



UNIVERSITY OF CAPE TOWN

Outcome of universal life-long ART for all HIV infected pregnant and breastfeeding women and children less than 24 months regardless of WHO stage or CD4 count (PMTCT option B+) – a case study in a rural district, Malawi

By

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ABBREVIATIONS

ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
AFASS	acceptable, feasible, affordable, sustainable and safe
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral drug
AZT	Zidovudine
BMI	Body mass index
CDC	Centre for disease control
CD4	CD4 cell or T4 ‘helper’ lymphocyte
CPT	Cotrimoxazole preventive therapy
d4T	Stavudine
ddl	Didanosine
DSS	demographic surveillance sites
EFV	Efavirenz
EMRS	Electronic medical record systems
FDC	Fixed dose combinations
FP	Family planning
GoM	Government of Malawi
HCC	HIV care clinic
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
ICASA	International Conference on AIDS and STIs in Africa
ICER	incremental cost effectiveness ratios (ICER)
LPV/r	Lopinavir/ Ritonavir
LTFU	Lost to follow up
MCH	Maternal and child health
MNCH	maternal newborn and child health (MNCH)
MDG	Millennium Development Goal

MDHS	Malawi demographic health survey
MMR	Maternal Mortality Rate
MOH	Ministry of Health
MOHP	Ministry of Health and Population
MTCT	Mother to child transmission
NAC	National AIDS commission
NAF	National HIV/AIDS Action Framework
NSP	National HIV/AIDS Strategic Plan
NVP	Nevirapine
OPC	Office of President and Cabinet
PCR	Polymerase chain reaction
PLWHA	People living with HIV/AIDS
PMTCT	Prevention of Mother to Child transmission
PSHD	Presumed severe HIV disease
PwP	Prevention with Positives
QECH	Queen Elizabeth Central Hospital
SD-NVP	Single dose Nevirapine
SPSS	Statistical Package for the Social Sciences
SSA	Sub-Saharan Africa
STI	Sexual Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir
TLC	Total lymphocyte count
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children Fund
WHO	World Health Organization
VL	Viral load
3TC	Lamivudine

DEFINITIONS USED IN THE STUDY

Alive on ART	Patient who is taking ART and is alive at the facility where he/she is registered, and has collected his/her own supply of drugs
Antenatal care	The regular medical and nursing care recommended for women during pregnancy.
ART stopped	Patient who has stopped ART treatment completely either because of side effects or other reasons
Death	Patient who has died for any reason while being registered on ART
Defaulted	Failure to attend an ART clinic for at least 3 months after the last scheduled appointment
Drug adherence	Is calculated as the number of doses of ART taken divided by number of prescribed doses of ART multiplied by 100, i.e. expressed as percentage. The drug adherence was calculated over a minimum period of 7 days.
Transferred out	Patient who has moved out permanently from one facility to another facility for treatment
PMTCT option B+	Initiation of life-long ART for HIV-infected pregnant or breastfeeding women regardless of their WHO clinical stage or CD4 count

ABSTRACT

Background

Malawi has one of the highest HIV/AIDS prevalence rates in sub-Saharan Africa. It has the ninth largest HIV burden in the world. Following the 2010 WHO PMTCT recommendations Malawi started providing lifelong ART to HIV-infected pregnant and lactating women regardless of clinical stage or CD4 count (option B+) in July 2011.

Aim

To assess the outcome of pregnant and lactating mothers receiving ART (option B+) and their infants less than 24 months in a rural health district of Malawi.

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Methods

A retrospective cohort study of option B+ women who were initiated on ART between 1st July 2011 and 31st December 2012 was conducted in Ntchisi district. Their exposed infants were also enrolled in the study. The study participants were followed up to 31st December 2013. Data was mainly collected from ART registers, ANC registers and ART patient master cards using structured questionnaires. Data analysis was done using Microsoft Excel and Statistical Package for Social Science (SPSS).

Results

A total of 201 option B+ mothers, 136 pregnant women and 65 lactating mothers were enrolled in our study. Their median age was 32 years. 19.9% of HIV pregnant mothers started ANC at less than 12 weeks gestation and 21% attended the recommended four ANC visits or more. The proportion of pregnant and lactating women tested for HIV was 89.6%. Uptake of ART in HIV positive pregnant and lactating women was 80.1%. Of 54 option B+ mothers enrolled in the July 2011 - December 2011 cohort, 70.4%, 64.8%, 57.4% and 55.6% were retained at 3, 6, 12 and 24 months respectively, and 73.5%, 66% and 65.3% of 147 option B+ mother enrolled in the January 2012 - December 2012 cohort were retained at 3, 6 and 12 months respectively. Out of 126 option B+ who remained in care in December 2013, 89 (70.6%) had adherence rate of 95% or more in the last visit of the October - December 2013 quarter. Of all women who commenced option B+ during pregnancy, 56/77 (72.7%) who remained in care during the October -

December 2013 quarter had adherence of at least 95%, while 33/49 (67.3%) of women who commenced option B+ during lactation and who remained in care during the October – December 2013 quarter had adherence of at least 95% or more. This difference was not statistically significant, OR = 1.2, 95% CI: 0.6 – 2.8.

A total of 198 exposed infants were enrolled and their median birth weight was 3.2 kg. Uptake of PCR/rapid test for the infants was 73.7%. 163/198 (82.3%) received NVP. Out of 53 exposed infants enrolled in July 2011 - December 2011 birth cohort, 81.1%, 67.9%, 51% and 17% were retained at 3, 6, 12 and 24 months respectively. In the January 2012 - December 2012 cohort the proportion of exposed infants retained were 89%, 81.2% and 47.6% at 3, 6 and 12 months respectively. Of all infants tested for HIV infection during the study period, a higher proportion who were enrolled in the July - December 2011 birth cohort became HIV-infected compared to those enrolled in the January - December 2012 cohort, 7/34 (20.6%) versus 4/112 (3.6%), OR = 7.0, 95% CI: 1.9 – 25.7. A significantly higher proportion of HIV-exposed infants born to mothers who initiated ART during lactation acquired HIV infection than those born to mothers who initiated ART during pregnancy, 7/43 (16.3%) versus 4/103 (3.9%), OR = 4.8, 95% CI: 1.3 – 17.4.

Conclusion:

Our research findings suggest that the PMTCT programme in the Ntchisi district can be improved. Late booking during pregnancy, initiation of ART late during pregnancy or only during lactation, low retention in care for HIV pregnant and lactating mothers and their HIV-exposed infants, inadequate HIV testing of HIV-exposed infants and low ART adherence rate of HIV pregnant and lactating mothers should be addressed in order to optimize the administration and effectiveness of option B+.

CHAPTER 1.0: INTRODUCTION

1.1 HIV/AIDS in Sub Sahara Africa

About 34.0 million people were living with HIV at the end of 2011 worldwide of which 69 % were from Sub Sahara region (SSA). In 2011 the HIV/AIDS related deaths were about 1.7 million worldwide (UNAIDS, 2012a). SSA contributed 70% of all deaths from AIDS in 2011 despite having registered a decline in the number of HIV/AIDS related deaths of 32% between 2005 and 2011. SSA has the highest number of children living with HIV and contributed about 88 % of all children living with HIV worldwide (UNAIDS, 2012a). In 2009, an estimated 15.7 million women above the age of 15 were living with HIV globally, and 1.4 million of them became pregnant. Nearly 90% of these expectant mothers were living in 22 countries in SSA and India (UNAIDS, 2011).

1.2 HIV/AIDS in Malawi

Malawi is one of the countries in SSA most highly affected by HIV/AIDS and has the ninth largest HIV burden in the world (UNAIDS, 2010). The first case of HIV in Malawi was identified in 1985. Since then the number of newly infected persons has been increasing each year up to 2001. From 2001 to 2012 the proportion of new HIV infections in Malawi fell dramatically by 73% (UNAIDS, 2012b). From 1985 to 1993, HIV sero-prevalence among antenatal women increased from 2 percent to 30 percent. By 2001, HIV prevalence among antenatal women had fallen to 20 percent and remained around 21 percent in 2003 (UNAIDS, 2004a). In 2007, estimates at selected sites in Malawi indicated that HIV prevalence in antenatal women aged 15-49 years was 17.1% in urban areas, 16.4% in semi-urban areas and 12.1% in rural areas (MOH, 2007a). In the adult population, HIV prevalence has fallen from 14 percent in 2003 to 10 percent in 2011. Similarly new annual HIV infections of both children and adult have been reduced from 100,000 in 2003 to 46,000 in 2011 (UNAIDS, 2012c). Malawi had an estimated 930,000 adults living with HIV infection, with an annual estimate of 70,000 new infections occurring across all groups in 2009. Malawi recorded about 51,000 HIV/AIDS related deaths in 2009 (UNAIDS, 2010).

1.3 Mother to child transmission (MTCT) for HIV

In the absence of preventive measures mother to child transmission rates of HIV range from 25% to 35% in developing countries compared to 15% to 25% in industrialized countries (UNAIDS, 1998). In the absence of any intervention the risk of mother to child transmission (MTCT) is 15% -30% in non-breastfeeding populations and breastfeeding by an infected mother increases the risk by 5% -20% to a total of 30% - 45% (De Cock, 2000). Factors that influence MTCT for HIV include high prevalence rate of HIV in women of reproductive age, high birth rates, a large population of women of reproductive age, and ineffective or incomplete coverage of MTCT prevention interventions (Onyango, 2006).

1.4 ART in Malawi

Malawi started providing ART in 2000 at Queen Elizabeth Central Hospital (QECH) at a small fee. In 2004 the Malawi government introduced free ART to public health facilities. The Malawi first line ART regime from 2004 to 2010 was Stavudine /Lamivudine/ Nevirapine, using a fixed-dose formulation, Triomune (MOH, 2008a). Thereafter the ART provision has been scaled up to reach universal access. In 2011, Malawi adopted WHO PMTCT guidelines which included option B + based on a regimen of Tenofovir, Lamivudine and Efavirenz. PMTCT option B + means starting lifelong ART in HIV infected pregnant and breastfeeding women regardless of CD4 count and/or clinical stage (MOH, 2011a).

1.5 Coverage of PMTCT in Malawi

In 2011, approximately 63,500 pregnant women were living with HIV and 53% of pregnant women living with HIV received therapy for PMTCT, single dose of Nevirapine (SD-NVP) at the onset of labour and a combination regimen of Zidovudine and Lamivudine (AZT/3TC) from the onset of labour until 7 days post-partum. In 2012 the ART coverage among people with advanced HIV infection was 69 % (WHO, 2013). Approximately 330,000 infants acquired HIV infection from their mothers in SSA in 2011 and 15,700 (5.2%) of these infants were born in Malawi (UNAIDS, 2012b). The estimate for 2010 from the UN for Malawi was that 29% of maternal deaths were AIDS related maternal deaths (WHO/UNICEF/UNFPA, 2012).

CHAPTER 2.0: LITERATURE REVIEW

2.1 Introduction

According to Hart, a literature review is defined as an objective, thorough summary and critical analysis of the relevant available research and non- research literature on the topic being studied (Hart, 1998). The literature review search and selection strategy were completed using several different electronic databases including Pub Med and Google Scholar, journals, books and websites (WHO, UNAIDS and Malawi ministry of health HIV). The literature review has been referenced using Harvard referencing style. The literature review covered the following sections; introduction, HIV / AIDS situation in Malawi, background of ART in Malawi, impact of ART in general population, overview of PMTCT in Malawi before option B+, report of PMTCT before option B+ in Malawi, overview of PMTCT option B+ in Malawi, studies of PMTCT option B+ in Malawi and studies on PMTCT option B+ in other countries.

2.2 Impact of HIV /AIDS in Malawi

Since the first AIDS case in Malawi was diagnosed and confirmed in 1985, it has increasingly spread across the country (NSF, 2000). Malawi has an estimated adult HIV prevalence of 10.5 % (NAC, 2011). HIV/AIDS poses a great public health burden in Malawi. The impact of HIV/AIDS in Malawi has been devastating. AIDS is the leading cause of death amongst adults in Malawi and is a major factor in the country's low life expectancy of just 54.8 years (UNDP, 2013). In 2010 there were 52,144 AIDS related deaths among adults 15 years or older and AIDS related deaths in children less than 15 years were 9,089 (NAC, 2011).

2.3 Mode of HIV transmission in Malawi

In Malawi unprotected heterosexual contact with an infected partner is the leading cause of HIV new infections. Mother to child transmission (MTCT) is the second major mode of transmission, accounting for approximately 25% of new infections (MOH, 2012a). Other modes of HIV infection transmission add up to a small percentage of the total, and together account for about 2% of HIV infections. These include use of infected blood during transfusion, infected needles and poor management of health care waste, intravenous drug use and homosexual sex. MTCT is the leading mode of HIV transmission in children in Malawi.

2.4 Malawi national policy of HIV and AIDS response

The Government of Malawi's response to the HIV/AIDS epidemic is captured through a series of five-year plans. The first five year plan from 1989 - 1993 primarily focused on HIV prevention that included blood transfusion safety, behaviour change communication and management of sexually transmitted infections (STIs) (MOHP, 2001). Malawi developed a second five year plan from 1994 to 1998 and its main focus was to combat HIV/AIDS with a multi-sectorial approach. However, there was little that was done to mitigate the impact of HIV/AIDS.

To achieve a national coordinated response to HIV/AIDS, the National AIDS Secretariat (NAS) in the Ministry of Health developed a 2000 - 2004 National HIV/AIDS Strategic Plan (NSP) targeting mostly prevention and behavior change interventions, as well as interventions to expand access to treatment, care, and support services, including antiretroviral drugs (ARVs). In 2001 the National AIDS Commission (NAC) was created in Malawi to oversee a number of prevention and care initiatives, including programmes to provide treatment, increase testing and prevent mother-to-child transmission of HIV. A national HIV/AIDS Policy was developed in 2003, laying down the guiding principles for all national HIV/AIDS programs and interventions (GoM, 2003).

The National HIV/AIDS Action Framework (NAF) 2005 - 2009 was developed to prevent the spread of HIV infection among Malawians, provide access to treatment for PLWHA and mitigate the health, socio-economic and psychosocial impact of HIV/AIDS on individuals, families, communities and the nation (MOH, 2005a). The NAF 2005 – 2009 was extended to 2012 to align to the Malawi Growth and Development Strategy (MGDS) (MOH, 2009). The Malawi Growth and Development Strategy (MGDS) 2006 to 2011 is the overarching development strategy, with the purpose of facilitating achievement of the Millennium Development Goals (MDGs).

The Malawi National Strategic Plan (NSP) 2012-2016 was formed to prevent the further spread of HIV infection, promote access to treatment for PLHIV and mitigate the health, social-economic and psychosocial impact of HIV and AIDS on individuals, families, communities and

the nation. Its aim was to reduce new infections by 20% and AIDS deaths by 8% including a 50% reduction in child deaths (MOH, 2011b).

