of the health workers in the community.

The quantitative study is only conducted on hospital level and not a health center level, the delay and LTFU on health center level could even be higher because of longer distances to central laboratory and higher workload for health staff.

Another limitation is that there is not much literature available about qualitative studies that investigated the motivation of caregivers to test their HIV exposed child to start or not to start with ART in HIV positive children. Unfortunately there is limited literature available about the context in Mozambique, the use of traditional healers in HIV exposed children, male involvement in HIV positive children and stigma for HIV caregivers in the communities of Mozambique.

Conclusion

1. The uptake for testing a HIV exposed child with a PCR test after delivery in Chiure district hospital was 87% in the years 2012-2015. The median age for testing was 1 month. 13% of all the PCR tests were positive for HIV but 41% of these children did not start with ART. Furthermore, the delay of 4 months incurred by the process from testing to starting the treatment calls for process improvements at the service provider level and better counselling to the caregivers. Such delays in the process may also be responsible for the high LTFU rate of HIV positive children. The high number of undefined laboratory results further underlines the limited experience of the nurses in the district and capacity issues of centralized laboratories in the Northern Region of Mozambique.

2. Different factors on the five levels of the McLeroy socioecological framework are influencing the EID cascade. On institutional level it is important to have a good working PMTCT cascade. In 2015 the institutional birth rate was 48%, which means that there are still many HIV exposed children born in the communities. Furthermore, the LTFU for HIV positive pregnant women on ART is high in the first year after starting. There are important factors on interpersonal and community level that are playing a role as well, like lack of father involvement, lack of social support, distance, fear and disbelief about HIV in children, stigma and the use of traditional healers.

3. Interventions described in the literature that could be effective are mother peer groups; which can improve knowledge, empowerment of women and increased disclosure among participants. A HIV family center approach and sending invitations letters to the father could improve the father involvement and social support. A specific HIV infant track system could play an important role for the future pediatric HIV care as this will link the health care providers with the laboratories and the HIV infected mothers. With the point-of-care PCR testing machine waiting time and collecting errors could be reduced. Next to this, it is important that HIV testing is integrated in other care programs like vaccination, nutrition or in- and outpatient clinics, in order to `catch` the children that never entered the system or that are LTFU in the EID cascade.

4. There is limited literature available about the motivation of caregivers for starting or not starting ART in their HIV positive children and there is hardly any literature that focuses on father involvement and the EID cascade. The role of traditional healers in the community regarding HIV positive children is also not (well) described in the literature

Recommendation

1. The district and provincial health authorities:

    a. Need to priorities the transport of PCR test to the central laboratories and they need to give continuous training and supervision to the nurses and laboratories to ensure the quality of collecting and processing DBS PCR HIV tests

2. District health authorities are important to stimulate:

    a. The use of mother peer groups in the community in order to empower the women. An educated HIV positive mother with a role model function could be used to supervise the groups to improve sustainability.

    b. To link conventional medicine with the health system especially for HIV exposed children by implementing regular meetings and a transfer system

3. The hospital management board are important to

    a. To link the PCR test results with the initiation of ART. Options are; guiding the mother to the right consultation room or using a tracking register system on paper and later digital. Community health workers could help in tracking the children in the communities as well.

    b. Introduce a HIV family treatment center could to stimulate the involvement of the father.

4. On national level:

    a. Decentralization of PCR HIV testing is needed in the future; point-of-care testing machine would be an option to realize this.

    b. Evaluation is needed to improve the adherence of positive HIV women that started on ART with Option B+ in Mozambique

5. All levels:

    a. There is a need for further qualitative research about how to motivate mothers to stay adherent with their HIV positive child and how to involve the fathers.

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Annex 1 – Overview of used search terms

Search terms (or with one of the synonyms)	First search (with filters)	Selection criteria - relevant	Excluded due to repetition	No access to full article	Included in study
-Infant -HIV -Early initiation -ART	49 articles	16	0	3	13
-Infant -HIV exposed -Early infant diagnosis -Barriers	11	8	1	1	6
-Child -HIV exposed -PMTCT -Loss to follow up	13	10	2	2	6
-Infant -HIV infected -Stigma -PMTCT	13	11	2	2	7
-Infant -HIV infected -Male involvement	44	6	2	1	3
-Infant -HIV -Health policy -ART	24	9	1	2	6
-Infant -HIV -Community -ART	42	12	2	2	8
-Child -HIV -Integrated health -Retention	21	9	2	0	7
-Child -HIV -Early ART -Interventions	72	17	7	2	8
Total articles	289	98	19	15	64

Annex 2 – Waiting time in days of PCR by year

Waiting time

	Total number of samples	Waiting time in days Of sending the samples			number of samples size	Getting back the test results to hospital			number of sample size	Getting back test result to caregiver			number of sample size
		1st quartile	median	3rd quartile		1st quartile	median	3rd quartile		1 st quartiel	median	3rd quartil	
2012	137	3	7	16	137	65	78	126	136	9	31	69	32
2013	247	2	4	8	238	35	53	84	226	5	11	19	47
2014	244	3	6	11	242	26	38	62	232	8	18	25	74
2015	257	5	10	19	205	44	61	101	154	14	42	93	24
Total	885	3	6	13	822	36	54	84	748	8	18	31	177