In 2011 the Malawi National HIV and AIDS Response policy was revised and the government renewed its commitment based on the three ones principle and the three zeros (zero new HIV infections, zero discrimination and zero AIDS related deaths) with increased Government of Malawi stewardship and ownership, respect for protection and fulfillment of relevant human rights and fundamental freedoms in accordance with the Constitution of the Republic of Malawi and existing international human rights standards (GoM, 2011). Three-one principles was formulated at the 2003 International Conference on AIDS and STIs in Africa (ICASA) where African governments, the UN, multilateral and bilateral development agencies, NGOs and the private sector reached consensus on the principles needed to strengthen the national response to HIV and AIDS (UNAIDS, 2004b). They were:

- One national AIDS action framework to coordinate the work of all stakeholders in a given country
- One national AIDS authority with a broad-based multi-sectorial mandate
- One agreed country level monitoring and evaluation system

2.5 Scaling up ART in Malawi

The goal of scaling up ART in Malawi was to reduce HIV related morbidity and mortality in adults and children. In 2004 the Malawi government started to provide free ART to public health facilities. By January 2004, there were about 3000 – 4000 patients accessing ART in 9 public health facilities around the country (MOH, 2006). By the end of 2005, there were 60 facilities in the public sector (central, district, mission, and defence force hospitals and clinics) delivering ART using national systems, and 37,840 patients had ever been started on therapy. The Ministry of Health developed a 5-year ART scale- up plan (2006 - 2010) with the aim to deliver ART to over 200,000 HIV-infected eligible patients by the end of 2010 (MOH, 2006). In 2008, Malawi developed a third edition of the national ART guidelines, which considered the experience of the previous ART implementation, and resolved to continue scaling up ART especially to remote areas (MOH, 2008a)

Table 1: Summary of ART eligibility in Malawi (MOH, 2003; MOH, 2006; MOH, 2008a)

Category	1 st edition 2003	2 nd edition 2006	3 rd edition 2008
Adults 15 year and above	<ol style="list-style-type: none"> 1.WHO clinical stage 3 or 4 2.CD4-lymphocyte count < 200/mm³ 3.WHO clinical stage 2 with TLC < 1200/mm³ 	<ol style="list-style-type: none"> 1.WHO clinical stage 3 or 4 2.CD4-lymphocyte count < 250/mm³ 3.WHO Clinical Stage 2 with TLC < 1200/mm³ 	<ol style="list-style-type: none"> 1.WHO clinical stage 3 or 4 2.CD4-lymphocyte count < 250/mm³ 3.WHO clinical stage 2 with TLC < 1200/mm³
Over the age of 18 months and less than 15 years	<ol style="list-style-type: none"> 1.WHO clinical stage III 2.WHO Stage I and II with CD4 percentage < 15% 	<ol style="list-style-type: none"> 1. WHO paediatric clinical stage 3 or 4 2. CD4-lymphocyte percentage < threshold 3. Assessed to be in WHO paediatric stage 2 with total lymphocyte count (TLC) < threshold 	<ol style="list-style-type: none"> 1. WHO paediatric clinical stage 3 or 4 2. CD4-lymphocyte percentage < threshold 3. Assessed to be in WHO paediatric Stage 2 with total lymphocyte count (TLC) < threshold
Under the age of 18 months	<p>Confirmed to be HIV seropositive by a virological test plus any one of the following</p> <ol style="list-style-type: none"> 1. WHO paediatric stage III disease. 2.WHO Stage I or II disease and a CD4 percentage <20% 	<ol style="list-style-type: none"> 1.WHO paediatric clinical stage 4 2.Have 2 or more of a) oral candida, b) severe pneumonia or c) severe sepsis 	<ol style="list-style-type: none"> 1. WHO paediatric clinical stage 4 2. Have 2 or more of a) oral candida, b) severe pneumonia or c) severe sepsis <p>- Under the age of 12 months where virological testing has been done:</p> <p>All confirmed HIV-infected infants (confirmed by virological testing) irrespective of their CD4 count or clinical</p>

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Table 2: WHO Proposed Immunological Classification of established HIV infection (MOH, 2008a)

HIV-Immune Deficiency	Age-related CD4-lymphocyte values			
	< 1 year	1yr – 3 yrs	3yr – 5yrs	≥ 5 yrs (cells/mm ³)*
Not significant	>35%	>30%	>25%	>500
Mild	30-35%	25-30%	20-25%	350-499
Advanced	25-30%	20-25%	15-20%	250-344
Severe	<25% CD4<2500 cells/mm ³ TLC<4000 cells/mm ³	<20% CD4<750 cells/mm ³ TLC<3000 cells/mm ³	<20% CD4<350 cells/mm ³ TLC<2500 cells/mm ³	<15% CD4 <250 TLC <2000

* Cells/mm³ except where % = percentage of lymphocytes

Eligibility criteria in children less than 18 months depend on whether or not a DNA-PCR test is available. A DNA-PCR positive test result in a child less than 18 months is an ART eligibility criterion regardless of clinical or immunologic status. When there is no DNA-PCR test available, ART eligibility criteria in children less than 18 months will include a diagnosis of a sign of severe HIV disease (last row of table 1) and include a CD4 < 20% in children 12-18 months and <25% in children less than 12 months. Severe immune deficiency in table 2, last row refers to the threshold criteria of CD4-lymphocyte and total lymphocyte count (TLC) threshold values used to start ART in children between 18 months and 15 years in Malawi.

2.6 Antiretroviral treatment regimens 2003 – 2010 (MOH, 2003; MOH, 2006; MOH, 2008a)

Malawi scaled up the use of one generic, fixed-dose combination treatment with Stavudine, Lamivudine and Nevirapine (Triomune) as the first line ART regime from 2003 to 2011 and was used for all eligible adults, pregnant mothers as well as children. The alternative first line

regimen in Malawi in case of drug induced severe peripheral neuropathy, pancreatitis and lactic acidosis was Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP). Malawi also used Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFV) as alternative first regimen when there were drug reactions due to Nevirapine (severe skin reactions, hepatitis). In case of treatment failure to the first line regimen patients were switched to second line regimen of Zidovudine (AZT) + Lamivudine (3TC) + Tenofovir (TDF) + Lopinavir/ Ritonavir (LPV/r) and Didanosine (ddI)+Abacavir (ABC)+ Lopinavir/Ritonavir (LPV/r) for adults and children respectively.

2.7 The Malawi clinical management of integrated ART/PMTCT 2011

The first edition of the Malawi Guidelines for Clinical Management of HIV in Children and Adults was developed in 2011 (MOH, 2011a). This edition was developed such that all previous ART guidelines as well as Prevention of Mother to Child Transmission (PMTCT) guidelines were incorporated and revised. The guidelines were developed based on Malawi's Revised Policy for PMTCT and ART which was endorsed by the Ministry of Health in June 2010 and which was guided by the release of the 2010 Revision of the World Health Organization (WHO) PMTCT and ART Guidelines. The first edition of the Malawi guidelines for clinical management of HIV in children and adults was developed in line with Malawi health services setting and follows a public health approach with the purpose of providing the best possible services for the largest possible number of persons in need of these services. Malawi started implementation of the Malawi Integrated ART/PMTCT guidelines in July 2011 including implementation of option B+ (MOH, 2011a). The ART eligibility recommendations include the following;

1. Infant under 12 months

- Universal ART-Confirmed HIV infection (DNA-PCR needed), regardless of WHO stage and CD4 count or CD4 %
- Presumed severe HIV disease (PSHD) - HIV antibodies (HIV rapid antibody test) and PSHD defining clinical conditions (Oral candidiasis, Severe pneumonia and Severe bacterial sepsis)

2. Child 12 months to less than 24 months

- Universal ART- Confirmed HIV infection (HIV rapid antibody test or DNA-PCR), regardless of WHO stage and CD4 count

3. Child 24 months to under-5 years

- Confirmed HIV infection (HIV rapid antibody test) and WHO stage 1 or 2 and CD4 ≤ 750 cells/mm³ or $\leq 25\%$, or WHO clinical stage 3 or 4 regardless of CD4 count
- 4. Child or adult 5 years and over
- Confirmed HIV infection (HIV rapid antibody test) and pregnant or breastfeeding women (regardless of the age of the child) regardless of WHO stage and CD4 count or WHO stage 1 or 2 and CD4 ≤ 350 cells/mm³, or WHO clinical stage 3 or 4 regardless of CD4 count.

2.7.1 Summary of national ART regimen for clinical management of HIV in adults and children in Malawi (MOH, 2011a)

The 2011 new regimen for clinical management of HIV in adults and children for Malawi developed from combinations of three different ARVs from at least 2 drug classes in order to avoid development of drug-resistant HIV. Some regimens use fixed dose combination (FDC) drug preparations while others are combinations of different tablets as follows:

1. Adults aged 15 years or older (except pregnant, lactating women and patients already on TB):
The first line regimen is d4T 30mg, 3TC 150mg and NVP 200mg twice daily. In case of severe neuropathy the alternative regimen is AZT 300mg, 3TC 150mg and NVP 200mg twice daily while when there is hepatitis the alternative regimen used is d4T 30mg and 3TC 150mg twice daily combined with EFV 600mg in the evening. The alternative first line regimen used when there is lipodystrophy is TDF 300mg / 3TC 300mg / EFV 600mg once daily. The second line regimen used is TDF 300mg / 3TC 300mg daily + LPV/r 200/50 twice daily when there is first line treatment failure.

2. Children under the age of 15:

The first line regimen is AZT 60mg / 3TC 30mg / NVP 50mg (paediatric formulation) given twice daily according to body weight. In case of side effect of anaemia the first alternative regimen is d4T 6mg / 3TC 30mg / NVP 50mg (paediatric formulation) given twice daily according to body weight. AZT 60 mg / 3TC 30mg given twice daily + EFV 200mg in the evening (paediatric formulation) is used as first alternative regimen when there is side effect of hepatitis and is also given according body weight. When there is treatment failure to the first line

regimen TDF 300mg / 3TC 300mg given daily + LPV/r 200/50 given twice daily (adult formulation) is used as a second line regimen and is also given according to the body weight of the child

3. Pregnant and lactating women and adults already on TB treatment:

The first line regimen is TDF 300mg / 3TC 300mg / EFV 600mg once daily. The first alternative regimen includes AZT 300mg / 3TC 150mg / NVP 200mg twice daily when there is renal failure. TDF 300mg / 3TC 300mg daily + NVP 200mg twice daily is used in case of hepatitis. The second line regimen used when there is first line treatment failure is AZT 300mg / 3TC 150mg + LPV/r 200/50 twice daily.

2.8 Impact of ART on the general population

Since the introduction and scaling up of free ART in Malawi, a reduction of HIV/AIDS related deaths has been reported. Using births and deaths information from demographic surveillance sites (DSS) including verbal autopsies in Karonga, northern region of Malawi mortality trends were analyzed comparing three time periods: pre-ART roll out in the district (August 2002 - June 2005), ART period 1 (July 2005 - September 2006) when ART was available only in a town 70 km away, and ART period 2 (October 2006 - September 2008) when ART was available at a clinic within DSS. The study showed that the all-cause mortality rate among people aged 15–59 years old was 10.2 per 1000 person-years in the pre-ART period (288 deaths / 28285 person-years). In ART period 1, the study revealed that the all-cause mortality fell by 16% and in ART period 2 it fell by 32%. Furthermore the study found that the AIDS mortality rate fell from 6.4 to 4.6 to 2.7 per 1000 person-years in the pre-ART period, period 1 and period 2 respectively. Treatment coverage among individuals eligible to start ART was around 70% in 2008 (Floyd, 2010).

According to Mary Shawa, Malawi's principal secretary in the department of HIV/AIDS in the Office of President and Cabinet (OPC), AIDS related deaths in Malawi have decreased by more than 75 % during the last four years in comparison to the number of AIDS-related deaths that occurred in 2003 – 2004 (Malawi Reuters agency, 2008). Scaling up of ART from 2004 may have contributed to decline of MMR trend in Malawi from 2005 to 2010 (Colbourn, 2013).

Another notable decline in AIDS related deaths was recorded from 49000 to 44000 between 2010 and 2011 (UNAIDS, 2012c).

A national survey of teachers on antiretroviral therapy in Malawi in 138 ART clinics country wide found that of 2380 teachers who were enrolled on ART, 1850 were alive and on ART. The probability of being alive and on ART for teachers at 6, 12, 18 and 24 months was 84 %, 79%, 75% and 73% respectively (Makombe, 2007). A similar survey among the army personnel in Malawi found that out of 547 who were enrolled 365 (66.7 %) were still alive and on ART and 71 (13 %) had died. The probability of being alive and on ART was 89.7 %, 83.5 % and 78.5 % at 6, 12 and 18 months respectively (Banda, 2008).

Another retrospective cohort analysis that was conducted in Malawi to assess treatment outcome on children less than 15 years on ART found that out of a total of 439 children who started ART between July 2004 and September 2006, 49 (11%) had died. The study results showed that the cumulative mortality incidence of mortality was 8 %, 12%, 13% and 15% at 3 months, 6 months, 12 months, and 24 months respectively (Bong, 2007). The Malawi National ART quarterly cohort data from October 2004 to December 2006 revealed that 72, 666 patients were initiated on ART and their estimated survival probability ranged from 85% to 88% at 6 months and 81% to 84% at 12 months (Lowrance, 2008)

Furthermore ART is reported to have some impact on the growth response in children. Weigel (2010) found that out of 497 children under 15 years who started ART their median weight for age z-score and height for age z-score increased from -2.1 (IQR -2.7 to -1.3) and -2.6 (IQR -3.6 to -1.8) to -1.4 (IQR -2.1 to -0.8) and -1.8 (IQR -2.4 to -1.1) at 24 months, respectively (P < 0.001) (Weigel, 2010).

2.9 PMTCT programme in Malawi before option B+

The PMTCT programme in Malawi started in 2001, initially as a pilot programme in Ekwendeni, Mzimba, Chiradzulu and Thyolo District Hospitals. The national PMTCT programme in Malawi was officially launched in 2003. The recommended PMTCT antiretroviral prophylaxis from 2001 to 2008 was single dose of Nevirapine (SD-NVP). In 2008, Malawi introduced AZT

combination prophylaxis with AZT/3TC being initiated at 28 weeks, followed by sdNVP during labour and postnatal an AZT/3TC tail for one week was used (MOH, 2008b).

In Malawi, PMTCT intervention is provided through antenatal care (ANC) clinics, maternity and labour wards as well as outreach programmes that incorporate antenatal care services (MOH, 2008b). The vast majority (94%) of pregnant women visit ANC at least once during their pregnancy and therefore this programme has the potential to achieve universal access to HIV prevention, care, treatment and support.

The first edition of the PMTCT scale-up plan was developed in 2004. Revision of these PMTCT guidelines was completed in 2008. The second edition of the PMTCT guidelines reflected new WHO guidance on specific PMTCT interventions such as combined ARV prophylaxis regimen, Cotrimoxazole preventive therapy (CPT) for HIV positive pregnant women and exposed infants, and revised infant feeding advice (MOH, 2008b) as follows:

- Exclusive breastfeeding is recommended for HIV-exposed infants for the first 6 months of their life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS) for them and their infants before that time. Exclusive breast feeding means feeding the child breast milk only with no other foods or fluids, not even water during the first six months of the child's life.
- When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected women is recommended.
- At six months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe, continuation of breastfeeding with appropriate complementary foods is recommended, while the mother and infant continue to be regularly assessed

The vision of the PMTCT programme in Malawi is to have an HIV-free generation with the goal of reducing paediatric HIV infection and improving the quality of life of exposed infants, and HIV-infected children and their parents. In developing this second edition PMTCT scale-up plan 2008 - 2013, the government of Malawi considered global, regional and national concerns about low uptake of PMTCT despite the availability of resources.

The number and proportion of health facilities offering PMTCT services were 31 (5.7%) out of 544 in 2004, 36 (6.6 %) out of 544 in 2005 and 119 (22%) out of 544 by October 2006. In 2005, the total number of pregnant women tested nationally was 52,904, which is close to 10% of the 540,000 women delivering. Out of 52,904 pregnant women nationwide who were tested for HIV in 2005, 7,052 (13.3%) were HIV positive, and 5,054 (72%) of the HIV infected women received ARV prophylaxis (MOH, 2008b). In 2007 the PMTCT facility coverage was increased to 64 percent of 544 health facilities. 50.2% of HIV positive pregnant women received ARV prophylaxis to reduce risk of MTCT in 2007 (MoH, 2007b).

In 2010 the number of health facilities providing ANC with PMTCT interventions had increased to 544. 78.9% of pregnant women attending ANC were counselled, and tested for HIV in 2010. An estimated 35% to 46% of infants born to HIV-infected women received ARVs for PMTCT in 2010 (MDHS, 2010). In 2010, 56% of HIV positive pregnant women were assessed with CD4 testing to determine if they were in need of treatment for their own health. 38.8% of HIV+ pregnant women received antiretrovirals to reduce the risk of mother-to-child transmission in 2010. Among pregnant women with HIV who received ARVs for PMTCT in 2010, 40% received single dose Nevirapine, a regimen no longer recommended by the WHO, while 34% received more effective ARV regimens and 26% received ART for their own health (MDHS, 2010).

In 2006, the survey of HIV/AIDS services in Malawi (MOH, 2006) identified the following challenges related to the delivery of comprehensive PMTCT services in Malawi:

- Limited access to and uptake of PMTCT service
- Shortage of staff at all levels
- An inadequate monitoring & evaluation system
- An inadequate procurement and supply chain management system
- Limited access to skilled attendance during delivery
- Poor follow up of PMTCT clients

Table 3: ARV prophylaxis regimen during pregnancy, labour and post- partum from 2008 - 2011 (MOH, 2008b)

Pregnancy	Labour	Postpartum	
		Mother	Infant
1. Women on ART	1.Continue ART as per usual schedule	1.Continue ART	1. AZT 4mg/kg twice daily for 7 days. Start within 12 hours.
2,Women who received at least 4 weeks of AZT 300mg before onset of labour	1.SD-NVP 200mg to be taken at onset of labour 2.AZT/3TC 600mg at onset of labour	1.AZT/3TC 300mg every 12 hours for 7 days	1.SD-NVP 6mg within 72 hours 2. AZT 4mg/kg within 12 hours every 12 hours for 7 days 3. Babies delivered at home should get SD-NVP and start AZT within 12 hours of delivery
3. Women who received less than 4 weeks of AZT	1.SD-NVP 200mg at onset of labour 12 hours for 7 2.AZT/3TC 600mg at onset of labour	1.AZT/3TC 300mg every 12 hours for 7 days 2.AZT 4mg/kg every 12 hours	1.SD-NVP 6mg within 72 hours 2.AZT 4mg/kg every 12 hours for 4 weeks
4.Women who present during labour and have not received AZT	1.SD-NVP 200mg to be taken at onset of labour 2.AZT/3TC 600mg at onset of labour	AZT/3TC 300mg every 12 hours for 7 days	1. SD-NVP 6mg within 72 hours 2. AZT 4mg/kg 12 hourly for 4 weeks 3. Babies delivered at home should get SD-NVP 6mg and AZT 4mg/kg 12 hourly for 4 weeks
5.Women who present late	None	None	1. SD-NVP 6mg immediately

in or after labour and have had no ARVs during pregnancy, and no ARVs during labour			2. AZT 4mg/kg every 12 hours for 4 weeks
6. In settings where only SDNVP is available	1. SD-NVP 200mg to taken at onset of labour		1. SD-NVP 6mg within 72 hours

2.10 Effectiveness of the PMTCT programme before option B+

The analysis of uptake of WHO recommended integrated perinatal PMTCT of HIV interventions between 1997 and 2006 in low and middle income countries showed that 96% (range 30 – 100%) of pregnant women were attending ANC, and 81% (range: 26 – 100%) were counselled and tested for HIV infection. However the study found that the overall median proportion of HIV positive women provided with antiretroviral prophylaxis in ANC and attending labour ward was 55 % (range 22 % - 99 %) (Tudor, 2013). Nigatu (2011) documented similar findings.

Another review analysis of PMTCT programs in SSA found that the rates of LTFU of mother-child pairs ranged from 19 % to 89.4 %. Among other things the study identified fear of HIV test, stigma, discrimination, home deliveries and socioeconomic factors as reasons for LTFU (Kalembo & Zgambo, 2012).

Chi (2013) highlighted that the integration of PMTCT and MNCH services improved the uptake and timely initiation of ART among treatment eligible pregnant women in public health settings. However, their review noted that postpartum care of HIV-infected mothers and HIV-exposed infants has been insufficient, although provision of integrated mother-infant clinics may increase retention. Additionally the study revealed that the integration of maternal HIV testing into childhood immunization clinics can increase the identification of HIV-exposed infants previously missed by traditional PMTCT models.

A systematic review and meta-analysis in low-income, middle-income, and high-income countries found a pooled estimate of 73.5 % of pregnant women had adequate ART adherence (>

80%). The analysis further found that the ART adherence was higher during antepartum than during postpartum, 75.7 % and 53.0 % respectively (Nachenga, 2012).

Cohort study of pregnant women who tested HIV positive for their first ANC visit between January and June 2010 in Johannesburg, South Africa showed LTFU of 57.7 % at 6 months post-delivery (Clouse, 2013).

Schechter (2014) conducted a study to explore barriers and facilitators to participation in PMTCT programmes for pregnant and postpartum women living with HIV in the Vallée du Bandama region of Côte d'Ivoire, West Africa. Among the barriers that were identified include individual discouragement and internalized stigma, gender inequalities, unclear information and post post-test counselling from health staff, as well as associated cost. While proper staff advice and having support groups were identified as key women participation in PMTCT.

Similarly integration of ART in ANC clinics resulted into increased enrolment of pregnant women in ART as well as ART coverage. However retention in ART was similar in ANC clinics with or without ART integration (Suthar, 2013).

A retrospective analysis of general ANC, delivery and PMTCT registers at Malamulo Hospital in Thyolo district, Malawi from 2005 to 2007 showed that the number of ANC pregnant mothers reached 4,528. The study found that the introduction of opt -out HIV testing increased the HIV testing among ANC attendees from 52.6% to 98.8% and 15.6 % of those tested were positive. Additionally the study found that the introduction of free maternity services increased ANC attendance by 42%. The introduction of free maternity services also increased the ratio of hospital deliveries to ANC attendees from 0.50:1 to 0.66:1. The study further showed that of all HIV-tested ANC attendees, 52.6% who tested positive delivered in the hospital and got Nevirapine at the time of delivery (Fyson, 2009).

A matched-cohort study of 360 HIV-infected and 360 HIV-uninfected mothers and their infants at 18-20 months post-partum in Zomba District found that 75 % of the HIV-infected mothers who were not on ART took sd-NVP and 66% of the exposed infants were given SD-NVP. The

study further found that only 18% of HIV-infected mothers followed all current recommended PMTCT options. HIV-infected mothers were found to breastfeed for fewer months than HIV-uninfected mothers (12 vs.18 months, respectively; $p < 0.01$). The study also found higher cumulative mortality rate (19 %) in exposed infants than in unexposed (5%) by 18-20 months postpartum (van Lettow, 2011). Both groups presumed to be remain uninfected.

A qualitative analysis of the barriers and facilitators to receiving care in a PMTCT program in Nkhoma, Lilongwe evaluated the response of 22 HIV-infected pregnant and postpartum women between April and May 2010. The following barriers were identified: transportation to clinic, stigma in the community leading to avoidance of HIV disclosure, food insecurity, and providers' poor attitudes towards HIV-infected pregnant women. (Iroezi, 2013).

2.11 PMTCT option B + in Malawi

Before July 2011, the Malawi ART guidelines for adults and adolescents including pregnant and lactating mothers were dependant on WHO clinical staging and CD4 cell count levels. Malawi adopted the WHO 2010 PMTCT guidelines and became the first country to implement a universal test and treat strategy known as option B+ in July 2011.

2.11.1 Malawi PMTCT strategy (MOH, 2011a)

The Malawi PMTCT strategy for 2011 has the following themes:

- I. Prong 1
Primary prevention of HIV infection in parents
- II. Prong 2
 - Prevention of unintended pregnancies among HIV-infected women
- III. Prong 3
 - Start of lifelong ART for all HIV-infected pregnant and breastfeeding women, regardless of CD4 count and/or clinical stage (option B+)
 - Provision of Nevirapine (NVP) prophylaxis for babies born to HIV-infected mothers up to age 6 weeks
 - Safe obstetric practices
- IV. Prong 4

- Provision of care, treatment and support for HIV-infected women, their children, and their families

Option B + which is the Malawi PMTCT strategy prong 3, recommends starting ART to HIV-infected pregnant and breastfeeding women for life, regardless of CD4 count and/or clinical stage. Malawi further recommended starting ART in all known HIV-infected infants less than 24 months regardless of WHO staging or CD4 count (MOH, 2011a).

2.11. 2 Starting ART for life in HIV positive pregnant and breastfeeding women (option B+) (MOH, 2011a)

Malawi believed that the introduction of option B+ would:

1. Increase access to ART among pregnant and lactating women in Malawi

- i. Because a positive HIV antibody rapid test result in a pregnant woman is the only eligibility criterion for ART, antenatal clinics serve as an ideal entry point for ART.
- ii. High ANC attendance rates (91% for quarter 2 in 2010) and availability of HIV rapid testing at all ANC sites enables a high ART coverage of HIV infected women

2. Reduce post-partum mortality rates in HIV-infected women:

- i. High mortality rates have been documented in post-partum women with high CD4 counts (> 350 cells/mm³ in pregnancy) who were not on ART

3. Reduce HIV transmission: Maternal ART reduces viral load (VL) which:

- i. Provides optimal protection during pregnancy, delivery and for subsequent pregnancies, especially given high fertility rates in Malawi
- ii. Enables safe breastfeeding and avoids the need for extended infant HIV prophylaxis
- iii. Reduces HIV transmission to sexual partners, especially for discordant couples

Table 4: Three options for PMTCT programmes (WHO, 2012)

WHO OPTIONS	Treatment for CD4 count ≤ 350 cells/mm ³	Prophylaxis for CD4 count > 350 cells/mm ³	Infant receives

Option A	Triple ARVs starting as soon as diagnosed, continued for life	Antepartum: AZT starting as early as 14 weeks gestation Intrapartum: at onset of labour, SD-NVP and first dose of AZT/3TC Postpartum: daily AZT/3TC through 7 days postpartum	Daily NVP from birth through 1 week beyond complete cessation of breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4–6 weeks
Option B	Triple ARVs starting as soon as diagnosed, continued for life	Triple ARVs starting as early as 14 weeks gestation and continued Intrapartum and through childbirth if not breastfeeding or until one week after cessation of all breastfeeding	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
Option B+	Regardless of CD4 count, triple ARVs starting as soon as diagnosed and continued for life		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method

On the analysis of the WHO 2012 PMTCT options Malawi thought that option A posed a technical challenge for existing capacities and Option B was dependent on the availability of CD4 count which is also limited in Malawi. Therefore, Malawi decided to introduce a modified option B (so called option B+) with a commitment to providing ART fixed dose combinations (FDC) of Tenofovir (TDF) 300mg /Lamivudine (3TC) 300mg /Efavirenz (EFV) 600 mg once daily as the first line regimen to all HIV+ pregnant and lactating women for life (MOH, 2011a). The choice was made in order to achieve optimal maternal and child health outcomes, based on the following reasons (MOH, 2011a):

- Regimens with NVP can cause severe toxicity in pregnant patients with high CD4 counts.
- Other patient groups do not start with such high CD4 counts

- TDF is more suitable than AZT for B+ women because it does not cause anaemia, a particular risk in pregnancy
- TDF is more suitable than d4T for B+ women as they will be on ART for longer periods and long-term side effects are less likely.

2.11.3 Use of EFV in women of reproductive age (MOH, 2011a)

EFV has been suspected to increase the risk of birth defects. However, this remains inconclusive and, if any, the risk is very low and the following pragmatic approach is taken:

- Wait with ART initiation until 13 weeks of pregnancy and start on TDF/3TC/EFV
- Don't change ART regimen if the woman became pregnant while on an EFV-containing ART regimen.

The reasons to start offering ART for all pregnant and breastfeeding women regardless of clinical stage or CD4 count was to increase access to ART to reduce in post-partum mortality rates in HIV infected women and reduce HIV transmission since ART reduces viral load (MOH, 2011a)

It is also expected that this simplified approach (option B +) would help to achieve the Global plan target of elimination of new paediatric HIV infections by 2015 as well as achieve the target of universal access to HIV treatment for mothers in a limited resource setting such as in Malawi (UNAIDS, 2011). The MTCT elimination global targets include the following reduction of population-level mother-to-child transmission rate (MTCT) to <5% and reducing the number of new paediatric HIV infections by 90% (MOH, 2012a).

Since ART will be offered to pregnant and lactating women using only a positive HIV antibody rapid test result, the Malawi Ministry of Health recommended integration of ART/PMTCT into antenatal and maternity services as ideal entry points. The integration of ART and PMTCT programs in antenatal and maternity services further provided opportunities to include additional HIV care services such as TB screening, ART initiation, treatment and follow-up, family planning (FP), STI treatment, and Prevention with Positives (PwP) – where women are assessed

and counselled on sexual activity, pregnant status, disclosure, positive living issues such as nutrition (MOH, 2011a).

2.12 PMTCT option B+ studies In Malawi

The initial experience with the implementation of option B+ in Malawi, which began nationwide in July 2011, has been very positive, with a more than 5-fold increase in the quarterly number of pregnant women initiating ART as compared to the period before option B+ was implemented (MOH, 2012b).

According to a Centre for Disease Control (CDC) press release implementation of option B+ resulted in a 748% increase in the number of pregnant and breastfeeding women starting ART, from 1,257 in the second quarter of 2011 (representing 5% of all new ART initiations) to 10,663 in the third quarter of 2012 representing 35% of all new ART initiations. Of the 3244 women starting ART, 1,847 pregnant (52%) and 1,394 (48%) lactating women in the third quarter of 2011 (the first quarter of option B+ implementation) who did not transfer care during follow up, 77% continue to receive ART at 12 months. This rate is similar to the 80% 12-month ART retention rate observed among adults who initiated ART in the second quarter of 2011, which is the last quarter before option B+ implementation (CDC, 2013).

During the first 9 months of the implementation of option B+, Malawi achieved a six-fold increase of the number of pregnant women starting ART (Schouten, 2012). Despite this increase Schouten noted that public acceptance and community support for ART for life is rather a challenge in the implementation of option B+ as some women are afraid of disclosing their HIV status to their husbands. Schouten further revealed that stigma and discrimination associated with disclosure, has a negative impact on adherence and retention in care. On the other hand implementation of option B+ will help to increase the number of women on ART, which may assist the progress towards achieving the virtual elimination of pediatric HIV infection, reduce maternal mortality and reduce HIV transmission to discordant male sexual partner(s) (Schouten, 2012).

A countrywide facility cohort study in Malawi found out that 17 % of the total registered option B+ mothers (21,939) were lost to follow up (LTFU) six months after ART initiation. The study

observed that LTFU was higher in large urban sites with electronic medical record systems (EMRS), in sites operated by the Ministry of Health, and in central hospitals. The study further observed that in large sites with EMRS, option B+ patients who started ART during pregnancy were five times more likely to fail to return to the clinics after the initial visit than patients who started with low CD4 cell count and/or in WHO clinical stage 3 or 4. Option B+ patients who started treatment while breastfeeding, were twice as likely to miss their first follow-up visit. Pregnant option B+ patients who started ART on the day they tested HIV+ were less likely to return to clinics than pregnant option B+ patients who started later (Tenthani, 2013).

A decision model simulation to assess the cost-effectiveness of option B+ in Malawi revealed if PMTCT option A, B and B+ are implemented according to WHO recommendations they would equally prevent new infections in infants yielding cost effectiveness ratios between US\$ 37 and US\$ 69 per disability adjusted life year averted in children. However, further analysis of the three options compared to the current practice found that the provision of ART to all mothers (option B+) not only prevents infant infections, but also improves the ten-year survival in mothers more than four-fold translating into a saving of more than 250,000 maternal life years, as compared to mothers receiving option A or option B, with savings of 153,000 and 172,000 life years respectively. On the other hand the study further found that option B+ also yields favorable incremental cost effectiveness ratios (ICER) of US\$ 455 per life year gained over the current practice (Fasawe, 2013)

The preliminary results from the impact assessment of PMTCT option B + in a rural district of Thyolo, Malawi from April 2012 to March 2013 using programme patient data as well as health facility data showed that 50 of 601 (8.3 %) pregnant mothers and 16 of 140 (11.4%) breast feeding mothers did not return after their first visit. The study further showed that at three months 16.5 % of all the women were LTFU and at 6 months 21.5 % women were LTFU (30.1 %) were women who were breast feeding). Furthermore the study showed that about 30 % of the infants (107) were LTFU at three months. The study reported low uptake of HIV testing among infants, where only 65.6 % were tested. Among the infants who were tested with HIV rapid test (109), only one (0.9 %) was found to be positive at 10 weeks but was not confirmed by PCR (Coulborn, 2012).

Cataldo (2012) conducted a cross-sectional qualitative study to explore patients as well as healthcare workers (HCWs) perspectives on the implementation of option B+ in six health facilities in the three main regional health zones in Malawi (Central west, South east, and South west). The study interviewed 48 HCWs and 24 option B+ women. The study results showed that confidentiality and privacy were major concerns in accessing PMTCT services within health facilities. Patients and HCWs also identified lack of male involvement as a barrier to access and retention in option B+. Another major concern that was identified during the study was the issue of same day test and immediate ART initiation during implementation of option B+.

2.13 PMTCT option B+ in other countries

A study at Mulago National Referral hospital in Uganda reviewed ANC data from 17th October 2012 to 28th February 2013, labour ward data from 25th October 2012 to 28th February 2013 and ART clinic records. The study found that women on Option B + were more likely to return for care if they had been enrolled in the antenatal clinic, than those who had been enrolled in the labour ward. Out of 190 women tested positive in ANC, 92% started on ART and a total of 82 % (155 of 190) returned to receive their CD4 results. On the other hand of 162 women who started on ART after labour began only 20 (12%) women returned for their CD4 count results (Namara, 2013).

Coutsoudis (2013) argued that option B+ is being considered only in resource-limited settings with a high HIV burden, to target pregnant women for non-pregnancy-related interventions such as treatment-as-prevention and early treatment initiation. However, there was no data to suggest that pregnant women have above average involvement in discordant relationships or that pregnant women contribute disproportionately to the horizontal transmission of HIV. Option B+ has many benefits such as increased ART coverage because CD4 cell count results are not needed to initiate therapy, added maternal health benefits and protection of discordant male partners. However, the medical benefits and safety of long-term ART including adherence and resistance should also be considered. Additionally, the success of option B + depends on the retention of women in treatment programmes which increases pressure on already strained health systems (Coutsoudis, 2013).

Bateman wrote that in 2013 South Africa would implement the use of standardized triple drug regimen to treat HIV infected pregnant women regardless of CD4 count during pregnancy and breastfeeding (option B). This may further enhance the success of the PMTCT programme in South Africa thus helping to reduce high maternal morbidity and mortality. Several HIV clinicians have encountered programmatic weaknesses with the current PMTCT guidelines (option A), such as inefficient support of women on AZT prophylaxis during pregnancy, and difficulties in the consistent use of Nevirapine prophylaxis for infants and that to them, the PMTCT guideline update including option B is a welcome. Although there are some concerns about option B+ such as it prioritizes women over men that could create community tensions over unequal access, and it raises concerns about lifelong treatment of women who may not understand the long-term costs and benefits. The benefits of option B+ on long-term HIV-free survival were questioned. In particular, drug resistance could emerge as a result of sub-optimal ART adherence. Furthermore, the economic benefit of the 3-in-1 intervention (PMTCT, treatment, and treatment as prevention) was questioned, and potentially low retention rates could render the economic argument for option B+ invalid (Bateman, 2013).

The experiences of women living with HIV using option B+ in Uganda and Malawi identified the following top three benefits in relation to option B+, (1) the potential for mothers to breastfeed their children for longer and the associated improved health of the child, (2) mothers feel healthier because they are on treatment, and (3) reduction of stigma towards mother and child. However, women in both countries felt that starting treatment before they were ready would not be conducive to good health or adherence, and would increase resistance to ARVs (Webb & Culler, 2013).

A cost analysis of WHO 2013 PMTCT guidelines in Zambia found that the implementation of option B or option B+) would result in 33 % reduction of the risk of HIV transmission among exposed infants compared to option A. on the other hand the analysis revealed that the risk of transmission to sero-discordant partners for a period of 24 months would be reduced by 72% with ARVs during pregnancy and breastfeeding and further reduced by 15% with lifelong ART. The analysis report further noted that the probability of HIV-infected pregnant women initiating ART would increase by 80%. Although option B/B+ would generate higher PMTCT costs than

option A, it would be cost-saving in the long term as it spares future treatment costs by preventing infections in infants and partners (Ishikawa, N., et al., 2014). A similar finding was also observed in Ghana (Van Deusen, 2015)

2.14 Research problem

Malawi adopted and started the implementation of option B + in July 2011 after WHO published updated PMTCT intervention guidelines in 2010 (WHO, 2010). Malawi was the first country to adopt this innovative approach to reduce MTCT. Implementation of option B+ has resulted in rapid expansion of integrated PMTCT/ART services to all maternal newborn and child health (MNCH) sites. The number of sites providing ART in Malawi increased from 300 in Quarter 2, 2011 to 641 in Quarter 3, 2012, with 573 of these clinics providing option B+ services. More than 70% of the pregnant women testing HIV positive were initiated on the B+ regimen (WHO, 2014).

Initial experience of implementing option B + in Malawi documented a substantial increase in ART coverage, especially among pregnant women. In Malawi, the number of pregnant and breastfeeding women started on ART per quarter increased by 748%, from 1,257 in the second quarter of 2011 (before option B+ implementation) to 10,663 in the third quarter of 2012 (1 year after implementation). Of the 2,949 women who started ART under option B+ in the third quarter of 2011 and did not transfer care, 2,267 (77%) continue to receive ART at 12 months (CDC, 2013).

The national facility cohort analysis in Malawi showed that at 6 months after starting ART 82% of women on option B+ were alive on ART and 17% had been lost to follow up (Tenthani, 2014). The study further found that option B+ women starting ART in pregnancy were 5 times more likely to be lost to follow up than patients initiating treatment with low CD4 and/or WHO stage 3 or 4 while option B+ women starting during breastfeeding were twice as likely to have no follow up visit. The study also noted that most of option B+ women who lost to follow-up started ART on same day of HIV testing.

In 2012 The WHO released programmatic updates on the implementation of the WHO 2010 PMTCT guidelines including option B+. In the updates WHO described option B+ as simpler for the PMTCT programme since the same regimen could be given to all HIV-infected pregnant women and that there is no initial distinction between treatment and prophylaxis and no change in regimen during the pregnancy/postpartum period as compared to regimen in option A. Furthermore, WHO highlighted that initial drug costs for options B and B+ are higher than for Option A. However, the cost of the drugs is decreasing and the benefits gained for the costs expended are likely to be much greater. The WHO further noted that successful implementation of option B+ requires that key challenges be addressed such as weak referral systems, weak postpartum services, suboptimal ART adherence, and inadequate maternal and child health (MCH) and ART linkage (WHO, 2012).

Testing clients and starting ART on the same day remains a concern as clients may not understand fully the implications of option B+. This may affect their cooperation and ultimately their adherence to treatment. Consequently, some women accept drugs but never take them or return to the facility (WHO, 2014). My study will assess the short-term outcomes of implementing option B+ in the rural district of Ntchisi in Malawi.

2.15 Significance of the study

The results of this study would be important to the Ministry of Health and other national HIV/AIDS stakeholders for understanding such programmatic issues as the utilization of services, drug adherence and treatment retention in the context of option B+ implementation in Ntchisi district so that necessary efforts can be considered for improving the success of the programme.

2.16 Research question

- What is the outcome of the pregnant and lactating mothers on ART (option B +) and their infants less than 24 months in a rural setting in Malawi?

2.17 Aim of the study

- To assess outcomes of pregnant and lactating mothers receiving ART (option B+) and their infants in the rural district of Ntchisi.

2.18 Specific objectives

- To estimate uptake of option B + in a rural district
- To determine the retention rate of pregnant and lactating women on option B+
- To determine adherence rate of pregnant and lactating women on option B +
- To estimate the polymerase chain reaction (PCR) testing uptake and HIV infection rate in infant

CHAPTER 3.0: METHODOLOGY

3.1 Introduction

In this chapter the research methods and strategies for achieving the study objectives were described. These included the research design, study population, sample size and sampling, data collection, validity and reliability, data management and analysis, and ethical considerations.

3.2 Study design

A retrospective cohort study was undertaken. Retrospective cohort studies involve using a previously existing data set, such as an administrative claims data set or medical record, to virtually assemble the exposure cohorts and ascertain and analyze what had occurred following cohort assignment. The hallmark of all cohort studies is the following of groups, or cohorts, of subjects through time (virtual or real) with ultimate ascertainment of the development of a disease or outcome. Group assignment in a cohort is typically defined by exposure or magnitude of exposure (Hartung & Touchette, 2009). This study design was chosen to enable the researcher to evaluate clinical outcomes of a cohort of pregnant and breastfeeding mothers commenced on option B+ and their infants less than 24 months.

3.3 Study setting

Figure 1: Map of Malawi showing Ntchisi district

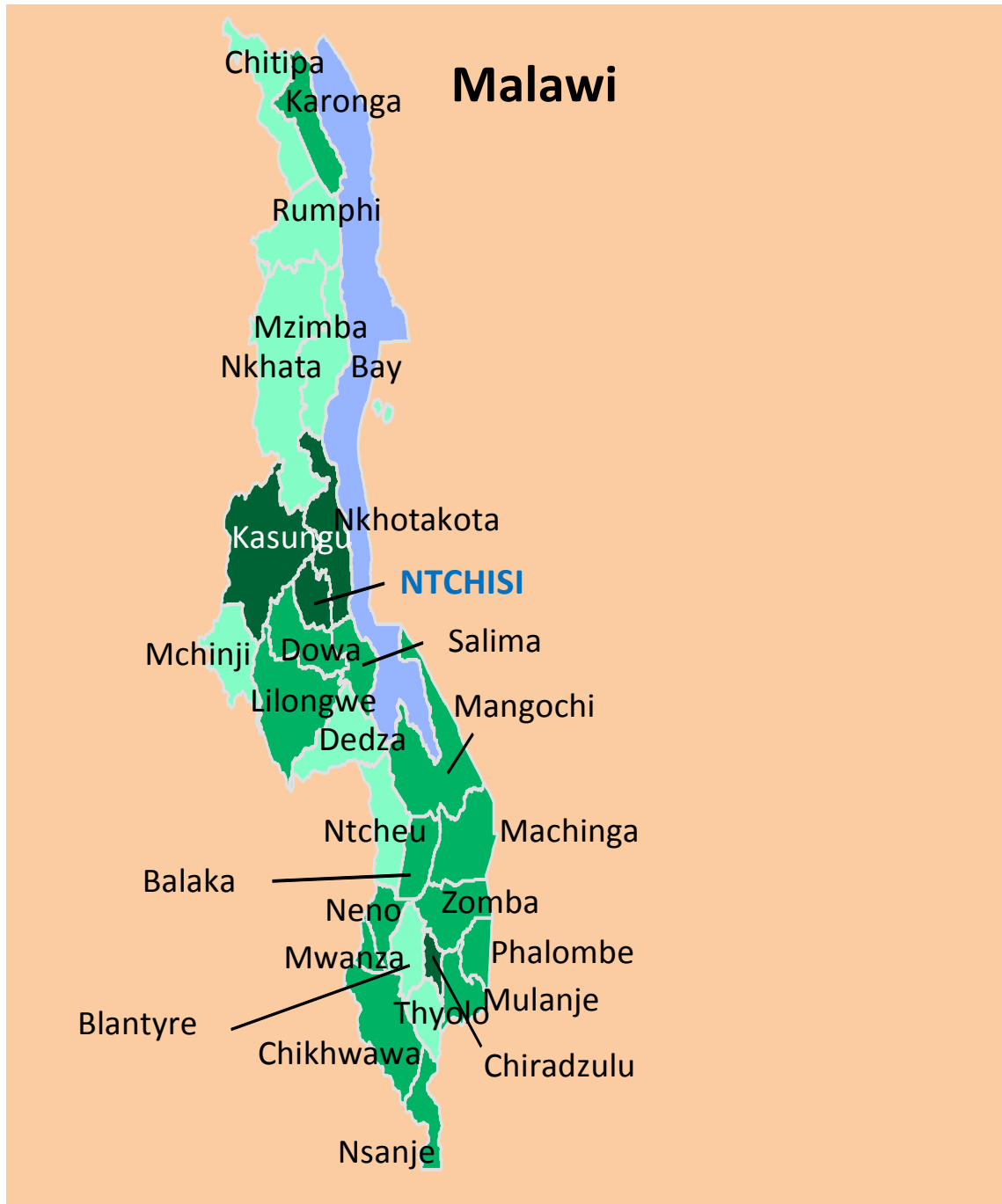
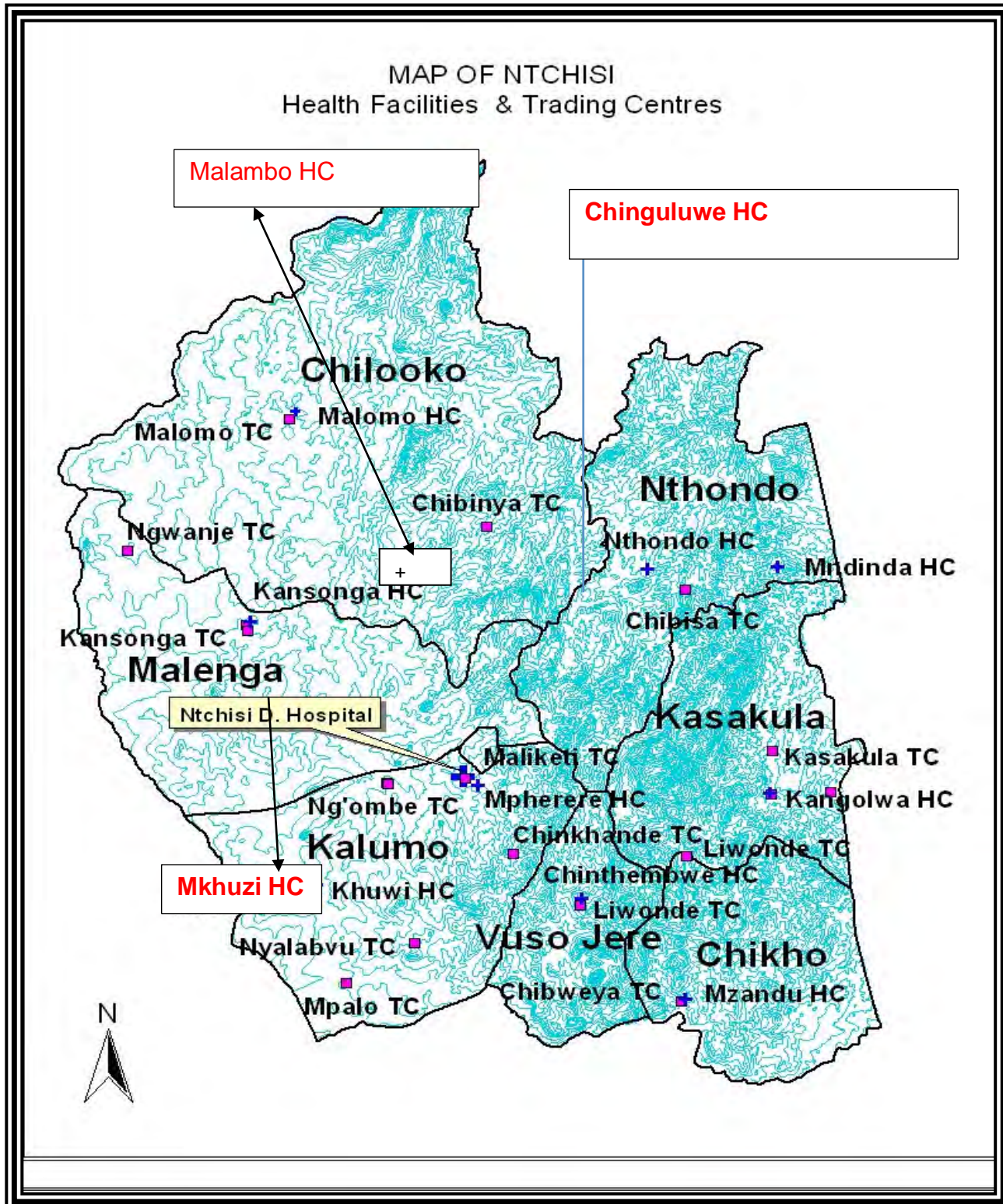


Figure 2: Map of Ntchisi showing health facilities and main trading centres

The study was conducted at Ntchisi district. Ntchisi district is located in the Central region of



Malawi. The total land area of the district is 1, 655 square kilometers with a population of about 249, 000. It is the fifth smallest district in the country and the smallest district in the central region. The district is 96 km North of Lilongwe, the capital city of Malawi. Most of the people in the district are poor and mostly depend on maize subsistence farming for food. There are 12 health facilities in the district. Out of 12 health facilities, 10 provide integrated ART/PMTCT services (option B+) and were eligible for the study. These 10 health facilities provide ART at ART clinic, ANC clinic and during labour or after delivery at maternity or postnatal ward.

Table 5: Ntchisi health facilities providing ART/PMTCT services (option B+)

No	Health facility	District from the main hospital (km)	ART/PMTCT site
1	Khuwi	15	Yes
2	Nkhunzi	29	Yes
3	Kamsonga	21	Yes
4	Malambo	35	No
5	Ntchisi district hospital (main hospital)	0	Yes
6	Malomo	30	Yes
7	Chinguluwe	17	Yes
8	Nthondo	35	Yes
9	Mndinda	53	No
10	Kangolwa	45	Yes
11	Chinthembwe	21	Yes
12	Mzandu	35	Yes

The other two remaining health facilities do not provide the ART/PMTCT services and were not eligible for the study. The district started provision of ART in 2005. ART and PMTCT services are now integrated in antenatal and maternity clinics with the implementation of option B +. At each of these 10 health facilities where integrated ART /PMTCT is provided, nurses and clinicians (task shifting) are all trained to provide services. The district does not have PCR services. Instead, dry blood samples (DBS) are collected and sent to Kamuzu Central Hospital, 96 km away from the district where they are processed. The district has an HIV prevalence rate

of 4 % (MDHS, 2010). In 2012, 12976 pregnant mothers in the district were counseled and tested for HIV infection, and 1.8 % tested HIV positive. According to Ntchisi district health information management system (HIMS) data, a total of 5,556 patients ever started ART in the district by December 2012, and 64% of these patients were still alive, 21% had died while on ART and 15% defaulted ART treatment.

3.4 Study population

The study population was HIV positive women aged 15 years or more who were pregnant, and lactating women (from delivery to 24 months post-partum) who were initiated on ART as part of the option B + PMTCT intervention from 1 July 2011 until 31 December 2012 in the Ntchisi district. The study population included HIV-exposed infants less than 24 months born to pregnant and lactating mothers who were receiving ART on the option B+ PMTCT programme during the same period.

3.5 Inclusion criteria

The following were the inclusion criteria:

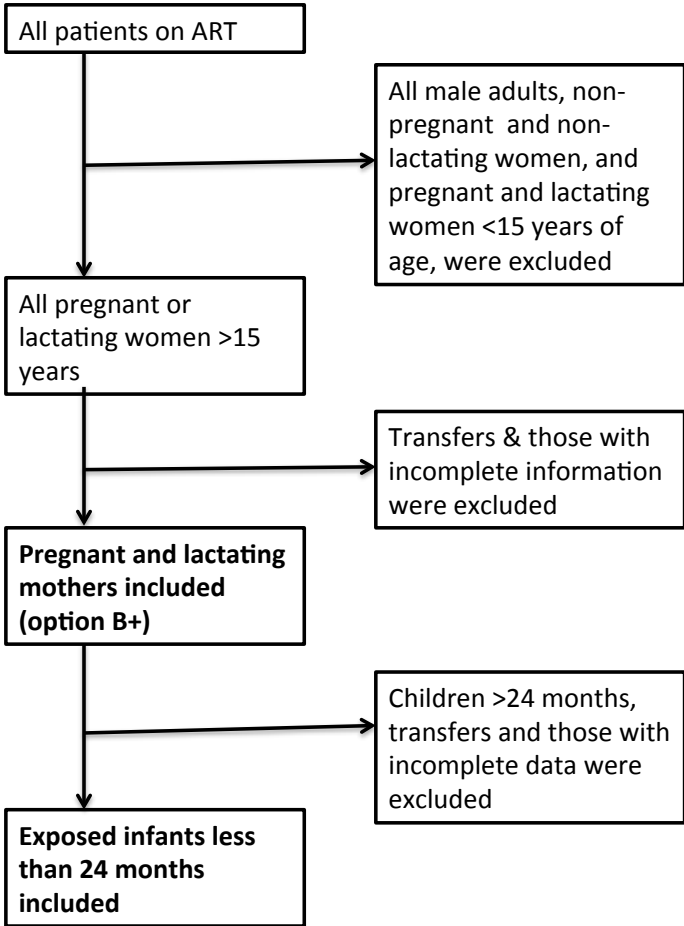
- All ART naïve HIV pregnant and lactating women aged 15 years or more who were enrolled and commenced ART (option B+) from 1 July 2011 to 31 December 2012 were included in the study. The study cohort was followed up to 31 December 2013.
- Infants born to pregnant and lactating mothers who are on ART (option B + programme) from the same period were also included in the study.

3.6 Exclusion criteria

The following were the exclusion criteria:

- All pregnant and lactating mothers on ART (option B +) transferred to or from other districts
- Pregnant and lactating mothers who were re- initiated on ART after defaulting or previously discontinuing ART
- HIV exposed infants transferred to or from other districts
- Subjects with incomplete data
- Pregnant and lactating women less than 15 years of age

Figure 3: Algorithm of study subjects inclusion and exclusion criteria



Retention rate

Retention rate in our study is defined as the proportion of patients on option B+ who were alive and remained in the ART the last visit of the quarter of October – December 2013. Excluded were those who died or stopped or transferred or defaulted treatment.

Drug adherence

Is calculated as number of doses of ART taken divided by number of prescribed doses of ART multiplied by 100, i.e. expressed as percentage. Adherence rate in our study was calculated on the last visit of the quarter of October – December 2013.

3.7 Sample size sampling procedure

This was a programme audit. Therefore, a sample size estimate was not calculated. All the 10 health facilities providing ART care and treatment services in the district were included in this study. All subjects who satisfied the inclusion criteria were enrolled into the study. Finally all those who fulfilled inclusion criteria were given the unique identification (ID) number in increasing order.

3.8 Data collection

Due to inadequate funding, the researcher collected the data himself and was able to successfully complete this task. Data were collected from ART patient master cards, ART clinic registers, HIV Care Clinic (HCC) registers, cohort analysis forms, maternity registers, ANC registers, Exposed Child under 24 Months Cards and PCR laboratory registers. The ART electronic patient records were used to check patient follow up visits. Data were extracted using structured data collection tools (see Appendix 1). The data collection tools were developed by the researcher using standard patient ART master cards and pre-ART registers, derived from the 2011 Ministry of Health ART guidelines. Data fields included maternal age, sex, marital status, employment status, weight and height, and from the infants birth weight and HIV testing information.

3.9 Validity and reliability

Reliability is defined as the extent to which an experiment, test or any measuring procedure yields the same results on repeated measurements while validity is the extent to which any measuring instrument evaluates what it intends to measure (Carmines & Zeller, 1976). To ensure validity and reliability of my research results, the data collection tools were properly designed and pretested, and the data collected were rechecked daily for completeness.

3.10 Data analysis

The data was cleaned and entered into Microsoft Excel. Microsoft Excel was used to analyze continuous data and categorical data. The mean/median value and percentages were calculated and results were presented using tables and graphs. Odds ratio (OR) and the corresponding 95% confidence interval (95% CI) were used to estimate the size and significance of an observed difference. The Kaplan – Meier survival analysis was done using Statistical Package for the Social Sciences (SPSS) version 16.0.

3.11 Ethical considerations

The research proposal was approved by University of Cape Town, reference number: HREC REF 588/2013. Written permission was obtained from Ntchisi District Health Officer (Appendix IV). Permission was also obtained from the health facility in-charge at all study sites. The data for this study was collected retrospectively and did not include personal identifiers. Therefore informed consent was not obtained. All the completed data collection forms were stored in a locked cupboard and would be kept for at least five years. The computer excel database was a password-protected file, which can only be accessed by the researcher. The study was completed in accordance with the Helsinki Declaration.

CHAPTER 4.0: FINDINGS / RESULTS

4.1 Results

A total of 1,029 new clients were managed on ART in the Ntchisi district between 1st July, 2011 and 31st December, 2012. Of these new clients 25 were transfers i.e. 16 were transferred in and 9 transferred out of the district. Of the remaining 1,004 clients who all started ART within the Ntchisi district, 6 were excluded because of incomplete data. 201 were either pregnant women or lactating mothers with HIV infection who were initiated on option B+, i.e. 136 HIV positive pregnant mothers and 65 HIV positive lactating mothers were enrolled into the study. Out of 201, 54 option B+ women were enrolled in the July - December 2011 cohort, 32 (59.3%) were pregnant women and 22 (40.7%) were lactating women. In the January - December 2012 cohort 147 women who were initiated on option B+ women were enrolled, 104 (70.7%) were pregnant women and 43 (29.3%) were lactating women. Median age of these 201 women at ART enrolment was 32 years. The age range was 16 - 48 years.

214 HIV-exposed infants born to women who were initiated on option B+ during pregnancy or lactation were registered in the same period. 7 were transferred out of and 6 transferred into the district. Three exposed infants were excluded because of incomplete demographic data. As a result 198 HIV-exposed infants were included in the present study. Out of 198 HIV-exposed infants, 135 (68.2%) were born to women who were initiated on option B+ during pregnancy and 63 (31.8%) were born to women who were initiated on option B+ during lactation.

There were 106 females (53.5%) and 92 males (46.5%). The median birth weight was 3.2kg, birth weight range (1.5kg – 4.1 kg).

Table 6: Maternal sociodemographic characteristics at ART enrolment

Variable	Total (N=201)	(%)
<hr/>		
Mother enrollment status		
Pregnant women	136	(67.8)
Lactating mothers	65	(32.2)
Age in years		
(15-19)	10	(5.0)
(20 -24)	38	(19 .0)
(25 -29)	69	(34.0)
(30 -34)	46	(23.0)
Missing data	38	(19.0)
Occupation		
Business	11	(5.5)
Farmers	63	(31.3)
House wife	115	(57.2)
Employed	8	(4.0)
Others	4	(2 .0)
BMI		
< 15.0 (very severe underweight)	5	(2.5)
15.0- 16.0 (severely underweight)	8	(4.0)
16.0- 18.5 (Underweight)	8	(4.0)
18.5 -25 (normal)	73	(36.3)
25.0-30.0 (overweight)	18	(9.0)
>30 (obese)	6	(3.0)
Missing data	83	(41.2)
<hr/>		

Table 7: Infant socio-demographic data

Variable	Number	(%)
	N = 198	
Gender		
Male	92	(46.5)
female	106	(53.5)
Birth weight		
1.5 -2.0	11	(5.6)
2.1 -2.5	19	(9.6)
2.6 - 3.0	43	(21.7)
3.1 +	73	(36.9)
Missing data	52	(26.2)

Uptake of option B+

Table 8: Uptake of option B+ among pregnant and lactating women		
	No.	(%)
Number of pregnant and lactating women registered	5,993	(100)
Number of pregnant and lactating women who were tested for HIV infection	5,369	(89.6)
Number of pregnant and lactating women who tested HIV positive	251	(4.7)
Number of pregnant and lactating women who tested HIV positive and started ART (option B +)	201	(80.1)

Table 8 shows that 5,369 (89.6%) out of 5,993 pregnant and lactating women were tested for HIV. The table further shows that of 251 pregnant and lactating women tested HIV positive, 201 (80.1%) were started on option B+ the period 1 July 2011 until 31 December 2012.

Figure 4: Mother's status at enrollment (percentage)

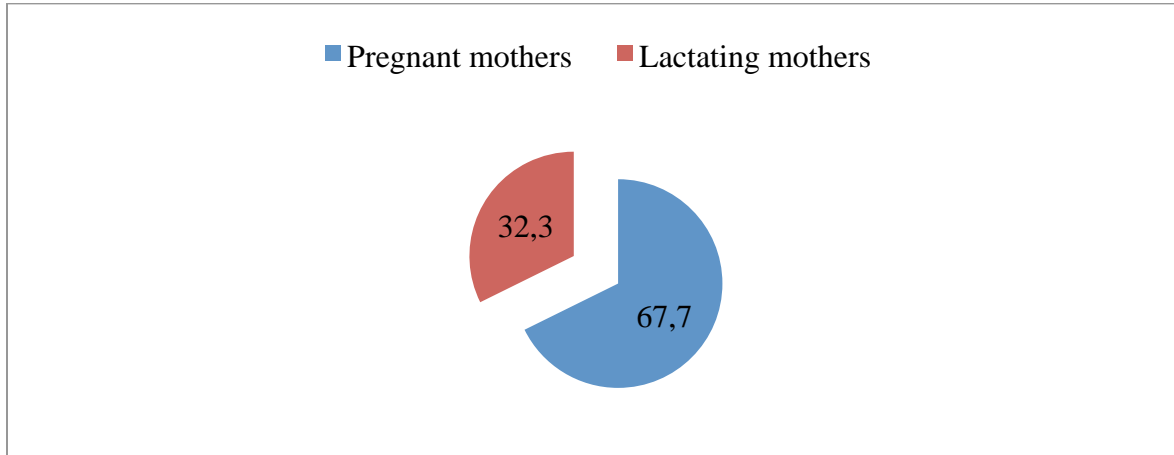


Figure 4 shows that out of 201 options B+ clients enrolled 136 (67.7 %) were pregnant mothers and 65 (32.3 %) were lactating mothers

Figure 5: Gestation age (weeks) at first ANC visit of pregnant women (n=136) initiated on option B+

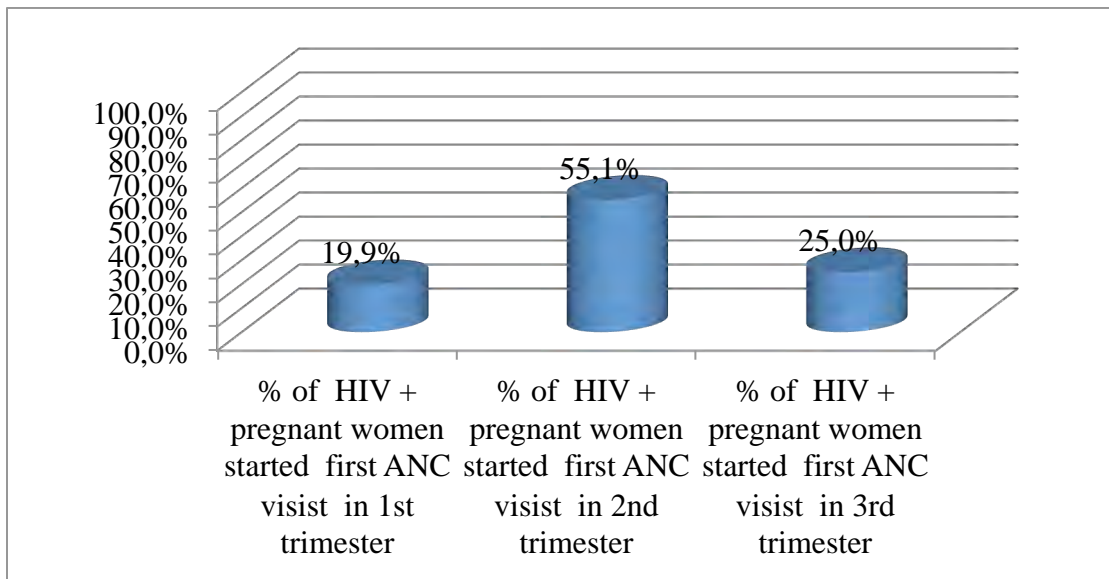


Figure 5 shows that out of 136 HIV positive pregnant mothers attending ANC, 27 (19.9%) started ANC at less than 12 weeks gestation (first trimester), 75 (55.1 %) started at 13-24 weeks gestation (2nd trimester)and 34 (25 %) started at 25 or more weeks gestation (3rd trimester).

Figure 6: Frequency of ANC visits during pregnancy

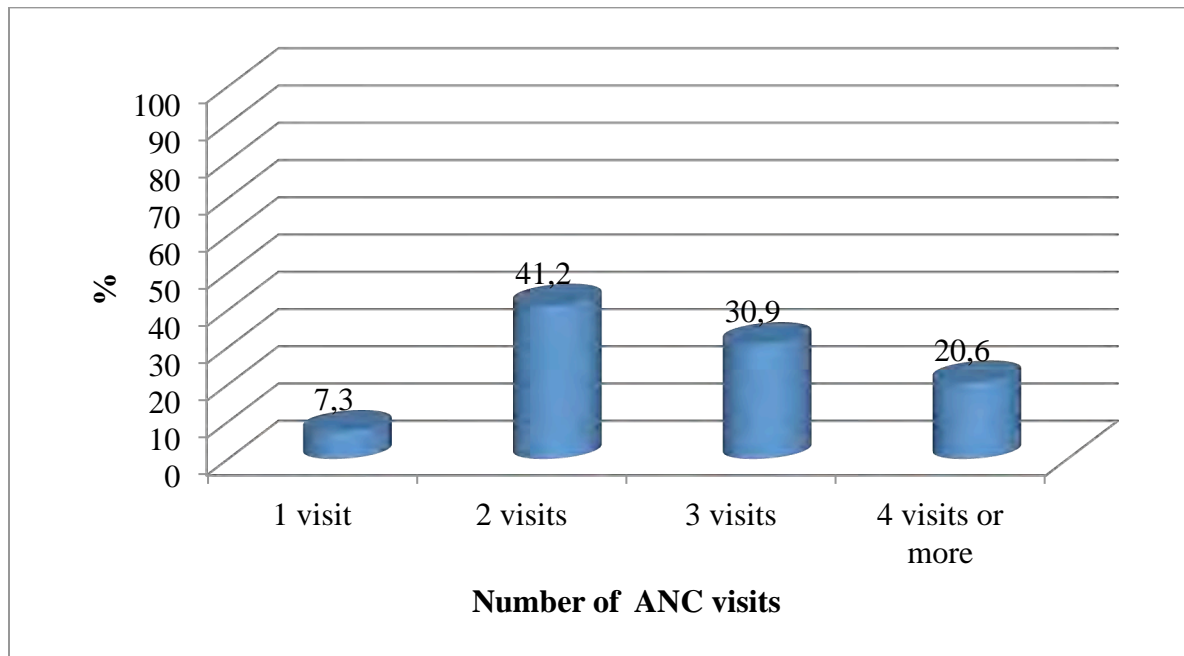
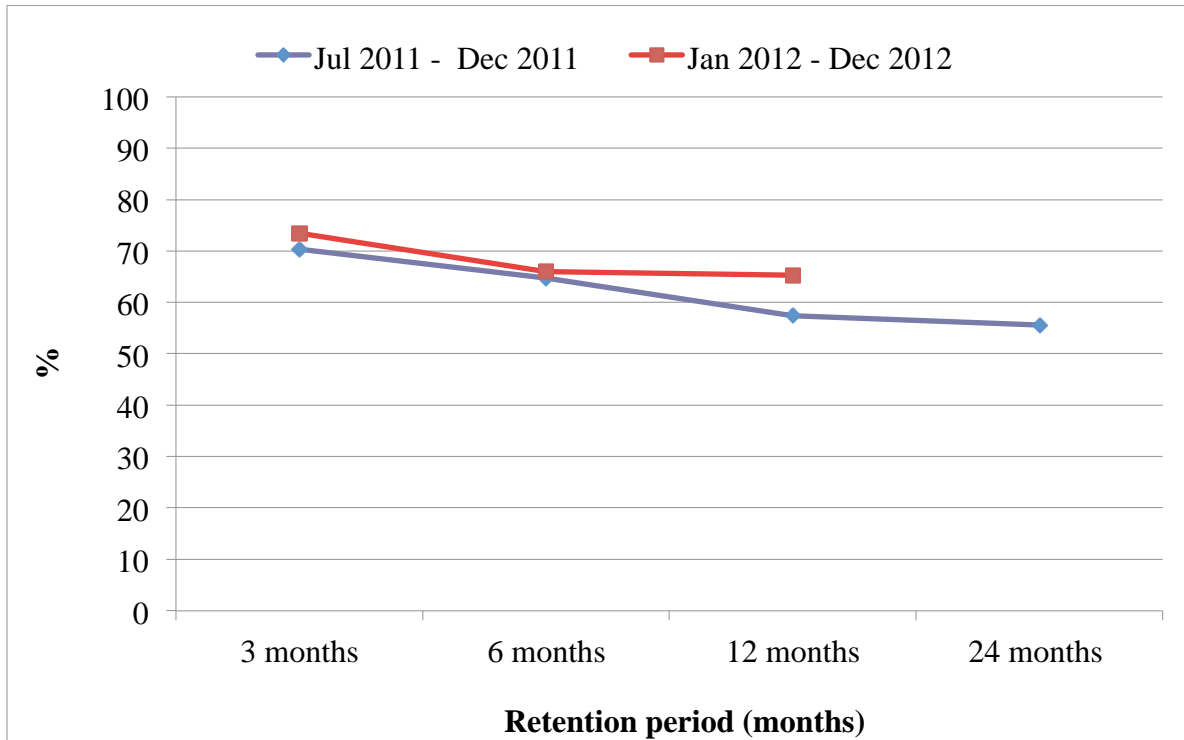


Figure 6 shows that out of 136 HIV positive mothers attending ANC, 10 (7.3%), 56 (41.2 %), 42 (30.9 %) and 28 (20.6%) attended 1 visit, 2 visits , 3 visits and 4 or more visits, respectively.

Figure 7: Percentage of mothers (option B+) retained at 3, 6, 12 and 24 months of ART



The figure 7 shows that 38/54 (70.4 %), 35/54 (64.8 %), 31/54 (57.4%) and 30/54 (55.6 %) of option B+ mothers were retained at 3, 6, 12 and 24 months respectively in the July 2011 - December 2011 cohort. Of the 24 mothers not retained 22 (90%) defaulted and 2 (10%) died. Of the 22 who defaulted 16 (73%) defaulted in the first three months.

108/147 (73.5 %), 97/147 (66%) and 96/147 (65.3%) of the mothers were retained at 3, 6 and 12 months respectively in the January 2012 - December 2012 cohort. Of the 51 mothers not retained 47 (92%) defaulted and 3 (6%) died and 1 (2 %) stopped treatment. Of the 47 who defaulted 39 (82 %) defaulted in the first three months. Therefore, a total of 75 women (37.5%) were lost to the program during the study period ie 24 from July 2011 - December 2011 cohort and 51 from January 2012 – December 2012 cohort .

Figure 8: Probability of option B+ women remaining in care determined by the Kaplan-Meier method

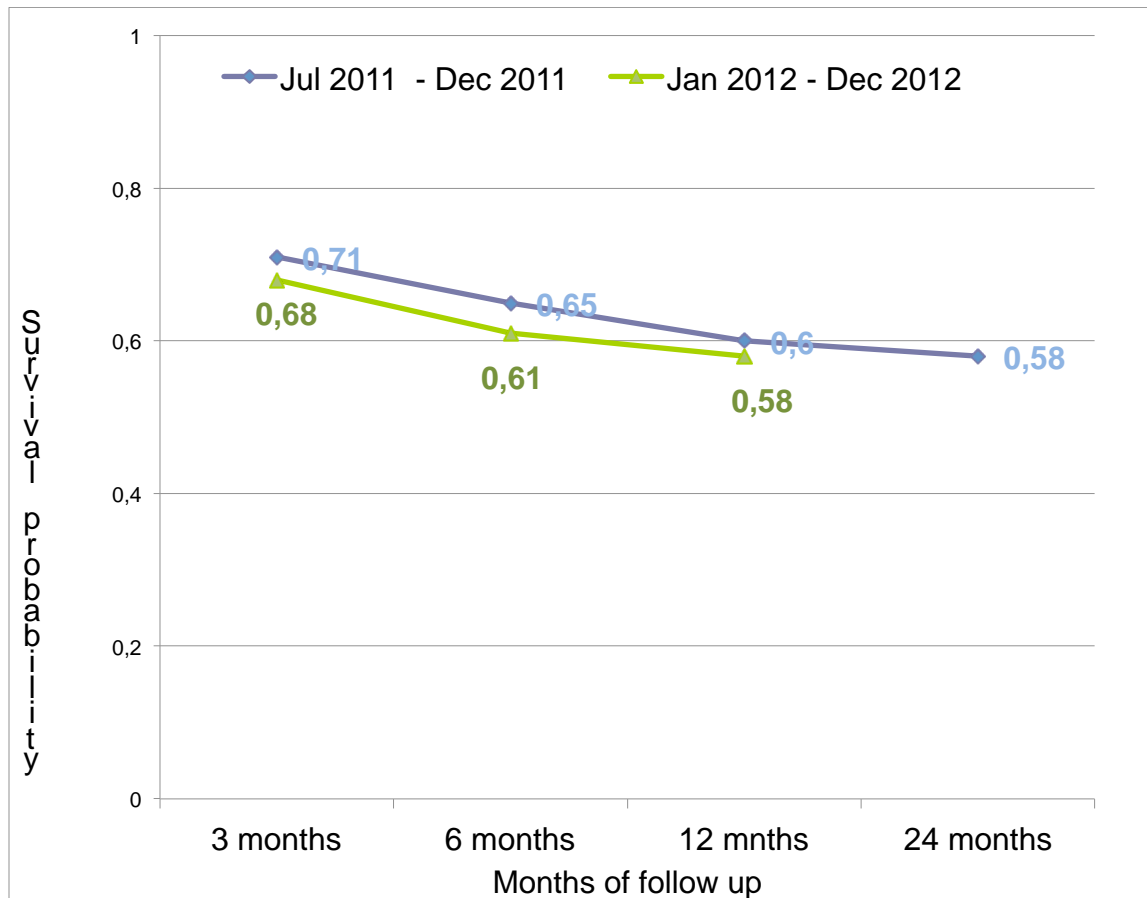


Figure 8 shows that the probability of option B+ women remaining in care determined by the Kaplan-Meier method was 0.71 (95% CI: 0.82–0.87), 0.65 (95% CI: 0.77–0.83), 0.60 (95% CI: 0.75–0.81) 0.58 (95% CI: 0.74 – 0.82) at 3, 6, 12 and 24 months respectively for July 2011-December 2011 cohort. For January 2012 - December 2012 cohort the probability of option B+ women remaining in care determined by the Kaplan-Meier method was 0.68 ,0.61 and 0.58 at 3,6 and 12 months respectively.

Figure 9 : Option B+ adherence rate

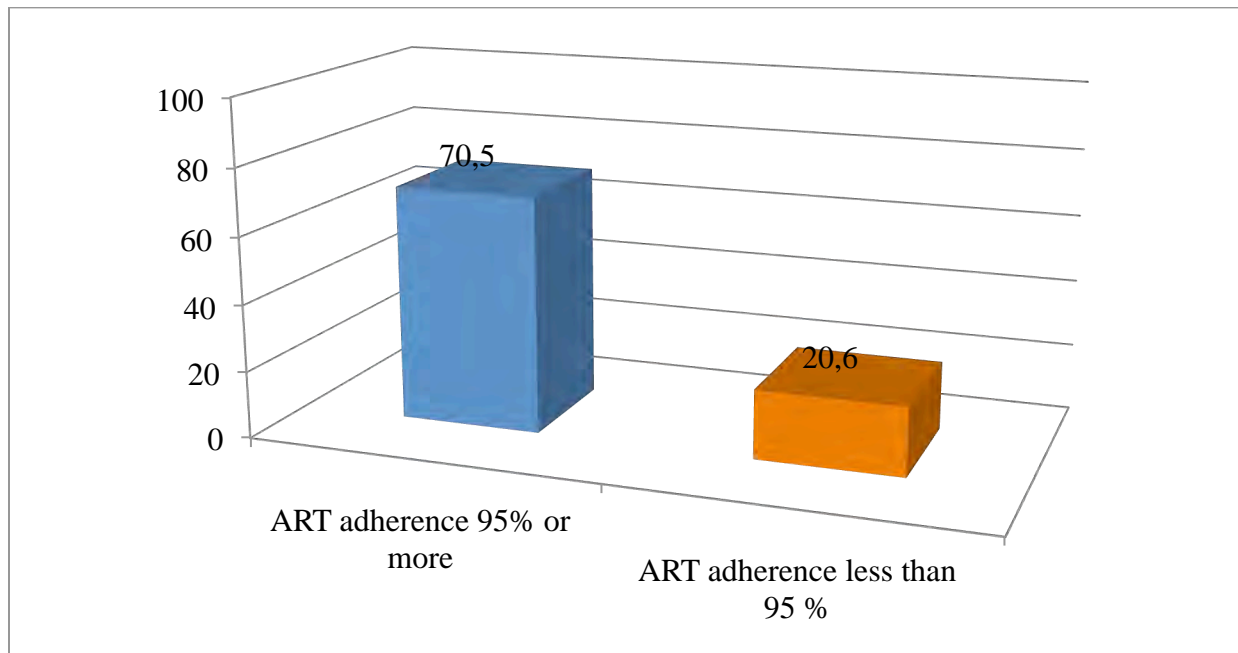


Figure 9 shows that out of 126 option B+ mothers who were retained by Dec 2013, 89 (70.6%) had adherence rate of 95% or more in the last visit of the October - December 2013 quarter.

Figure 10: The prevalence of adherence in women who initiated ART during pregnancy and those who initiated ART during lactation

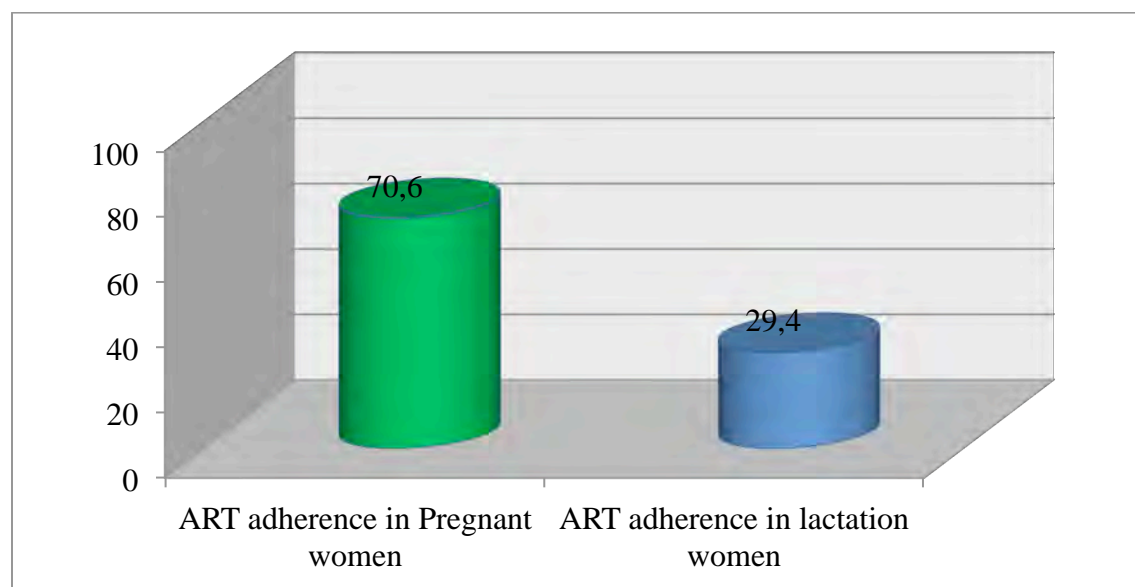


Figure 10 shows that out of all women who commenced option B+ during pregnancy, 56/ 77 (72.7%) who remained in care during the October - December 2013 quarter had adherence of at least 95%, while 33/49 (67.3%) of women who commenced option B+ during lactation and who remained in care during the October -December 2013 quarter had adherence of at least 95% or more. This difference was not statistically significant, OR = 1.2, 95% CI: 0.6 – 2.8

Infant outcomes

Table 9: Percentage of infants ever tested for HIV infection during the study period

Category	N = 198	(%)
PCR / Rapid Tested	146	(73.7)
Never tested	52	(26.3)

Table 9 shows that of 198 exposed infants enrolled in the study, 52 (26.3 %) were not tested for HIV infection during the study period

Figure 11 : Infants NVP uptake

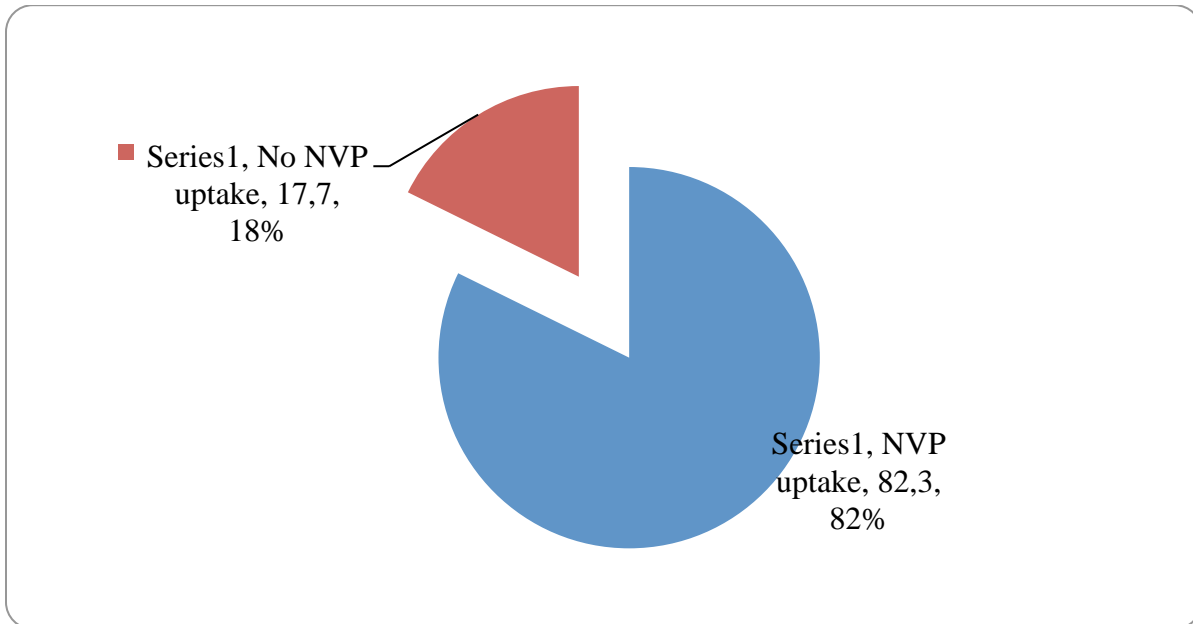
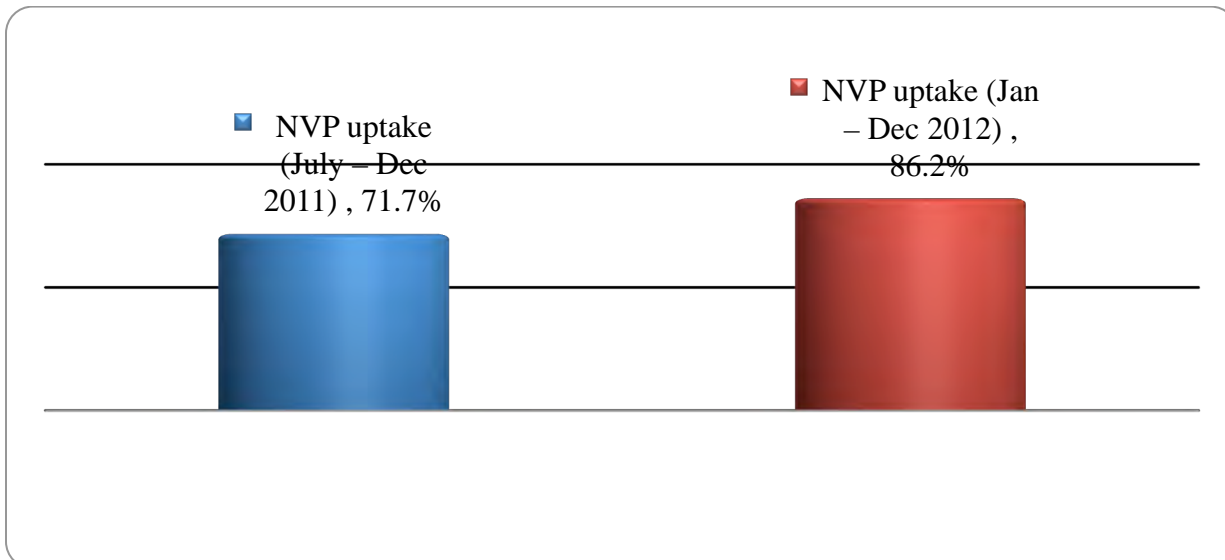


Figure 11 shows that out of 198 infants enrolled 163 (82.3) took NVP and 35 (17.7 %) never took NVP

Figure 12: NVP uptake in the 2011 (Jul - Dec 2011) and 2012 (Jan - Dec 2012) cohorts



The figure 12 shows that out of 53 exposed infants in the July -December 2011 cohort 38 (71.7%) took NVP and in the January -December 2012 cohort 125/145 (86.2%) took NVP. This difference was not significant, OR = 0.5, 95% CI: 0.2 – 1.02.

Figure 13: Uptake of Cotrimoxazole preventive therapy (CPT) in pre ART care of infants

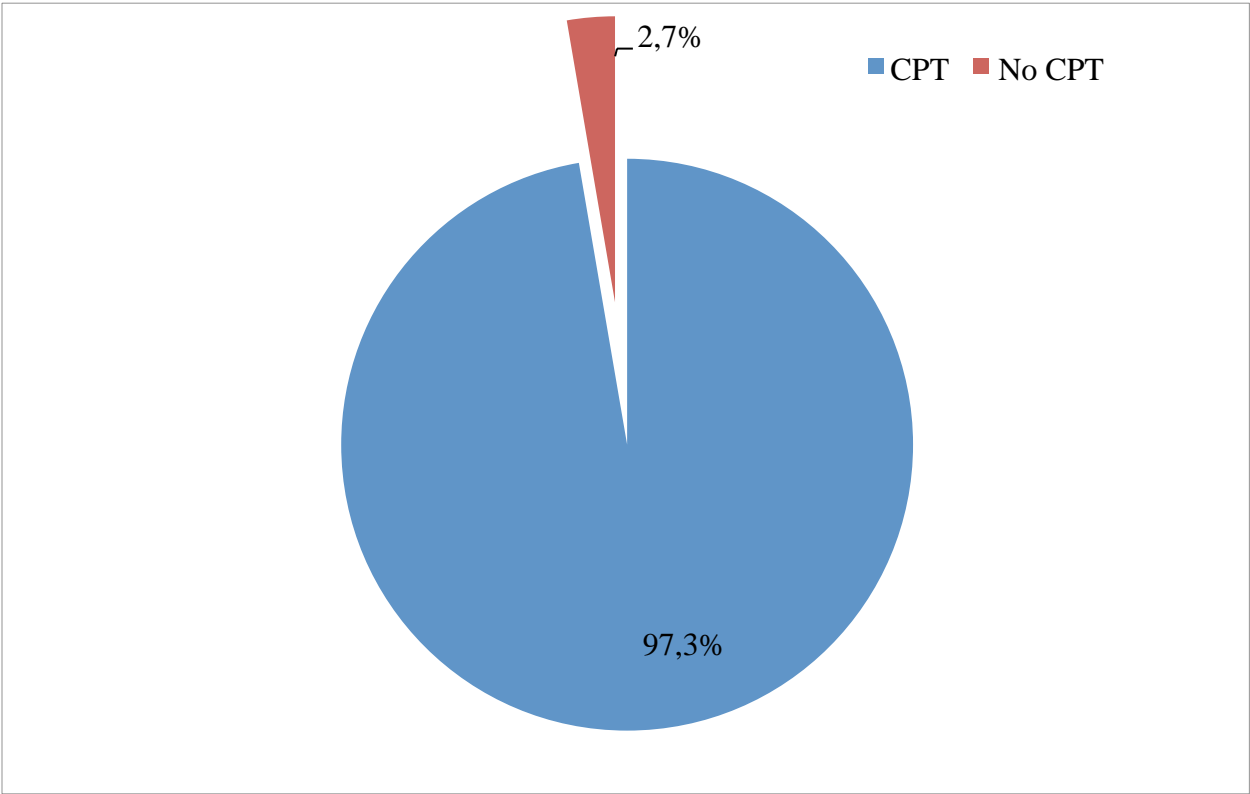


Figure 13 shows that out of the 198 exposed infants enrolled in the study, 5 (2.5%) were not on CPT

Figure 14: Percentage of HIV-exposed infants remaining in pre-ART clinical care

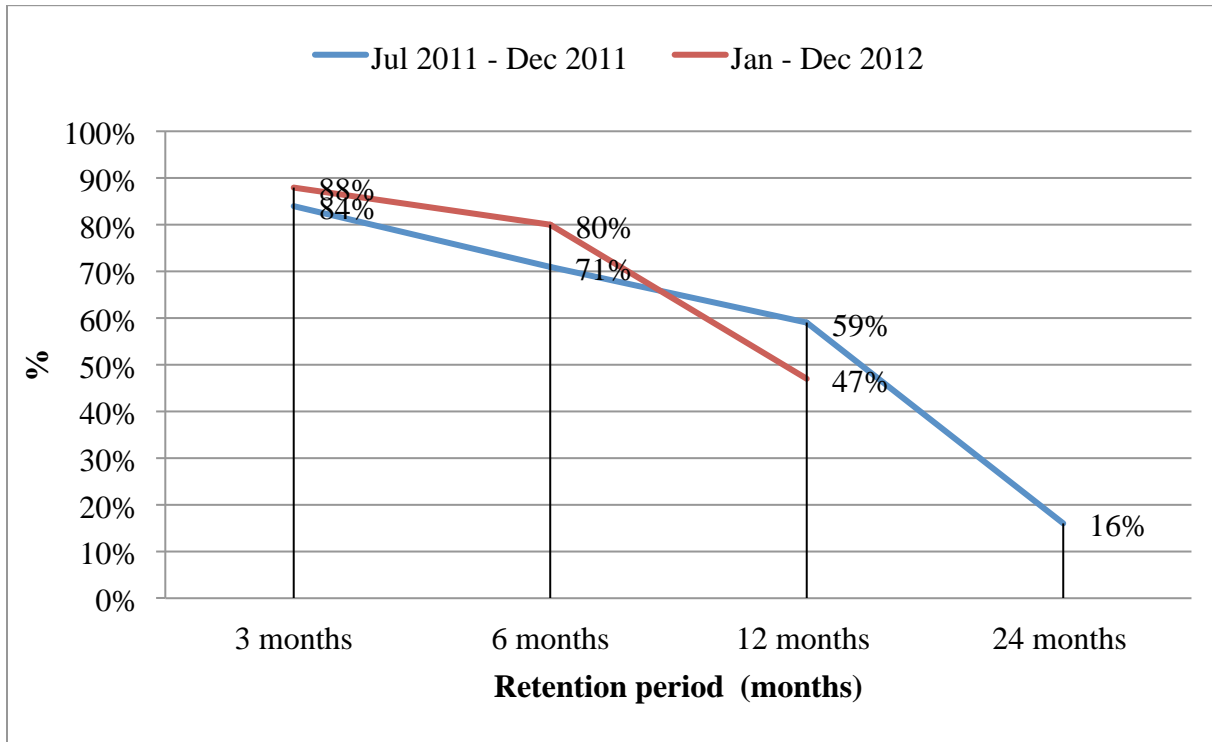


Figure 14 shows that among the HIV-exposed infants in the July 2011 - December 2011 birth cohort (n=53), 81.1 %, 67.9%, 51% and 17% remained in care at 3, 6, 12 and 24 months respectively. In the January 2012 - December 2012 HIV-exposed cohort (n=145), 89%, 81.2% and 47.6% infants remained in care at 3, 6 and 12 months respectively. Among the 44 exposed infants in the July 2011 - December 2011 birth cohort who did not remain in care, 29 (65.9 %) defaulted, 7 (15.9%) started ART (tested HIV positive) and 9 (20.5 %) were discharged uninfected and there were no deaths. Among 76 infants in the January 2012 - December 2012 who did not remain in care, 67 (88.2%) defaulted, 2 (2.6%) died, 4 (5.3%) started ART and 3 (3.9%) were discharged uninfected.

Table 10: Number of exposed infants tested and infected with HIV at 12 months and at 24 months

	Jul - Dec 2011 (n=53)		Jan - Dec 2012 (n=145)
	At 12 months	At 24 months	At 12 months
No. of exposed infants tested for HIV	32 (60.4%)	34 (64.2%)	112 (77.2%)
No. of exposed infants infected with HIV	6 (18.6%)	7 (20.6%)	4 (3.6%)

Table 9 shows that among the 53 infants who were enrolled in the July 2011 – December 2011 birth cohort 32 (60.4%) were tested for HIV and of these 6 were shown to be HIV- infected representing an 18.8% transmission rate at 12 months. Of 53 exposed infants enrolled in July 2011 - December 2011, 34 (64.2%) had been tested by 24 months and of these a total of 7 (20.6 %) were shown to be HIV-infected. Of 145 infants in the January 2012 - December 2012 cohort, 112 (77.2 %) were tested for HIV infection, and 4 (3.6%) were HIV-infected at 12 months. Thus during the study period, the prevalence of HIV infection in the July – December 2011 cohort was 7-fold higher than in the January – December 2012 cohort, 7/34 (20.6%) versus 4/112 (3.6%). This difference was statistically significant, OR = 7.0, 95% CI: 1.9 – 25.7. Overall, during the study period, 11/146 (7.5%) HIV-exposed infants, who were tested, became HIV-infected.

Table 11: HIV infection among infants born to mothers who initiated option B+ during pregnancy and infants of mothers who initiated option B+ during lactation

	No. tested for HIV	No. tested HIV positive
HIV infection among infants born to mothers who initiated option B+ during pregnant	103	4 (3.9%)
HIV infection among infants of mothers who initiated option B+ during lactation	43	7 (16.3%)

Table 11 shows that among the 103 HIV- exposed infants born to mothers who initiated option B+ during pregnancy who were tested for HIV, 4 (3.9%) became HIV infected. Out of 43 HIV- exposed infants of mothers who initiated option B+ during lactation who were tested for HIV, 7 (16.3%) became HIV infected. Thus a significantly higher proportion of HIV-exposed infants born to mothers who initiated ART during lactation acquired HIV infection, than those born to mothers who started ART during pregnancy, OR = 4.2 95% CI: 1.3 – 17.4

CHAPTER 5.0: DISCUSSION

The results from our retrospective study suggest that low rates of vertical transmission of HIV can be achieved in pregnant and lactating women managed on option B+ in a resource-constrained rural district. We documented a 3.6 % HIV vertical transmission rate in the January - December 2012 birth cohort at 12 months. The significantly higher HIV vertical transmission risk in the July - December 2011 cohort suggests that the option B+ programme was not functioning optimally during the initial months of the programme. However, the low transmission rate during 2012 suggests that once the implementation of option B+ had improved, a dramatic reduction in the vertical transmission rate was achieved. Of course with very wide confidence interval this result might not represent the actual facts on the ground probably because size of the group of the infants who were tested was not optimal.

Furthermore our study found a lower vertical transmission rate (3.9%) among HIV-exposed infants from mothers who initiated ART during pregnancy compared to 16.3% vertical transmission rate of HIV-exposed infants from mothers who initiated ART during lactation. The significantly higher risk of vertical transmission in mothers who initiated ART during lactation, may relate to the longer period of exposure of the unborn or newly born baby to an unsuppressed maternal viral load, extending over the antenatal, perinatal and postnatal periods. In the January - December 2012 cohort the percentage of women who started ART during lactation was lower (29.3%) compared to those in the July - December 2011 cohort (40.7%). Thus a higher proportion of women in the January – December 2012 started ART earlier, which probably contributed to the lower vertical transmission rate documented in the January - December 2012 cohort. Maternal primary HIV infection during late pregnancy or during the early post-natal period may also have contributed to this increased transmission risk during lactation. The limited data analysed in our study did not permit us to identify women with primary HIV infection or explore this possibility.

Our study further found that only 19.9 % of the HIV pregnant mothers started ANC during the first trimester. This showed that majority of the pregnant women entered ANC late thus resulting in ART initiation late during pregnancy. Thus if more women are initiated on ART earlier in their pregnancies, a further decline in vertical transmission may have resulted. This finding can

be compared with other studies, which showed the importance of early ART initiation to reduce /mother to child transmission. In Zambia a retrospective cohort study of 1,813 HIV- infected pregnant women found mother to child transmission of HIV occurred in 59 (3.3 %). This study further showed that the odds of vertical transmission increased 5.5 times among women on ART for 4 weeks or less before delivery compared to those who received ART 13 weeks or more (Chibwasha, 2011). A retrospective study of 3,071 HIV-positive mothers and their infants attached to Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) clinics in Malawi and Mozambique found that the longer mothers had received ART during pregnancy, the lower the infant HIV transmission and infant mortality rates. This study found that transmission and/or death rates at 12 months was 14 % for infants of women who received less than 30 days of ART before delivery compared 6.9 % for infants of women who received at least 90 days of ART before delivery (Marrazzi, 2010). Studies completed in Malawi, South Africa and Cameroon also showed that ART started early in pregnancy reduces mother to child transmission rate (Fitzgerald, 2010; Hoffman, 2010; Tchendjonet, 2010; Kim, 2013)

Our study found that the uptake of HIV testing in pregnant and lactating women was 89.6%, and that 80.1% of those with HIV infection started ART on the option B+ programme. A cohort study of pregnant women newly identified as HIV-infected at 141 ANC facilities in 6 districts of Malawi identified 4 models of option B+ service delivery care: 75 facilities where newly identified HIV-infected women were initiated and followed on ART at the ANC clinic until delivery, 38 facilities where women received only their first dose of ART but were then referred to an ART clinic for further follow up, 18 facilities where women were referred to an ART clinic for ART initiation and follow-up and 9 facilities serving as ART referral sites but not providing ANC. Furthermore, the proportion of women tested for HIV during ANC was highest (82 %) in facilities where newly identified HIV-infected women are initiated and followed on ART at ANC clinic until delivery and lowest (68 %) in facilities where women receive only the first ART dose at ANC clinic, with subsequent follow up at ART clinic (von Lettow, 2014). Other studies in Uganda and Vietnam also registered high uptake of HIV testing among pregnant women in PMTCT (Kizito, 2008; H anh, 2011). A higher proportion of women were tested for HIV in our study. This may relate to the integration of PMTCT and ART services in the 10 health facilities providing option B+ in the Ntchisi district. Despite differences in HIV testing

rates, von Lettow found that the uptake of ART among HIV-infected women was 81% with no difference between models (von Lettow, 2014). This result is similar to the option B+ ART uptake documented in our study.

Our results showed low uptake of HIV testing in exposed infants. Initial results of implementing routine PMTCT option B+ in Thyolo district in Malawi between April 2012 and March 2013 found similar results. The study in Thyolo showed that 60.3% of infants aged ≥ 6 weeks ($n = 68$) had at least one PCR test as recommended in the national guidelines. The study also documented an excellent uptake of NVP of 96.2% (Coulborn, 2012). We observed a high uptake of NVP among HIV-exposed infants (82.3%) in the Ntchisi district, but the uptake was lower than in the Thyolo district.

We found a lower retention rate of option B+ patients on ART than in the general HIV population where ART is administered to patients with a low CD4 cell count or with WHO clinical stage 3 or 4 diseases. We showed that 70.4%, 64.8 %, 57.4% and 55.6% of option B+ mothers were retained at 3,6,12 and 24 months respectively in the July – December 2011 cohort, and 73.5%, 66% and 65.3% of the mothers in the January – December 2012 cohort were retained at 3, 6 and 12 months respectively. In contrast, Ntchisi district quarter 4 ART cohort report of 2013 showed a general ART retention rate of 81% at 12 months (Ntchisi ART cohort report, 2013). Furthermore, the national, routine programme reported a slightly higher retention rate of 77 % (2267) among 2,949 women who started ART on the option B+ programme during the third quarter of 2011, at 12 months (CDC, 2013), and Tenthani documented a retention rate of 82 % at 6 months among option B+ women during a countrywide evaluation of facility level data among a total of 21,939 women located at 540 sites and patient-level data on 28,428 women treated at 19 ART sites (Tenthani, 2013). Why Ntchisi district has lower retention rates than the national average is not clear. It is important to pursue this in further research so that corrective action may be implemented. Furthermore, similar research to our study may be able to determine whether lower retention is a general feature of rural settings rather than urban regions.

Additionally, this latter study revealed that Option B+ patients who initiated ART during pregnancy were 5 times more likely not to return to the clinic after their initial visit than patients

who started with a low CD4 cell count or with WHO clinical stage 3 or 4 diseases (Tenthani et al., 2013). A national Malawian analysis of data from July 2011 to December 2012 recorded a retention rate of 78 % at 12 month for option B+ which was similar to rate of 81% among other adults (Tippett Barr, 2013). Similarly another study in a large antenatal clinic in Lilongwe, Malawi found that of 3,030 pregnant or breastfeeding women who started ART between July 2011 and September 2013, 596 (20%) missed scheduled clinic appointment after one year representing an 80 % retention rate (Tweya, 2014). Many more studies have also reported high lost to follow up in PMTCT program (Nachenga, 2012; Clouse, 2013, Kalembo & Zgambo, 2012; Sibanda, 2013).

As expected our study showed that majority of the mothers (option B+) who defaulted did so within three months of commencing ART. This period remains critical for improving the retention of mothers in care. Lack of comprehensive counseling could be an issue affecting retention and may require improvement. Organization of health service delivery including integration would be essential to promote continuity of care with health care worker. There is a need to provide community awareness to communities and general public to mitigate stigma associated with LTFU in PMTCT. The health care system should be improved in such a way that fear of being stigmatized is eliminated. Providing community linkages through support groups to support may encourage mothers on option B+ to avoid LTFU (Schechter, 2014). Strengthening community engagement and social mobilization could help to address gender issues affecting retention in the option B+ program. While the problem of high LTFU in option B+ should be addressed, successful implementation of option B+ can be expected to increase health staff and economic costs (Rosen, 2007; Coutoudis, 2013). Incentives for health workers aimed at improving work performance may help to improve the effectiveness of the option B+ program. In the long term, increasing the number of health workers and health workers salary alongside increased levels of supervision and mentorship could provide some of the solutions to effectively implement option B+ (HIV/AIDS KMCC, 2012)

Our data showed ART adherence rate of 72.7 % for pregnant women and 67.3 % for lactating women. Similarly Nachenga (2012) observed a lower adherence rate during the post-partum

period, than during pregnancy. Furthermore, poor ART adherence rate in option B+ might pose a risk ART drug resistance (Coutsoudis, A., 2013).

Our study showed a maternal mortality rate of 2.4% (240/100,000) although some women who defaulted might have actually died. The higher defaulter rate will probably increase the maternal mortality rate. The causes of the deaths were not clear mainly because of inadequate or missing information. However, two women who died had low BMI at ART enrolment and three others defaulted ART before death. The first three months appears to be critical period as 3 (60%) of the five deaths that occurred during the first three months after commencement of ART.

Our data showed low retention rate of exposed infants in the Pre- ART clinic of the PMTCT programme. Low retention rate of exposed infants was similarly observed in preliminary results of routine PMTCT option B+ in Thyolo, Malawi where out 107 infants enrolled approximately 27 % were lost to follow up at three months (Coulborn, 2012). Similarly a systematic review and meta-analysis reported LTFU of infants within 3 months of delivery, a range of 4.8% –75% (Sibanda, 2013)

5.1 Strengths and limitations of the study

A major strength of this study is that it evaluated the implementation of option B+ in a rural setting. A large part of the population in Malawi lives in rural settings similar to those in the Ntchisi district. Thus the observations made in our study may be relevant to other parts of Malawi and should be considered when initiating option B+ in other rural African settings. In 2014, globally 46 % of the people were living in rural areas. In Africa, people who live in rural settings account to 60 % (UN, 2014). The low vertical transmission rate documented in the January 2012 – December 2012 cohort is reassuring and suggests that even in rural settings characterized by major resource constraints, option B+ can be effectively implemented.

Another strength of the study is that it analyses routine programme data, reflecting some of the realities and limitations of clinical care on the African continent.

5.2 Limitations

An important challenge in this study was missing and incomplete data. Since the study used routine programmatic data, issues with inconsistent / incomplete data, missing data could have an effect on the study outcomes. The study revealed areas of important gaps in data documentation/collection, fragmented and uncoordinated data collection tools and linkages between sites of ART/PMCT services provision. For example ANC and ART registers could not be linked with any unique identification number. There was no mother–pair follow-up system in the ART/PMTCT system as a result maternal factors associated with vertical HIV transmission to the baby could not easily be identified. This made data collection difficult. Outcome was also greatly affected as either registers or patient master cards were not updated. As such missing data about the reason for existing the programme might have contributed to study outcomes. Some patients considered lost to follow-up may have transferred to other facilities, died or tested negative for HIV or discharged from the programme in case of exposed infants.

Another limitation that should be mentioned is that adherence was assessed at one time point and the option B+ programme in Malawi does not allow an independent assessment of adherence through viral load monitoring. Thus the percentage of women who were virologically suppressed on option B+ could not be evaluated.

Because of the shorter duration of follow-up of the January – December 2012 cohort, we have an incomplete understanding of the retention rates in mothers and babies, and vertical transmission and HIV status of infants enrolled in this study at 24 months.

Furthermore, the short enrolment period (July 2011 until December 2012) does not allow us to determine whether there were further improvements to the option B+ programme during 2013 and whether or not the low vertical transmission rate documented in the 2012 cohort was maintained during 2013. An extended study period will also increase the sample size, improving the reliability of the results.

Despite these limitations the study findings have provided a useful initial description of the impact and challenges of option B+ in a rural district in Malawi. Follow-up studies, ideally

prospective studies are required to address the methodological weaknesses of the present study and answer questions generated by our study findings, particularly whether program improvements may result in higher uptake of option B+ and higher rates of retention in care.

CHAPTER 6.0: RECOMMENDATIONS AND CONCLUSION

6.1 Study recommendations

- There is a need to explore individual, family, community and health care system factors associated with lost to follow-up of mothers and their infants
- Women should be encouraged to enroll in ANC within the first trimester to get maximum benefit of option B +. Starting ANC earlier means a woman may start ART at an earlier gestational age if tested positive. If this was accomplished in the Ntchisi district the overall HIV transmission rate could be reduced below 2%
- Uptake of HIV testing in exposed infants should be reinforced. Decentralization of the PCR / DBS testing in the district could help to motivate mothers as well as to health staff to increase the infant HIV testing coverage. Consequently, delay in testing children for HIV infection and missing of PCR / DBS results may be reduced.
- Pregnant women should be encouraged to attend the recommended number of ANC visits (four visits) so as to not miss opportunities to start ART during pregnancy.
- The district health authorities should support the evaluation of the impact of option B+ over a longer period to determine whether the effectiveness of option B+ can be maintained or even improved.
- The linkage between the PMTCT program and community support groups should be strengthened to facilitate retention of mothers.
- Implementation of a text messaging service to remind mothers to attend follow up visits may be a useful support mechanism.
- Integration of child immunization clinics with PMTCT to improve follow up of HIV-exposed infants.
- Health worker motivation and support are needed to improve quality and successful implementation of option B+.
- Increase community engagement and social mobilization to address gender related issues that hinder effective implementation of option B+
- An increase in the number of health of workers is needed to improve the implementation of option B+

6.2. Conclusion

Despite high enrolment to option B+ among HIV-infected pregnant and lactating women in the 2012 cohort with consequent low vertical transmission, several findings suggest that the PMTCT programme in the Ntchisi district can be improved. Particular concerns include, late booking during pregnancy, initiation of ART during late pregnancy or only during lactation, low retention rate in care for HIV pregnant, lactating mothers and all infants, and inadequate HIV testing of HIV-exposed infants. These programmatic challenges should be addressed in order to optimize the administration and effectiveness of option B+.

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GANTT CHART – 2013/2014

	May 2013	Jun 2013	Jul 2013	Aug 2013	Sept 2013	Oct 2013	Nov 2014	Dec 2014	Jan2014	Feb 2014	Mar 2014	Apr 2014	May 2014	Jun 2014	Jul 2014	Aug 2014	Sept 2014	Oct 2014	Nov 2014
Study proposal																			
Tools pretest																			
Data collection																			
Data analysis																			
Report writing																			
Results dissemination																			

Budget

ITEM/ACTIVITY	COST (Malawi Kwacha)
Lunch allowance	24,000
Transport	36,000
Stationery- printing, photocopy	15,000
Contingency	10,000
TOTAL	85,000 (2,000 Rands)

ANNEX I

Checklist for pregnant and lactating mothers on ART (option B+)

Health facility

ID

1. Age

2. Marital status

3. Education level

4. Occupation

5. Date of starting 1st line ART regimen

6. Reason for starting ART: pregnant lactating

7. Wt

8. Ht

9. Body mass index

10. WHO stage

12. Follow up care

	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J
Wt (kg)																									
Ht																									
BMI																									
CPT																									
FP																									

ANNEX II

Exposed Children under 24 checklist

Health facility

ID

1. Date of birth

2. Sex

3. Enrolment date

4. Birth weight

5. Gestation at birth _____

6. Exposed child under 24 months - Follow up dates/care

	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J
Wt (kg)																									
Ht																									
MUAC																									
CPT																									
WHO stage																									
CD4 sample																									
CD4 results																									
IPT																									
PCR sample																									
PCR results																									
- 2 months																									
- 12 months																									
- 24 months																									
F/up outcome																									

ANNEX III

ANC clinic ART checklist

Health facility

ID

1. Age

2. Sex

3. Occupation

4. Gestation weeks no first ANC visit

5. Total ANC visits

a.1

b.2

c.3

D.4+

6. CPT given

7. Infant NVP given

ANNEX 1V: REQUEST FOR AUTHORISATION TO CONDUCT A STUDY AT YOUR INSTITUTION

From Packson Tsiku
University of Cape Town
School of Child and Adolescent Health

To District Health Officer
Ntchisi District Hospital
Po Box 44
Ntchisi

Date: 10/07/2013

Dear sir/ madam,

RE: REQUEST FOR AUTHORISATION TO CONDUCT A STUDY AT YOUR INSTITUTION

I write to request for your authorization to conduct a research titled 'Outcome of universal life-long ART for all HIV infected pregnant and breastfeeding women and children less than 24 months regardless of WHO stage or CD4 count (PMTCT option B+) – a case study in a rural district hospital, Malawi' at your institution as a part of fulfillment for the Master degree in maternal and Child health (M.Phil) at University of Cape Town.

I will be very grateful if my request is considered.

Yours faithfully,

Packson Tsiku

ANNEX V: AUTHORISATION LETTER



NTCHISI DISTRICT HEALTH OFFICE

All correspondence to be addressed:

The District Health Officer
P.O. Box 44
NTCHISI

Tel: 01285297/01285264

Date: 22nd July 2013

Mr. Packson Tsiku

Dear Sir,

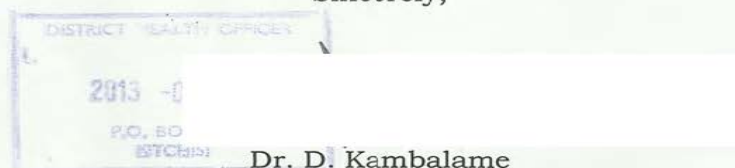
**OUTCOME OF UNIVERSAL LIFE-LONG ART FOR ALL HIV INFECTED
PREGNANT AND BREASTFEED WOMEN REGARDLESS OF CD4 COUNT OR
IMMUNOLOGY STAGE (PMTCT OPTION B+)**

The above subject refers.

I write to inform you that the permission has been granted to you to carry out your study here in Ntchisi as the topic seems to be relevant.

While conducting the study it is my sincere hope that all measures will be taken to uphold the ethics.

Sincerely,



Dr. D. Kambalame

DISTRICT HEALTH OFFICER

for: