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A Systematic Review and Document Analysis on the Prevention-of-Mother-To-Child Programmes to Prevent Vertical Transmission of Human Immuno-Deficiency Virus

By

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A dissertation submitted in fulfilment of the requirements for the degree of

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Declarations

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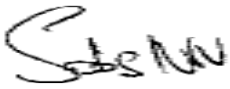
Signature:  Date: 31 March 2017

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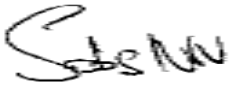
Signature:  Date: 31 March 2017

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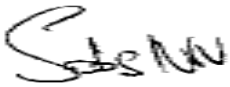
Signature:  Date: 31 March 2017

Abstract

Background: The National Strategic Plan 2012-2016 is advocating for zero new infections due to vertical transmission. This goal has not yet been achieved. This study evaluated whether the prevention of mother-to-child vertical transmission (PMTCT) of Human Immuno-deficiency Virus (HIV) programmes in South Africa are based on evidence.

Aim: The aim of this study was to conduct a systematic review of the available literature comparing PMTCT antiretroviral regimens published between the years 2000 to 2015 and to do a document analysis of the current implemented PMTCT programme to evaluate if it is based on best evidence.

Rational: The rational of the systematic review and the document analysis were to assess whether the latest PMTCT policy was based on evidence and to critically analyse published articles that addressed aspects related to efficacy and efficiency of PMTCT programmes to reduce transmission of HIV from mothers to their infants.

Methods: Overall 25 randomised controlled trials and primary studies that assessed efficacy of ARV regimens to prevent mother-to-child transmission of the HIV during pregnancy, labour and the postnatal periods were systematically reviewed. In 1997 the first trial began and the last one ended in 2012.

Twelve guidelines referring to PMTCT were sampled and they were published by WHO and Department of Health South Africa from 2001 to 2015. The document analysis was only based on *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April, 2015.*

Findings: The systematic review illustrated that significantly fewer infants tested HIV-positive when exposed to a longer ARV regime although there was no significant difference once the infants reached six months of age. Different ARVs have a similar

effect on maternal deaths; however a double or triple combination of ARVs is superior to monotherapy to decrease infant deaths. Common maternal adverse reactions to ARVs include anaemia, bronchopneumonia, and maculopapular rash. Infant adverse events included septicaemia, pneumonia, gastroenteritis, fever and maculopapular rash.

The document analysis has shown that the PMTCT policy is mainly based on evidence from randomised controlled trials and systematic reviews. Occasionally some statements are still based on lower categories of evidence such as non-experimental descriptive studies.

Conclusion: The systematic review showed that double and triple ARV therapy is superior to monotherapy and that the longer the mother and her infant are exposed to ARV therapy the better the results are to prevent MTCT. Adverse events are always posing a challenge and as with any other medication, caregivers must be aware of potential adverse reactions.

The National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015 is based on evidence, but the policy itself does not include any reference to evidence.

Keywords:
Human Immuno-deficiency virus, mother-to-child-transmission, PMTCT guidelines, antiretroviral treatment, pregnant women, infant.

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Disclaimer and Conflict of Interest

I, Nwabisa Nokuzola Sobetwa, (200805713) declare that, “This work is based on the research supported in part by the National Research Foundation” of South Africa Grant recipient: Prof V C Nikodem, National Foundation Indigenous Knowledge, Maternal and Child Health Research Grant. Reference: CSUR13091843239, Grant No: 87693. Furthermore, “Any opinion, finding and conclusion or recommendation expressed in this material is that of the author(s) and the NRF does not accept any liability in this regard”.

Dedication

Sindiswa Zibi, my source of inspiration from 1999 to date. For us it was not just the crossing of paths it was destiny. She immediately became a breath of fresh air where it was desperately needed and instilled in me the urge to pursue this career. She laid down layers of moral foundation all the time ensuring progress and giving moral support. Most importantly, she made me believe in my inner strength in fighting for my rights. She provided a lot of mentoring in all spheres of my livelihood. I would not be where I am today. To her I express my everlasting gratitude.

Acronyms

3TC	Lavimudine
AIDS	Acquired Immuno-Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
CD_4	T-Helper Lymphocytes Cluster Difference 4
d4T	Stavudine
EBP	Evidence Based Practice
EFV	Efavirenz
FDC	Fixed-Dose Combination Containing: Emtricitabine, Efavirenz and Tenofovir
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immuno-Deficiency Virus
IMR	Infant Mortality Rate
MMR	Maternal Mortality Ratio
MDG	Millennium Development Goals
MTCT	Mother-to-child Transmission
NSP	National Strategic Plan for HIV, STI and TB
NVP	Nevirapine
PMTCT	Prevention of Mother-to-Child Transmission
PSP	Provincial Strategic Plan
TDF	Tenofovir
sd-NVP	Single Dose Nevirapine
UNAIDS	Joint United Nations Programme on HIV/AIDS
UN	United Nations
WHO	World Health Organization

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Chapter One
Orientation to the Study

1.1 Introduction

This study evaluates whether the prevention of maternal to child vertical transmission (PMTCT) of Human Immuno-deficiency Virus (HIV) programmes in South Africa are based on evidence. A systematic review was embarked on to critically appraise and review the current challenges in relevant primary literature related to the implementation of prevention of mother-to-child transmission of HIV-1 (PMTCT) in HIV-positive women population. In addition a document analysis of the latest published *National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults – April 2015* was undertaken to evaluate whether the guideline was based on best available evidence (National Department of Health [NDOH], 2015).

Chapter one introduces the reader to the background of the research problem and gives the problem statement. The aim, objectives, and research questions are formulated and the theoretical framework is discussed.

1.2 Background to the Problem

The National Prevention of Mother-to-child (PMTCT) programmes began in 2002 in South Africa (Leach-Lemens, 2011; Barron et al., 2013). The prevalence of HIV among pregnant women attending public antenatal clinics in South Africa has stabilised around 29.5% and remained unchanged since 2004 (National Department of Health [NDOH], 2013b). The highest prevalence, 30.2%, of HIV among pregnant women attending public antenatal clinics in South Africa was recorded in 2010 (NDOH, 2013b). Goga et al. (2015) asserted that 32% of live infants were HIV exposed at the height of the HIV epidemic. Maternal-to-child-transmission (MTCT) of the HIV from HIV-positive women to their

infants showed a steady decline in prevalence from 14.6% in 2008 to 2.7% in 2011 (Bhardwaj et al., 2014). This decrease was not enough though, as South Africa was advocating for "Zero new infections due to mother-to-child transmission" (Heywood, 2011, p.12). The Eastern Cape Provincial Strategic Plan aimed to decrease the vertical transmission due to Human Immuno-deficiency Virus to less than 2% by 2015 (Eastern Cape AIDS Council, 2011).

In 2012, the World Health Organization (WHO) introduced the option B+ antiretroviral (ARV) programme to prevent mother-to-child transmission (World Health Organization [WHO], 2012b). Unlike the previous options (A & B), Option B+ recommended the Highly Active Anti-Retroviral Treatment plan (HAART) to all pregnant women, irrespective of what their T-helper lymphocytes cluster difference 4 cell (CD_4), counts (WHO, 2012b). In addition the plan recommended that women who started the treatment should stay on the drugs for life (WHO, 2012b). To support pregnant women further Minister Motsoaledi announced in December 2012 that as from the 8th of April 2013, all pregnant HIV-positive women were to commence the fixed-dose combination pill (FDC), regardless of their CD_4 count (South African Press Association [SAPA], 2013). Women were to stay on treatment until they completed breastfeeding. Thereafter, women were to continue on treatment should their CD_4 count be 350 or below (NDOH, 2013b). Cullinan (2014) reported that Minister Dr Aaron Motsoaledi mentioned in his speech on 23 July 2014 that all pregnant HIV-positive women were to go onto lifelong antiretroviral treatment in January 2015 irrespective of their CD_4 count.

1.3 Problem Statement, Aim, Objectives and Research Questions

The problem of concern was that despite the implementation of internationally recognized PMTCT programmes there was insufficient evidence of whether the PMTCT programmes in South Africa were based on best evidence. The set goal of Zero maternal to child transmission rate has also not yet been achieved. The question that can be asked is whether the South African PMTCT programmes are based on best evidence?

The aim of this study was to conduct a systematic review of the available literature comparing PMTCT antiretroviral regimens published between the years 2000 to 2015 and to do a document analysis of the current implemented PMTCT programmes to evaluate if it is based on best evidence.

The specific objectives were to:

- Systematically review literature that assessed the efficacy of ARV regimens to prevent mother-to-child transmission of the HIV during pregnancy, birth, and the postnatal period;
- Embark on a document policy analysis to evaluate whether the current PMTCT policy guidelines were formulated based on best evidence.

Research questions:

- What was the evidence from randomised control trials on the efficacy of PMTCT regimes?
- To what extent was the latest PMTCT policy based on evidence?

The purpose of the systematic review and the document analysis were to assess whether the latest PMTCT policy was based on evidence and to critically analyse published articles that addressed aspects related to efficacy and efficiency of PMTCT programmes to reduce transmission of HIV from mothers to their infants.

1.4 Theoretical and Conceptual Framework

Best practice clinical guidelines are based on systematic reviews, but promoting action on research implementation in health services (PARIHS) and implementing change to improve quality care of patients through research is complex and not easy (Rycroft-Malone et al., 2013). Evidence is the integration of knowledge that has been found to be credible (Rycroft-Malone et al., 2013). A systematic review based on the Cochrane systematic review principles is regarded as a foundation for Evidence Based Practice (EBP) as evidence based practice closely relates to the definition of evidence based medicine that was pioneered by Sackett, Rosenberg, Muir, Gray, Haynes and

Richardson, (1996, p. 71), where evidence based medicine was referred to as …"the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient". Evidence Based Practice means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Polit & Beck, 2008). Rycroft-Malone et al. (2013), argue that successful implementation of evidence based research principles involves three elements: evidence, appropriate context and sufficient facilitation for change.

The theoretical framework used for this project was to establish whether PMTCT policies and guidelines were generated from evidence, synthesised, and implemented to be efficient and effective in order to reach the zero infection rate as advocated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and South Africa. The evidence based theoretical framework can be closely applied to the aim and objectives of this study as existing literature was used to evaluate whether formulation and implementation of PMTCT guidelines were based on evidence. Polit and Beck (2008) state that an important step in implementing evidence based care includes creating clinical policies based on evidence. The policy document analysis was supported by the systematic review of evidence that provided information of whether the policy was based on efficient and effective scientific data (Polit & Beck, 2008).

The underlying conceptual and theoretical framework was based on a combination of evidence based practice and content analysis theory framework described by Haynes and Haines (1998) and Krippendorff (2004). Haynes and Haines (1998) developed a conceptual framework on evidence based practice (EBP) as depicted in Figure 1.1. Krippendorff (2004) developed a content analysis framework which was incorporated into the EBP framework of Haynes and Haines (1998) for the purpose of this study.

The underlying assumptions of the framework are:

- Processing uses a circular format, where the one phase precedes the second and once completed the circle commences again;
- Research is generated from merited published evidence and document analysis aids this process by analysing constructs from the PMTCT guidelines;
- Evidence is critically appraised for synthesis and inferences are logically reasoned;
- To enhance scientific rigor results need to be validated;
- Validated facts are incorporated in the development of evidence based policy and guidelines;
- These EBP guidelines warrant policy and guidelines to be implemented and evaluated for efficiency (Haynes & Haines, 1998; Krippendorff, 2004).

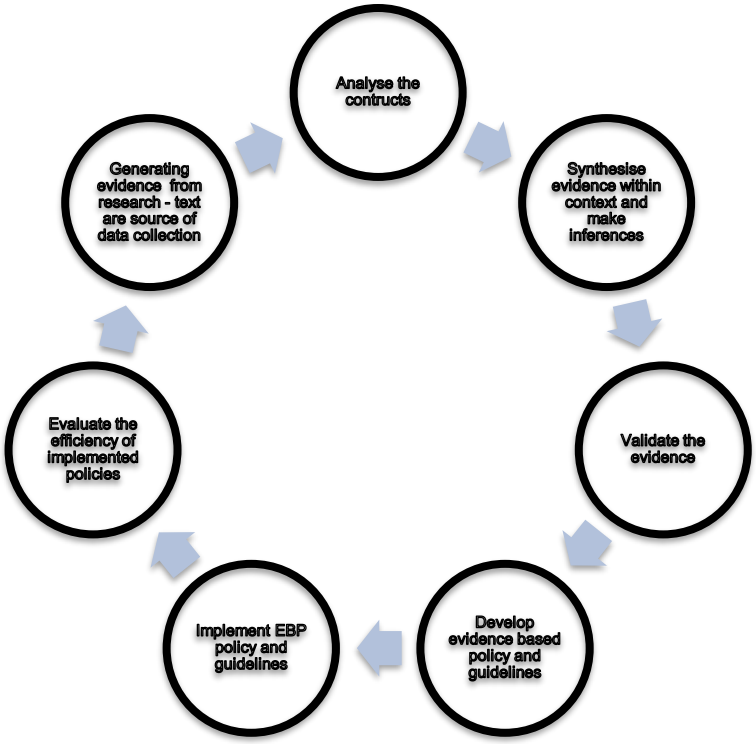

Figure 1.1 Conceptual Framework (Based on Haynes & Haines, 1998 and Krippendorff, 2004).

Transfer of information to health professionals and health systems in systematic reviews can be done through electronic media, training, publications, and decision making support systems. Transfer of evidence consists of meticulous development strategies aimed to identify target audiences namely: policy makers; clinicians; managers and consumers and to design information transfer packages that can be understood and implemented by decision makers (Hemingway & Brereton, 2009).

1.5 Ethical Considerations

This is a review of already published material and therefore does not need ethical clearance per se. Given the extensive use of literature, a potential ethical problem might be plagiarism or copyright issues. The reviewer acknowledged all sources consulted using the recommended American Psychological Association (Sixth edition) reference style method.

1.6 Intellectual Property Consideration

No intellectual property for economic gain was envisaged and information will be freely disseminated through publication and at conferences to policy makers.

1.7 Structure of the Dissertation

The structure of the dissertation consists of six chapters. The author introduced the overall study in chapter one. A literature review on the history of PMTCT programmes and prevalence of HIV/AIDS globally and locally will be engaged with in chapter two. Chapter three will explain the research methodology used to do the document analysis and the systematic review. Chapter four will present the content analysis of the latest PMTCT policy guidelines. Meta-analysis of published articles related to the efficiency and efficacy of the use of antiretroviral treatment programmes for the PMTCT will be discussed in chapter five. Conclusions, recommendations, and implications for practice and further research will be discussed in chapter six.

1.8 Summary

The reader has been familiarised with the direction this study is going to take. A brief discussion on the background to the problem has been presented. The aim and objectives of the current study have been clearly stated. The theoretical and conceptual framework of document analysis and systematic review have been discussed. Chapter two will unfold the literature review pertaining to the history of HIV/AIDS and critically review the literature related to the objectives of the study.

Chapter Two
Literature Review

2.1 Introduction

The overall goal of chapter two is to review literature concerning concepts related to the prevalence of Mother-to-child Transmission (MTCT) of HIV, morbidity and mortality related to HIV/AIDS and prevention strategies as advocated by the World Health Organisation (WHO), Joint United Nations Programme on HIV/AIDS (UNAIDS) and the South African Department of Health. Challenges that hindered the implementation of policies and guidelines in South Africa, and conceptual and operational definitions will be formulated from the literature. The history of HIV/AIDS international and nationally will be a starting point of this literature review.

2.2 History and Time Line of HIV

Glanz (2013, p. 14) argued that the "issue of the origin of the HIV could go beyond one of purely academic interest…[but] how it evolved could be crucial in developing a vaccine against HIV and more effective treatments in the future." The time of the origin of the HIV cannot be exactly determined and we do not know accurately how many people got infected before the identification of the HIV, but what we know for sure is that the beginning of our understanding of the AIDS epidemic officially began on 5th June 1981 (Katrak, 2006; Glanz, 2013). Both, Professor Luc Montagier from the Pasteur Institute in Paris and Professor Robert Gallo from the National Institute of Health in United States of America (USA), claimed that they discovered the HIV (Katrak, 2006). The controversy of who discovered the virus was laid to rest when a decision was made in 1987 that both Montagier and Gallo would be jointly recognised as the co-discoverers of the HIV (Katrak, 2006).

Although the claim of who identified the HIV has been settled, the theoretical argument over the mystifying origin of the HIV still continues. Not one of the theories can be fully proven, neither is anyone completely accepted, but four of the main theories continue to provoke thoughts in many researchers' minds.

The four main theories that speculate the origin and widespread of HIV/AIDS are:

- The contaminated oral polio vaccine theory;
- The cut hunter theory or natural transfer theory;
- The contaminated needle theory;
- The colonialism theory (Moore, 2004; Katrak, 2006).

Edward Hooper, author of the controversial book 'The River' is most probably the most devoted supporter of the contaminated oral polio vaccine (OPV) theory (Moore, 2004; Katrak, 2006). Katrak (2006) claimed that the OPV theory originated from Dr Snead, a San Antonio physician who suggested that OPV was contaminated with simian immune-deficiency virus (SIV) from the African green monkey and that started the HIV/AIDS epidemic. The thought of contaminated OPV stimulated Louis Pascal, a non-medical person, who argued that the kidneys of chimpanzees and not green monkeys were used to manufacture the OPV and claimed that there was a relationship between the vaccination sites and the earlier cases of AIDS in Africa (Katrak, 2006).

The OPV theory has undergone extensive critical scrutiny and is readily rejected for two reasons:

- Firstly, the origin or the Eve HIV-1 has been found in a tissue sample predating the development of the OPV vaccine and is estimated to date from 1930 (Cohen, 2001; Katrak, 2006; Pickrell, 2006; Glanz, 2013);
- Secondly, extensive research done on OPV theory including examining samples from the Wistar Institute where the polio vaccines were produced, concluded that the OPV theory is extremely unlikely to be the origin of the HIV epidemic (Martin, 2001; Katrak, 2006). Despite this scientific conclusion 87% of pre -1981 known HIV-1 samples came from people who lived within 160 km of the CHAT polio

vaccination areas from 1957-1960 (Glanz, 2013). The CHAT vaccine strain was named after the child, Charlton, who donated the precursor virus (Gellin, Modlin & Plotkin, 2001).

The cut hunter theory also supports the concept similarly like the OPV theory that AIDS has a zoonotic origin and postulated that the simian immune-deficiency virus got transmitted to humans, especially hunters, via blood-to-blood contact with infected mangabey monkeys or chimpanzees (Moore, 2004). Another theory is that HIV-1 originated in humans after SIV infected chimpanzee's meat was consumed by people in the Congo (Martin, 2001; Katrak, 2006). It is postulated that the SIV entered the hunters blood through cuts and overtime mutated to HIV. It is generally accepted that HIV mutated from the SIV and unlike the OPV theory it is difficult to reject the cut hunter hypothesis as very little evidence is available to disprove the theory, but the question that arises is, hunters have been doing it for centuries so why did the SIV only change in the mid 70's? (Katrak, 2006).

The contaminated needle theory originates from the 1950's with the introduction of disposable plastic syringes (Moore, 2004). The challenge was that between 20% and 40% of health care providers could not afford to dispose syringes after single use. The plastic syringes could not be boiled therefore there is a possibility that unsterile plastic syringes were reused (Katrak, 2006). Marx, a virologist, supported this theory as he felt that the reuse of unsterile syringes ignited the HIV epidemic (Katrak, 2006). The serial passage of transferring the SIV caused the virus to mutate to HIV (Katrak, 2006). The colonialism theory refers to the harsh circumstances that people in the Congo had to live under the leadership of King Leopold II of Belgium, and about 10 million people died in Belgium Congo during his reign (Moore, 2004; Katrak, 2006). The theory is that HIV/AIDS stayed contained in the Congo until the English pulled out. The people of the Congo were then free to travel, migrate and this may have assisted in the epidemic spread of the virus (Glanz, 2013).

As stated before, science may never discover the actual origin of HIV and AIDS and whether it was the mutation of the SIV or not, is not important, what is important now is to find a vaccine that can eradicate the spread of HIV.

Retrospective scientific evidence done on blood samples showed that the HIV has been positively identified in two unrelated cases of men who died in 1959 (Garner, 2011). The first case was identified through analysis of a stored blood plasma sample that was taken from an adult male who lived near Leopoldville (present-day Kinshasa), Democratic Republic of Congo, in 1959 (Glanz, 2013). The second case showed that the HIV was identified in preserved lungs of a 49 year old Jamaican American shipping clerk, Ardouin Antonio, who died of *Pneumocystis Carinii* Pneumonia (PCP), a disease known to be prevalent in immune compromised patients, such as HIV/AIDS (Garner, 2011).

The emergence of HIV-2, a viral alternative of HIV-1, most commonly found in West Africa can be traced back to 1960 (Pickrell, 2006). It is believed that this was another Zoonosis virus that was transferred from the “sooty mangeby” monkey in Guinea Bissau to humans (Garner, 2011). It is believed that the first person dying from HIV-2 was Mr. Joseph (*Senhor* José) a Portuguese man who died in 1978. It is claimed that the disease was contracted in 1966 when he was in Guinea-Bissau (Pickrell, 2006).

Geographic sequencing of the HIV-1 gene was done on samples recovered from archival laboratories of Haitian patients and it was concluded that the virus spread from Africa to Haiti around 1966, between the years 1962-1970 (Gilbert et al., 2007). Furthermore, the spread of the heterosexual epidemic HIV-1 virus circulated globally before it was recognised as the cause of AIDS in the USA in 1980-1981 (Gilbert et al., 2007).

A few cases can be traced back to the 1970, when blood and tissue samples were re-analysed. Dr Memory Elvin-Lewis assisted Dr William Drake in the autopsy of Robert Rayford, an 18 year old male teenager who died in St Louis, Missouri in 1969. They established that Rayford had Karposi sarcoma, but were mystified with all the symptoms he presented with at death. Dr Elvin-Lewis therefore decided to store tissue and blood

samples with the hope that advances in medical sciences with time would be able to provide answers to the diagnosis. The stored tissue and blood samples of Rayford were reanalysed in 1987 and confirmed to be the earliest HIV/AIDS case in North America. It has been confirmed that Rayford stated that he experienced symptoms as early as 1966 and that he never left his home town, but engaged in homosexual prostitution (Nicholas, 2007).

Doctors practicing in African countries observed an increase in wasting and the incidence of opportunistic infections among patients during the early 1970's (Serwadda et al., 1985; South African History Online [SAHO], 2016). Grethe Rask a Danish homosexual physician, who worked in Africa between 1972 and 1975 most likely, contracted HIV through the contamination of open wounds and blood from her patients. Re-analysis of her blood samples confirmed HIV infection (Shilts, 2011). The case of Arvid Noe, a Norwegian sailor who died in 1976, supported the heterogenic transmission of HIV (Kreston, 2012). Arvid Noe was known to have sexual encounters with West African women (Kreston, 2012). It was recorded that he was treated for lung infection and lymphoedema as well as gonorrhoea and developed dementia and motor control difficulties later in life (Kreston, 2012). He died in 1976 and it was later identified that Noe was infected with the HIV-1, which was prevalent in Cameroon. His wife and daughter (9 years), died a year later in 1977, and records of blood samples from his wife and daughter were re-tested in Oslo National Hospital (Kreston, 2012). The results confirmed that his wife and daughter also had HIV (Kreston, 2012).

The USA is the first country to bring HIV into the public domain as early as 1980 when The Centre for Disease Control (CDC) with Kaposi's sarcoma (KS) reported that Ken Horne a San Francisco resident died of AIDS on the 24 April. He also suffered from an opportunistic AIDS related disease, Cryptococcus pneumonia (Siddik, 2011). Doctor James Groundwater sent blood and tissue samples of a pimple like lesion that was on Rick Wellikoff's thigh, a gay Brooklyn school teacher in New York, for testing in 1980, which came back positive for HIV (Morse, 2005).

Rumours about a “gay disease” responsible for killing gay men came about in the early 1980’s when Lawrence Mass, a journalist for the New York Native gay paper published an article with the headlines of “Disease Rumors Largely Unfounded” (Mass, 2006). He raised awareness about the “deadly” disease that was killing gay men. At the time Pneumocystis pneumonia was being recorded as the cause of death for five homosexual men in Los Angeles. Further reports stated that 41 gay men in New York and San Francisco had Kaposi’s sarcoma. It was more or less the same time when the United Kingdom (UK) reported their first case of death due to AIDS (Pickrell, 2006). A total number of 121 deaths were ascribed to AIDS in Gay men in 1981 (Pickrell, 2006).

The association of Kaposi sarcoma and homosexual men led to the “disease” being referred to as “gay cancer” or Gay Related Immune Deficiency” (GRID) (Grmek, 1993; Glanz, 2013). After the Institute Pasteur stated that AIDS is caused by the HIV, the CDC pronounced that GRID was not only a gay related disease but a heterosexual disease as well. To silence the controversy of whether AIDS or the exposure to substances such as amyl nitrate were the cause of Kaposi sarcoma, the CDC disputed that at a meeting held on 27 July 1982 and pronounced that Kaposi sarcoma was not only a “Gay Related Immune Deficiency” (GRID) disease (Glanz, 2013). In August 1982, Dr James Curran, the then head of CDC recommended that Acquired Immune Deficiency Syndrome (AIDS) be included in the medical terminology when referring to the disease that display the specific symptoms such as Kaposi sarcoma (Glanz, 2013).

The spread of HIV via blood transfusion was identified in 1982, when a 20 month old sick infant received a blood transfusion from an HIV infected donor, in California (Curran & Jaffe, 2011; Glanz, 2013). People at high risk of being infected with HIV were urged not to donate plasma products or blood, and the USA Public Health Service developed guidelines on who may be at risk of spreading HIV via blood donations. By 1982 AIDS had spread to over 14 different countries in the world and HIV/AIDS was known as a global disease (Glanz, 2013). The spread of HIV through contaminated blood was further emphasised in an 18 year old haemophiliac boy Ryan White who resided in Kimono, Indiana in the United States of America. Ryan was diagnosed in 1984 of being HIV-

positive after he received contaminated blood products (Health Resources and Services Administration [HRSA], n.d.). There was an uprising against his admission to school. He won the case, but unfortunately passed away a year before his graduation from school. The Ryan White Comprehensive AIDS Resources Emergency (CARE) health programme was established to ensure HIV-positive children had access to schools (Health Resources and Services Administration HRSA, 1987).

The earliest cases of mother-to-child transmission were reported as follows: In San Francisco, a prostitute, who died in May 1987, gave birth to three children in the 1970's who were later diagnosed as being infected by the HIV (Shilts, 2011). This is most likely the first reported case of mother-to-child transmission (Shilts, 2011). The next recorded maternal to child infection could be traced to a sixteen year old, drug user, who gave birth to a baby around 1974. The child died at the age of five and re-analysis of stored tissue confirmed HIV infection (Shilts, 2011). Lastly, an HIV-positive infant was born in December 1980, to a New York woman who confessed to be an intravenous drug abuser (Glanz, 2013). The infant died in November 1981, of Pneumocytis carinii pneumonia (Glanz, 2013). Dr James Oleske, a practicing paediatrician, supported the concept that HIV was not only a gay disease as he had recognised the disease in infants (Campbell, 2006).

2.3 Notable People Who Had HIV/AIDS

Freddie Mercury a multi-talented bisexual rock star (singer and writer) was diagnosed with HIV in 1987 but kept his diagnosis a secret. It was mentioned that off stage he was perceived as a shy character and was never comfortable talking about his relationships in public. He died at age 45 on 24 November 1991 of bronchial pneumonia an AIDS related illness (Johnson, 2011). Liberace was born in 1919 and started playing piano at the age of four. He entertained the world during 1950-1970 and was said to be the highest paid entertainer at some stage. Liberace was never open about his gay or his HIV status. The facts were only revealed when his bodyguard sued him for palimony in 1982. Liberace died on 4 February 1987 of cardiac arrest and his HIV-positive status was

confirmed on his autopsy (David, 2010). Rock Hudson, another highly paid actor in 1970's, also kept his status secret for just over a year. He was diagnosed with HIV on 5 June 1984, which he claimed was due to a blood transfusion. Rock Hudson only released his status a year later on 25 July 1985 when he announced that he had AIDS. He died on 2 October 1985 of an AIDS related illness (Archerd, n.d.).

Perry Ellis was born on 03 March 1940 and owned "Perry Ellis International" one of the biggest designer companies globally. Ellis conceived a daughter through artificial insemination with a long-time friend Barbara in 1984, both are still alive, and HIV free. Ellis and his life partner, Laughlin Barker, were both diagnosed with HIV/AIDS and died a few months apart. Ellis died on 30 May 1986, because of viral encephalitis an AIDS related disease (Louie, 2011). Another well-known American, Arthur Ashe who was the only black tennis player to win the Wimbledon, United States and Australian Opens tennis championships contracted HIV from a blood transfusion during surgery. Ashe was born and bred in Virginia, Richmond and had a heart problem. Arthur's wife kept his HIV status private until 8 April 1992 and only made his status public in 1992 when he appeared skeletal and skinny. He passed away on February 1993 due to pneumonia (This day in history, 1993).

Esteban De Jesus a World Boxing Light weight Champion was born in 1951. His career spiraled after defeating the "undefeated" Roberto Duran in 1972. After he retired from boxing he unfortunately became involved in a traffic dispute in 1981 and shot a 17 year old due to road rage. Esteban was jailed for life, where he apparently became involved with drugs. It is believed that he may have contracted HIV through drug injection and died at age 37 on 11 May 1989 (Rogers, 1989). A ballet dancer Rudolf Nureyev was born in 1938 in Siberia. Nureyev, although open about his gay status, was in denial of HIV. He became seriously sick in 1990 and died at age 54 in 1993 (Lauritsen, 1993).

Anthony Perkins, an American actor was born in 1930 and acted in films such as *Psycho*, a Hitchcock thriller. In 1989 he was diagnosed with HIV and kept his status secret as he was worried that he would not get acting roles (Weinraub, 1992). He was married to Berry

Berenson and they had two children. He died of HIV related pneumonia on 12 September 1992. A homosexual playwright famous for writing the lyrics of *Beauty and the Beast* named Howard Ashman, born in 1950, died after a lengthy fight with the disease in March 1991. Ashman was honoured in 2001 as a Disney Legend (Sunderland, 2013).

The last of some of the ten most famous people according to Johnson (2011) was Keith Haring a homosexual painter of murals who was born in 1959. It is suspected that he was infected with HIV through unprotected sex or drug injections. He died in 1990 at age 31. Haring's art was widely used to increase AIDS awareness (Sussman, 2008).

2.4 HIV/AIDS Awareness in South Africa

It has been said that "South Africa has had a turbulent past and this history is relevant to the explosive spread of HIV in the country" (HIVSA, n.d. para.1). Some of the myths during the late eighties and early nineties that supported the controversy on the spread of HIV were published in the official publication of African National Congress (ANC), claiming that HIV could have been developed in the laboratory with others suggesting it was spread by police teargas (Pope, White & Malow, 2009).

The first diagnosed case of HIV in South Africa can be traced back to a white, homosexual man, employed as an air steward in 1982 (Gobind, 2014). He died of Pneumocystis carinii pneumonia, an HIV related disease, shortly after returning from the United States of America (Gobind, 2014). HIV was then coined as a "gay disease". In the late 1980's as evidenced in Sher (1989), 125 HIV positive cases were reported from homosexual or bisexual population thus terming HIV as a gay disease. In 1987, the first Black heterosexual male was diagnosed in South Africa (Brand, 2006). The prevalence among heterosexual males was low in South Africa during those years, but high in countries such as Botswana (Barz & Cohen, 2011) and Malawi (Iliffe, 2006) .

Surveillance studies during 1988-1989 showed that the HIV was present in all racial groups irrespective of sexual preference, but the prevalence was low (Sher, 1989).

Anonymous testing on antenatal blood collected during 1988 from 90 307 women showed that the prevalence of HIV was only 0.08% (Sher, 1989; National Department of Health [NDOH], 2007).

Sher (1989, p. 317) emphatically stated that as early as 1989 HIV infection was a social disease and "what is important is not [the source] where it came from but where it is going and what are we going to do about it". He further emphasized the fact that there was an exponential growth of HIV/AIDS cases and society should be educated on sexual behavioural changes in the light of the absence of a vaccine or cure (Sher, 1989). Sher (1989, p. 317) further posed a very striking question when he asked "How many more people must die before we do something about the disease?" Sadly his plea was not acknowledged by policy makers. Sher (1989, p. 317) predicted that "in 5 years' time it will be too late" unfortunately became a reality as the prevalence of HIV reached pandemic proportions by 1990 (Barron et al., 2013).

In 1990 Chris Hani, a political activist, supported the writings of Sher (1989) and warned the country that if the issue of HIV in South Africa was left unattended it would cause grievous harm to the citizens (Brand, 2006). In 1990 the prevalence amongst pregnant women had risen to 10% (Barron et al., 2013). It was estimated that in 1995, 2.1% (nearly one million people) of the total population were living with HIV in South Africa and Thabo Mbeki the then Deputy President acknowledged the gravity of the pandemic for the first time (HIV AIDS in South Africa [HIVSA], n.d.). The prevalence soared and increased to an all-time high of about 40.7% prevalence amongst pregnant women in KwaZulu Natal in 2006 (United Nations Children's Fund [UNICEF], 2007). It is thus no wonder that South Africa is named "home of HIV/AIDS" (The Joint United Nations Programme on HIV/AIDS [UNAIDS], 2009, p.1.)

The time period of 10 May 1994 to 14 June 1999 was an era characterised by transition from apartheid to democracy. President Nelson Mandela was the first democratic elected President in South Africa and Nkosazana Dlamini-Zuma was appointed as National Minister of Health. President Mandela was actively involved in the HIV fraternity before

and after his Presidential status. Prior to his Presidency he addressed the newly formed National Convention of South Africa (NACOSA) which was established in 1992. Mr Mandela informed them to implement a national strategic plan to address the HIV pandemic. One of the government strategies was to establish a toll free AIDS helpline to promote national awareness and health education (HIVSA, n.d.). Another successful innovation was the implementation of the television series Soul City which spread awareness about HIV/AIDS since 1995 (Soul City, n.d.).

Although President Mandela's term ended in 1999, he had been in the forefront of HIV and was perceived as a global awareness icon and allowed his prison number, "46664" to be used at musical concerts for fundraising. The "46664" was named after the prison number allocated to him while incarcerated in Robben Island. The "46664" concert started in 2003 and was held in Cape Town. Funds raised were used to uplift humanitarianism and a lobby towards social injustice (South Africa.info, n.d.)

Several scandals tainted the activist-government relationships such as: Sarafina II (a controversial AIDS play) and the Virodene scandal (an untested AIDS remedy), to mention a few (Mbali, 2013). Virodene was thought to be an antiretroviral drug and Nkosazana Dlamini Zuma allowed virodene researchers to present pilot findings to the cabinet. These results were neither peer-reviewed nor controlled, yet the government sponsored the project with an amount of 3.7 million to conduct further research. It was later established that virodene was an industrial toxin used for dry cleaning. An independent panel led by the Medicines Control Council (MCC) found that the main ingredient of Virodene was dimethylformamide, a toxic solvent used in drycleaners (Gumede, 2007). The MCC halted all virodene related clinical trials and any further research on virodene (Mutume, 1997).

President Mbeki took office as president of South Africa on 14 June 1999 and appointed Manto Tshabalala- Msimang as the National Health Minister. Together, they were severely criticised by the "HIV world" for their misinterpretation of the cause and treatment of the HI-virus. They focussed on nutrition rather than on treatment. Their philosophy

about HIV was criticized and included the issue about HIV denialism, misinformation and they strongly relied on acquiring information from non-accredited researchers such as Dr Rath (Leclerc-Madlala, 2005).

President Thabo Mbeki politicised the HIV/AIDS issue and prior to the 13th international HIV Conference in April 2000 he wrote a letter to world leaders declaring his distrust of western solutions regarding the HIV/AIDS pandemic among African states (Marais, 2000). Durban hosted the 13th International HIV Conference on 9-14 July 2000. International and national researchers presented data on the efficiency of ARV's in reducing mother-to-child transmission. Several authors who presented papers at the conference, and later published the results showed that Nevirapine was effective in reducing MTCT (Guay et al., 1999; Onyango-Makumbi, 2011; Moodley et al., 2003).

At the 13th International HIV Conference President Thabo Mbeki refuted the argument that HIV causes AIDS and stated that HIV was closely related to poverty (Mbeki, 2000). He was later interviewed by the *Time* magazine on September 2000 and he asserted that an immune-deficiency cannot be solely attributed to the HIV (Leclerc-Madlala, 2005). President Mbeki was continuously on the hot seat and interviews were conducted regarding HIV in 2001. Deborah Patta interviewed President Mbeki on 24 April 2001, his response was that HIV testing would not solve the health needs of South African citizens (Schneider, 2002). President Mbeki not only refuted that HIV is transmitted via a virus but he also questioned the validity of HIV testing (HIV Treatment Bulletin, 2001).

On 6 August 2001, President Mbeki was interviewed on *World's Hard Talk* at the British Broad Casting station by Sebastian Tim where he denied that the mortality in South Africa was AIDS related (Murphy, 2003). President Mbeki went so far to openly declare that he knew no-one who had died or is living with HIV meanwhile the prevalence among pregnant women was estimated at 26.5% among South African pregnant women in 2002 (Murphy, 2003).

President Mbeki was further criticized for supporting the Castro Hlongwane document that alleged that Parks Mankahlane a presidential spokesperson and Nkosi Johnson a young HIV activist died because they were forced to take the poisonous antiretroviral medication (Kindra, 2002). Peter Mokaba the then President of the ANC Youth League and strong supporter of Mbeki, denied his own HIV diagnosis and eventually died of an AIDS related illness, in June 2002. President Mbeki was criticised for not silencing Peter Mokaba as he led the youth and promoted the concept of not taking antiretroviral medication (Smith, 2002).

Further confusion regarding antiretroviral treatment was caused by Dr Roberto Giraldo, a scientist that served in the Advisory Committee of Thabo Mbeki's Presidency. Giraldo explained that person to person transmission of HIV was not based on scientific validation (Altenroxel, 2003). Giraldo emphasised good nutrition as a solution to AIDS and therefore supported Dr Matthias Rath's nutrition theory (Altenroxel, 2003). Dr Rath was a vitamin salesman who criticised the use of antiretroviral medication as being poisonous and dangerous (Boseley, 2008).

President Mbeki gave a lecture at Fort Hare University on 12 October 2001 where he shared information about fundamental explanations of sexually transmitted diseases. He argued that the explanations were racist and assumed that black people were the carriers of germs (Forrest & Streek, 2001) The above interviews made the world lose confidence in President Mbeki for not providing an action plan in dealing with the HIV/AIDS pandemic. President Mbeki also perceived antiretroviral medication as a money-making scheme by United States (US) pharmaceutical companies and accused the Central Intelligence Agency (CIA) of working secretly with the pharmaceutical companies. He also stated that the activists from the Treatment Action Campaign (TAC) were sponsored by these drug companies (Barrell, 2000).

Zacke Achmat an HIV/AIDS activist openly declared that he was living with HIV in August 1998 (Mbali, 2013). He was instrumental in the formation of the Treatment Action

Campaign which was formed in December 1998 (Brand, 2006; Mbali, 2013). The Treatment Action Campaign advocated for the following:

- Accessibility of HIV treatment to every citizen that is eligible for it;
- Information sharing about affordability and availability of treatment;
- Empower and educate people about issues surrounding HIV.

The TAC's advocacy is carried through public awareness's and through TAC's quarterly newsletter (Brand, 2006).

Under President Mbeki's reign the national prevalence of HIV among antenatal attendees continued to rise from 24.5% in 2000 to 24.8% in 2001 (Barron et al., 2013). On 14 December 2001, the Pretoria High court ruled in favour of the Children's Rights Centre (CRC), Save Our Babies (SOB). The TAC filed a case against the South African government stating that Nevirapine should be made available in public health centres (Heywood, 2003; Mbali. 2013). The Treatment Action campaign was also involved in another court case where they filed a manslaughter case against Alec Erwin and Manto Tshabala- Msimang for hindering production of antiretroviral generics. The Treatment Action Campaign then got involved in a civil disobedience campaign (Treatment Action Campaign [TAC], 2003). President Jacob Zuma remedied the situation by appealing to TAC for political space and the campaign was suspended on 17 May 2003.

The SA government was ordered to develop a national programme to reduce mother-to-child transmission with effect from 31 March 2002. The KwaZulu Natal Province, ruled by Inkatha Freedom Party, rolled out its PMTCT programme on February 2002. The South African government wanted the court to revoke the order, unfortunately that was unsuccessful and delayed rolling out of treatment while it continued in several provinces (Heywood, 2003). The Treatment Action Campaign then applied for the execution of the order. On July 5 2002 the Constitutional Court ordered the SA government to make Nevirapine freely available to public health hospitals and clinics without further delay (Heywood, 2003; Mbali, 2013).

Although the national PMTCT programmes started in 2002, there were activities that took place and could be traced back to 1998. Several individuals, researchers, and provincial governments implemented the prevention of mother-to-child transmission programme (PMTCT), before the official launch of the 2002 by the South African government. The two provinces (Western Cape and KwaZulu Natal) that were not under African National Congress (ANC) rule started advancements in the HIV prevention of mother-to-child transmission arena as early as 1998. The Western Cape Department of Health started the PMTCT programmes in 1998–1999 at two midwifery obstetric units in Khayelitsha, Cape Town (Barron et al., 2013). The Eastern Cape followed in the footsteps of KwaZulu Natal and Western Cape. On the 24 March 2000, Dr Costa Gazi the then head of public health in Mdantsane Cecilia Makiwane Hospital and Pan African Congress Health Secretary, announced that he was willing to supply Nevirapine antiretroviral drug out of his pocket to pregnant women (Dickson, 2000; Stein, 2003, Marlink & Kotin, 2004). Dr Gazi stated that, “Nevirapine was by then going to be given to twenty local clinics in the Eastern Cape and was to be administered under his supervision” (Dickson, 2000, para. 2).

In addition, heavy criticism on the inactive approach by the South African government encouraged scientists to lobby for the availability of ARV’s. The pressure resulted in Manto Tshabalala-Msimang recommending the establishment of two research sites in each of the nine provinces (eighteen sites) for a period of two years (Barron et al., 2013). The aim was to get a better understanding of safety and challenges associated with the use of antiretroviral medication during pregnancy. The regimen consisted of a single dose Nevirapine (sd NVP) given to the mother during labour followed up by a single dose Nevirapine syrup to the infant within 72 hours after birth.

In 2003 the National Department of Health issued a new operational plan for treating and caring for HIV-positive individuals. Therefore the first official national PMTCT programme in South Africa commenced after 5 July 2002 (National Department of Health [NDOH], 2008). The plan increased provision of nevirapine and the treatment was extended to all HIV-infected pregnant mothers and their children. This led to the development of health-

care related services, such as voluntary counselling and testing. In 2004 the National Department of Health introduced an all-inclusive care management and treatment of HIV-infected individuals. Gauteng was the first province to roll out antiretroviral medication and other provinces followed suit. The eligibility criteria included pregnant women with a CD_4 T-cell count < 200 cells/mm^3 (NDOH, 2008). In 2005 national ARV sites were established in South Africa but the number of people receiving ARV's was lower than expected (HIVSA, n.d.).

More people started to disclose their HIV status as awareness spread and treatment became available. In 2003 a famous Yfm DJ named Khabzela (Fana Khaba) pre-recorded his disclosure and it was aired in the breakfast show. DJ Khabzela then passed away on 14 January 2004 after defaulting on his antiretrovirals (Siyayinqoba Beat It!, 2004). To promote awareness both Dr Mangosuthu Buthelezi, head of the Inkhata Freedom Party and President Mandela shared a common platform to inform the country about their sons (Happold, 2005). The son of Dr Mangosuthu Buthelezi, Prince Benedict Nelisuzulu died on 29 April 2004 and President Mandela's son, Makgatho Mandela died in 2005. Both died of HIV/AIDS related illnesses (Happold, 2005). Sowetan columnist, Lucky Mazibuko, was the first self-declared HIV-positive journalist in South Africa and a strong HIV-activist (Dlamini, 2014). He stated that the government of the time (2003) was not doing enough to stop the discrimination and wrote "We must rise up, defy the social ills, and stand up for our right to life. Aluta continua! - Fare thee well!" (Point of view, 2003, para.21).

Lucky Mazibuko also received an award in 2011 for actively fighting the HIV/AIDS pandemic (Xaba, 2011). The aim of these disclosures was to strip HIV/ AIDS of stigma and raise awareness that HIV is a disease of humans. The awareness would enable those infected and affected by HIV/AIDS to go and look for ways of limiting HIV's progression to AIDS.

The South African HIV/AIDS "drama" continued, when it caused another world fiasco at the XVI Global AIDS Conference held in Ontario Toronto from 13-16 August 2006. The

then National Health Minister Manto Tshabalala-Msimang got her world known name “Doctor Beetroot” at this conference as she insisted that the South African display stall consisted of beetroot, lemon and garlic, promoting nutrition rather than antiretroviral drugs. After severe international public criticism of the stall, South Africa hastily put two bottles of antiretroviral medication on the stand. In the closing ceremony South Africa was ruthlessly criticised by the Africa’s AIDS Special Envoy UN general secretary for mismanagement of HIV/AIDS in the country (Health-E, 2006).

There was slight political improvement when Nozizwe Madlala-Routledge, an HIV activist, served in the second term of President Mbeki’s cabinet as a Deputy National Minister of Health, she started to promote the prevention of HIV through awareness programmes (Sexuality Information and Education Council of the United States [SIECUS], n.d.). Madlala–Routledge was a Communist Party member since 1984 and was appointed as the National Deputy Minister of Health during April 2004 to 8 August 2007. Madlala Routledge is famously known for her anti denialist response to HIV and a strong advocator of antiretroviral medication. She promoted access to antiretroviral treatment, spoke openly to TAC and tested herself for HIV in public (SIECUS, n.d.). On 8 August 2007 Nozizwe Madlala–Routledge was officially fired by President Thabo Mbeki, shortly after returning from Spain where she attended an international AIDS conference, because she acted against Mbeki’s approach to HIV/AIDS (SIECUS, n.d.).

South Africans only really had sufficient support from the government from 2008 when the interim President Kgalema Mothlanthe and the then National Minister of Health Minister Barbara Hogan, launched the National Strategic Plan 2007–2011 which enhanced “Option A” PMTCT programme. The paramount aim was to reduce mother-to-child transmission of HIV from 12% in 2008 to less than 5% by 2011 (Barron et al., 2013). In 2008 South Africa implemented dual therapy that included azidothymidine (zidovudine) and nevirapine. The TAC criticized government for not giving the best available treatment to pregnant women that would have included Lamivudine during labour and in postpartum period (Barron et al., 2013).

Exponential progress was made after the inauguration of President Jacob Zuma who appointed Dr Aaron Motsoaledi as a National Health Minister. On the 02 November 2005 another scandal rocked the HIV community after Jacob Zuma was accused of having unprotected sex with an HIV-positive woman. He claimed that he took a shower after the deed so as to cleanse himself of HIV ("SA's Zuma 'showered to avoid HIV", 2006). It has been noted in the above paragraphs that antiretrovirals are superior in slowing down AIDS progression.

2.5 Development of Antiretroviral Drugs

South Africa is viewed as the largest antiretroviral therapy user in the world as about 2.5 million people are on ARV medication (Bekker et al., 2014). Multiple drugs are used to control the progression of HIV into AIDS. The main objective of multiple drug use is to counteract drug resistance and retain the effectiveness of the drugs. Dr. Jerome Horwitz, a chemist and medical researcher at the Barbara Ann Karmanos Cancer Institute and Wayne State University synthesized zidovudine (AZT) in 1964 in search of a cure for cancer (Langer, 2012). Zidovudine was not a cure for cancer but 23 years later in 1987, became the first drug registered at the American Food and Drug Administration (FDA) for the treatment of HIV infection (Langer, 2012). Monotherapy of AZT was shown not to be effective due to the HIV's ability to develop resistance and researchers introduced a combination of drugs in 1995, which in the beginning were referred to as cocktails (Scott et al., 1996; Verville, 2013). Cocktails contained two or more ARV's and was commonly called Highly Active Antiretroviral Theraphy (HAART) (Verville, 2013). Due to the possible development of resistance when a person is on monotherapy most countries have started using at least two Nucleoside Reverse Transcriptase Inhibitors (NRTI) and one Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) or Protease inhibitor (Verville, 2013).

Currently five drug classes are used as ARV therapies:

- Entry inhibitors (fusion inhibitors) blocks the HIV's ability to enter CD_4 cells (Rusconi, Scozzafava, Mastrolorenzo & Supuran, 2007; Verville, 2013);

- Integrase inhibitors inhibit the HIV from inserting its genetic material into cells as HIV requires integrase to complete the replication (Parczewski, Bander, Urbańska & Boroń-Kaczmarska, 2012; Verville, 2013);
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) cause molecular disruption of a key protein and thus prevent HIV from binding and disables replication of the virus (MacArthur et al., 2006; Verville, 2013);
- Nucleoside Reverse Transcriptase Inhibitors (NRTI) prevents incorporation of other nucleosides by HIV (Schweinsburg et al., 2005);
- Protease inhibitors (PIs) inhibit protease and prevent HIV from splitting by forming buds in the host membrane (Fun et al., 2011; Verville, 2013).

Table 2.1 shows the most common antiretroviral drugs and the time that the FDA approved the drug for treatment.

Table 2.1 FDA Approved Antiretroviral Drugs(AIDS info, 2015)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
Abbreviation	**Generic name**	**Brand name**	**FDA approved**
3TC	Lamivudine	Epivir	17 November 1995
ABC	Abacavir	Ziagen	17 December 1998
AZT/ZDV	Zidovudine	Retrovir	19 March 1987
D4T	Stavudine	Zerit	24 June 1994
Ddl	Didanosine	Videx EC	31 October 2000
FTC	Emtricitzbine	Emtriva	02 July 2003
TDF	Tenofovir	Viread	26 October 2001
Combined Nucleoside Reverse Transcriptase Inhibitors (CNRTI)			
Abbreviation	**Generic name**	**Brand name**	**FDA approved**
ABC + 3TC	Abacavir/Lamivudine	Epzicom (US) Abacavir/Lamivudine Kivexa (Europe)	02 August 2001
ABC+ AZT + 3TC	Abacavir/Lamivudine + Zidovudine	Trizivir	14 November 2000
AZT + 3TC	Lamivudine + Zidovudine	Combivir	27 September 1997
TDF + FTC	Emtricitzbine + Tenofovir	Truvada	02 August 2004
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
Abbreviation	**Generic name**	**Brand name**	**FDA approved**
DLV	Delavirdine	Rescriptor	04 April 1997
EFV	Efavirenz	Sustiva (US) Stocrin (Europe)	17 September 1998
ETR	Etravine	Intelence	18 January 2008
NVP	Nevirapine	Viramune	21 June 1996
	Rilpine	Edurant	20 May 2011
Protease Inhibitors			
Abbreviation	**Generic name**	**Brand name**	**FDA approved**
APV	Ampenavir	Agenerase	15 April 1999
FOS-APV	Fosamprenavir	Lexivar (US) Telzir (Europe)	20 October 2003
ATV	Atazanavir	Reyataz	30 June 2003
DRV	Darunavir	Prezista	23 June 2006
IDV	Indinavir	Crixivan	13 March 1996
LPV/ RTV	Lopinavir+ Ritanovir	Aluvia	15 September 2000
NFV	Nelfinavir	Viracept	14 March 1997
RTV	Ritonavir	Narvir	01 March 1996
SQV	Saquinavir	Invirase	06 December 1995
TPV	Tipranavir	Aptivus	22 June 2005
Fusion or entry Inhibitors			
Abbreviation	**Generic name**	**Brand name**	**FDA approved**
T-20	Enfuvirtide	Fuzeon	13 March 2003
MVC	Maraviroc	Celsentric (Europe) Selzentry (US)	18 September 2007
Integrase inhibitors			
RAC	raltegravir	Isentress	12 October 2007
Fixed Dose Combination (FDC)			
TDF, FTC/3TC, EFV		Atripla	12 July 2006

2.6 Burden of HIV/AIDS

Globally, it is estimated that between 71 million to 87 million people have been infected with the HIV since the beginning of the HIV/AIDS pandemic (The Joint United Nations Programme on HIV/AIDS [UNAIDS], 2014; World Health Organization [WHO], 2014b). It is estimated that between 36.9 million people were living globally with HIV by the end of 2014 (The Joint United Nations Programme on HIV/AIDS [UNAIDS], 2015). The global prevalence of people living with HIV has steadily increased since 2001 from between 29.8 million to 41.4 million in 2014 (UNAIDS, 2015). An estimated 15.8 million people had access to antiretroviral treatment by June 2015 and is one of the Sustainable Development Goals (SDGs) for the AIDS pandemic by the year 2030 (UNAIDS, 2015).

In Sub-Saharan Africa an estimate of 25.8 million people were living with HIV in 2014, which is approximately 70% of the global number of people living with HIV, this means that nearly one in every 20 adults is infected with HIV in Sub-Saharan Africa (UNAIDS, 2015). The incidence of new HIV infections decreased globally from 3.1 million in 2000 to 2 million in 2014 (UNAIDS, 2015). The total new HIV infections reported in Sub-Saharan Africa in 2014 was between 1.2 million and 1.5 million (UNAIDS, 2015). Nearly 25% (6.4 million) of people infected with HIV in 2013 lived in South Africa (Shisana et al., 2014; Avert, 2015). It is estimated that in 2015 about one-fifth of South African women were HIV-positive. Nearly 6.19 million people were living with HIV/AIDS in South Africa and the HIV prevalence was estimated to be at 11.2% (Statistics South Africa, 2015a).

The prevalence of children living with HIV in Sub-Saharan Africa during 2014 was estimated to be between 2.2 and 2.5 million (UNAIDS, 2015). Worldwide a decline of 58% in new HIV infections amongst children has been reported since 2000 (UNAIDS, 2015). The total new infections in children declined from 520 000 in the year 2000 until 200 000 in 2014 (UNAIDS, 2015). Despite several intervention programmes South Africa continues to have the highest burden of HIV disease (Table 2.2).

Table 2.2 Prevalence of HIV in selected countries in 2011(UNAIDS, 2012)

Country	People Living with HIV	Women with HIV	Children with HIV
Botswana	300 000	100 000	15 000
Kenya	1 600 000	800.000	220.000
Lesotho	320 000	170 000	41 000
Malawi	910 000	430 000	170 000
Nigeria	3 400 000	1 700 000	440 000
South Africa	5 600 000	2 900 000	460 000
Swaziland	190 000	100 000	17 000
Uganda	1 400 000	670 000	190 000
Tanzania	1 600 000	760 000	230 000
Zimbabwe	1 200 000	600 000	200 000

Programmes for the prevention of mother-to-child transmission were internationally implemented since 2000, although South Africa started to implement these programmes in 2002. The results of the first national antenatal survey on the prevalence of HIV amongst pregnant women in South Africa was conducted in 1990 and found that 0.8% of pregnant women were infected (Barron et al., 2013). The prevalence of HIV rose remarkably over the years from as low as 0.8% in 1990 to as high as 40.7% in KwaZulu-Natal in 2004 (Barron et al., 2013). The antenatal HIV prevalence varies between the provinces and has stabilised round about 29.5% since 2004 (NDOH, 2013b).

2.7 Mortality and Economic Burden Related to HIV/AIDS

Knowledge of the HIV/AIDS pandemic became global and to spread awareness December the 1st was declared as a “World AIDS” day and has been commemorated since 1988 (South African History Online [SAHO], (n.d.) . People dying of AIDS or AIDS related illnesses has declined from 2.7 million in 2005 to 1.6 million in 2014 (UNAIDS, 2015). Co-morbidity with tuberculosis is still a danger although the percentage of tuberculosis people who commenced ARV treatment has risen to 77% by 2014 (UNAIDS, 2015). This decrease may be due to the increase of antiretroviral medicine coverage (UNAIDS, 2015). South Africa continued with the highest HIV burden and reported 270 000 HIV related deaths followed by Nigeria at 210 000 deaths in 2011 (UNAIDS,

2012). Co-morbidity with tuberculosis is a major contributory factor in AIDS related deaths (UNAIDS, 2015).

The overall number of deaths increased sharply in South Africa and deaths directly linked to HIV and AIDS reached a peak of 345 607 in 2005 (Statistics South Africa, 2015a). Since the availability of ARV's the AIDS related deaths have declined to 162 445 in 2015 (Statistics South Africa, 2015a). The infant mortality rate is a good indicator of the level of health in a country and presents the number of deaths of infants under the age of one year given per 1 000 live births in that same year (Indexmundi, 2015). The increase in infant mortality rate could also be ascribed to the increase in HIV prevalence. The infant mortality rate, increased from 44 deaths per 1000 infants in 1990, and reached a peak of 62.84 in 2004 (Indexmundi, 2015). The infant mortality rate has declined steadily after the implementation of PMTCT programmes to about 34.4 per 1 000 in 2015 (Statistics South Africa, 2015a). Although South Africa is still ranked number 55 amongst the 221 countries with high infant mortality rates, the steady decrease is an achievement (Countries of the world, n.d.).

South Africa also had a very high maternal mortality rate (300/100 000 live births in 2010) (Indexmundi, 2015). Maternal deaths related to HIV infection complicated by tuberculosis accounted for 40.5% of the maternal deaths (National Department of Health [NDOH], 2012). Pattinson, Fawcus and Moodley (2012) reported a decrease of institutional maternal mortality rate (iMMR) due to non-pregnancy related infections (HIV/AIDS) for underlying maternal causes of death from 71.29 % in 2008-2010 to 53.26 % in 2011-2012. Although the overall death rate due to HIV/AIDS has decreased there was an increase in maternal deaths related to antiretroviral therapy complications from 3.7% in 2008-2010 to 10.2% in 2011-2012 (Pattinson et al., 2012). Although complications of ART are reasonably rare it is of concern and the increase in death due to ART complications most probably may be attributed to the use of NVP, which may lead to liver failure or Stevens-Johnson syndrome (Chweneyagae et al., 2012).

Four million of the 130 million babies born globally every year die within thirty days after their birth, with nearly 100 million of these deaths occurring in Sub-Saharan Africa (Lloyd & de Witt, 2013; Research Unit, 2013; You, Bastian, Wu & Wardlaw, 2013). In Sub Saharan Africa one in every nine children dies before celebrating his/her fifth birthday (Lloyd & de Witt, 2013; Research Unit, 2013; You et al., 2013). One of the Millennium Development Goals (MDG) was to decrease the infant mortality rate to 18 deaths per 1000 live births by 2015, but this goal was not reached as the infant mortality rate was still as high as 23.6 deaths per 1 000 live births in 2013 (Statistics South Africa, 2015b). One of the major pathological preventable and treatable causes of neonatal and infant deaths is the successful implementation of PMTCT programmes to prevent HIV transmission (Velaphi & Rhonda, 2012).

Infant mortality rate (IMR) refers to the number of children who died under the age of one year, divided by the number of live births in that particular year (Bradshaw, 2007). Infant mortality has declined steadily after the implementation of PMTCT programmes to 54 per 1 000 live births in 1998 to 23.6 deaths per 1 000 live births (Statistics South Africa, 2015b). Although South Africa is still ranked amongst the countries with the highest infant mortality rates (55/221), the steady decrease is an achievement (Countries of the world, n.d.). In addition to the loss of lives and income it is estimated that about 21.7 billion USA dollars are being spent on HIV/AIDS resources, such as research, programmes and treatment (UNAIDS, 2015).

2.8 Prevalence of Maternal to Child Transmission of HIV

The transmission of HIV from women to their infants occurs during pregnancy, birth and through breast feeding. An exponential decrease has been observed since 2008 when nurse initiation of ARV therapy (NIMART) was implemented at all primary healthcare facilities (Barron et al., 2013). Maternal to child HIV vertical transmission decreased from 9.6% in 2008 to 2.4% in 2012, but the target of “Zero new infections due to mother-to-child transmission“ (Heywood, 2011) has not yet been reached (Sherman, Lilian, Bhardwaj, Candy & Barron, 2014). With 2.4% prevalence in 2012 it may well be possible

to reach a less than 2% maternal to child vertical transmission (MTCT) as proclaimed by the Eastern Cape Provincial Government by 2015 (ECAC, 2011).

2.9 Antiretroviral Coverage

Fitzgerald, Penazzato and Gibb (2013) argued that despite on-going innovations in antiretroviral medication and scaling up of coverage, only 28% of children versus 58% of adults globally received ARV treatment. The UNAIDS factsheet showed very little improvement in access to ARV treatment in 2013 (UNAIDS, 2014). There is an urgent need to offer treatment to children younger than two years as they are easily susceptible to drug resistance (Fitzgerald et al., 2013). In 2013 an estimated 12.9 million people received antiretroviral treatment globally compared to 5.2 million in 2009 (UNAIDS, 2014). This represents only about 37% of all people living with HIV (UNAIDS, 2014). Furthermore, fewer men (67%) than women are receiving ARV treatment (UNAIDS, 2014). Nearly 80% of people living with HIV in Nigeria do not have access to ARV treatment, whilst nearly 41% (2.6 million) of all people living in South Africa are receiving antiretroviral treatment (UNAIDS, 2014). By June 2015, less than half (15.8 million) of the 36.9 million people living with HIV had access to ARV medication (UNAIDS, 2015).

2.10 Millennium Development Goals

The research took place before the end of the Millennium Development Goals (MDGs), 2015. The Eight Millennium Development Goals (MDGs) were established at the Millennium Summit of the United Nations that was held from 6-8 September 2000 in New York where all the United Nations member states committed to uphold the adoption of the goals (United Nations, 2000). The world leaders stated unanimously that "Only through broad and sustained efforts to create a shared future, based upon our common humanity in all its diversity, can globalization be made fully inclusive and equitable" when they adopted the eight MDGs on 8 September 2000 (United Nations, 2000, para.1). All leaders agreed to achieve these goals by the year 2015. South Africa was among the member states and agreed to tailor its policies according to the MDG's. Four of the MDG's are

relevant to this project and will be discussed below (The Joint United Nations Programme on [HIV/AIDS] UNAIDS, 2011).

2.10.1 MDG 3: Promote Gender Equality and Empower Women

The promotion of gender equality and empowerment of women ensures that policy makers draft policies that address reproductive health issues, such as access to ARV treatment for all women and their partners. Ensuring the right to education allows women to read information or literature that could assist them to be knowledgeable about transmission and treatment of HIV. Empowered women are at a better stance to make decisions of how many and when they would like to have children in an effort to save their own lives. Furthermore, empowered women are in a better position to care and protect their children (UNAIDS, 2011).

South Africa has made considerable advancement to promote gender equality and to empower women in South Africa by achieving five of the seven indicators by 2015 (Statistics South Africa, 2015b).

2.10.2 MDG 4: Reduce Child mortality

Child mortality is four to six times higher in children who have lost their mothers (Atrash, 2011). Treatment, care and support of infants and children born from HIV-positive mothers need to be prioritized so as to reduce infant/child mortality. Maternal health should be improved to ensure optimal feeding practices of infants and children. Family, child infant and neonatal care environment needs to be improved (UNAIDS, 2011). None of MDG 4 targets were met, but important progress has been made by increasing the vaccination coverage of children (Statistics South Africa, 2015b). One of the major impediments has been the unsuccessful implementation of programmes such as the PMTCT programme to decrease child mortality (Statistics South Africa, 2015b). The new Sustainable Development Goals (SDGs) has once again prioritised child survival (Statistics South Africa, 2015b).

2.10.3 MDG 5: Improve Maternal Health

Health systems need to be strengthened and all mothers must have access to antenatal care and the right to be assisted by a skilled health worker during pregnancy, labour birth and the postpartum period. Health systems need to be strengthened to ensure early detection of HIV and early enrolment in treatment programmes to ensure the safety of each birth. Appropriate family planning should be given to all women including HIV-positive women in an effort to lessen the chances of unplanned pregnancies. Availability of ARV treatment or any other required treatment, care or support to HIV-positive mothers should be prioritized (UNAIDS, 2011; WHO, 2014b).

2.10.4 MDG 6: Combat HIV/AIDS, malaria and other disease.

Comprehensive and appropriate knowledge regarding HIV prevention, testing and treatment should be made available to all women of childbearing age. All women with HIV/AIDS should have access to ARV treatment. Mothers who are HIV-positive and who choose to breastfeed should also be encouraged to do so and receive ARVs to prevent vertical transmission to their infants. Early detection of co-morbidity with tuberculosis and malaria should be identified and treated (UNAIDS, 2011). Sadly, none of MDG 5 indicators were met and the maternal mortality remains high in South Africa (Statistics South Africa, 2015b). Acknowledgement needs to be given to the strong support for PMTCT programmes the last few years, which not only saved maternal lives but also decreased MTCT of the HIV. It is estimated that more than 80% of HIV-positive women received ARV treatment by 2014 (Mureithi, 2015).

2.11 Intervention Strategies

Prevention of mother-to-child transmission (PMTCT) refers to a four-pronged strategy to prevent new HIV infections in children and keeping mothers alive and families healthy. The four prongs are: halving HIV incidence in women; reducing the unmet need for family planning; providing antiretroviral prophylaxis to prevent HIV transmission during pregnancy, labour, delivery, breastfeeding; and providing care, treatment; and support for

mothers and their families. Some countries prefer to use the term “vertical transmission to acknowledge the role of the father/male sexual partner in transmitting HIV to the woman and to encourage male involvement in HIV prevention” (Heywood, 2011, p. 7).

The vertical transmission of the HIV from an HIV-positive mother to her foetus or infant could occur during pregnancy, labour, delivery, and breast or mixed feeding and each phase confers a different risk (European Centre for Disease Prevention and Control [ECDC], 2012). Mother-to-child transmission (MTCT) of the HIV was acknowledged as one of the major sources of new HIV infections (ECDC, 2012). Researchers recorded different rates of MTCT of HIV in the absence of any ARV treatment during the different stages of childbearing. It is stated that the risk of MTCT, in the absence of ART, varied between 5-20%, during pregnancy, 10-40% during labour and delivery and between 5-20% during the postpartum period (Bertolli et al., 1996; National Department of Health [NDOH], 2008). It is further claimed that with appropriate antiretroviral therapy, MTCT of HIV can be reduced to 2% (World Health Organisation [WHO], 2006).

The World Health Organization has developed and distributed four different PMTCT programmes in an effort to try and reduce MTCT of HIV over the last 13 years with the first recommendations being published in the year 2000 (World Health Organisation [WHO], 2001). South Africa has implemented four PMTCT programmes since 2002 and has embarked on a new PMTCT programme in 2015 (NDOH, 2015).

The World Health Organization improved its guidelines based on new evidence that became available and issued the second PMTCT guidelines in 2006 that was referred to plan Option A (WHO, 2006). In 2008 the Minister of Health launched the National Strategic Plan 2007–2011 which included some of the aspects of the original WHO Option A PMTCT programme, but did not include Lavumidine (3TC) during labour and the postpartum period. The paramount aim was to reduce mother-to-child transmission of HIV from 12% in 2008 to less than 5% by 2011 (Barron et al., 2013).

The HIV/AIDS activist organisation, Treatment Action Campaign (TAC), criticized the government for not giving the best available treatment to pregnant women which would have included Lamivudine. At World AIDS Day 2009 President Zuma mentioned additional treatment changes that would be executed in 2010. This gave the HIV/AIDS pandemic a political stature (Barron et al., 2013). South Africa reaped the fruits of political back up by President Zuma and introduced the third set of guidelines during 2010, which were fully aligned with WHO option A guidelines.

The Department of Health established a national action framework for eliminating vertical transmission of HIV in line with a call from global agencies (Barron et al., 2013). In 2011 National Health Minister of South Africa (Minister Dr. A Motsoaledi, issued a policy that breastfeeding should be exclusively used at public health facilities and formula milk be solely kept for medical indications and that the free formula milk should be stopped.

In 2012, WHO introduced a third option called B+. Option B+ recommends inclusion of pregnant women at all levels of CD_4 count for HAART. Option B+ proposed not only providing the same triple ARV drugs to all HIV infected pregnant women beginning in the pre-birth clinic but also continuing this therapy for life for all of these women (WHO, 2012b). The latest amendment to PMTCT treatment programmes was announced on 8 April 2013 when the Minister of Health launched the fixed dose combination (FDC) (NDOH, 2013a). The FDC is a combination of emtricitabine (FTC), efavirenz (EFV) and tenofovir (TDF) antiretroviral drugs. Expectant mothers would stay on treatment until they complete breastfeeding. Women would continue on treatment should their CD_4 count be 350 or below, this policy once again deviated from WHO guidelines (National Department of Health [NDOH], 2013c).

Dr Aaron Motsoaledi, Minister of Health, in 2014, made an announcement that overruled the previous stance on terminating ARV use for pregnant women who have a CD_4 count that is above 350 after cessation of breastfeeding (SAPA, 2014). President Zuma affirmed the statement made by Dr Motsoaledi, and said that to enhance health care all pregnant HIV-positive women should continue after cessation of breastfeeding, on

lifelong ARV's irrespective of their CD_4 count (The Presidency, 2014). This conforms to the 2013 WHO guidelines.

South Africa has tried to stay abreast in adjusting the PMTCT policies but the question that can be asked is whether the policy is based on best evidence.

2.12. The National Committee for the Confidential Enquiries into Maternal Deaths

The National Committee for the Confidential Enquiries into Maternal Deaths (NCCEMD) has been in operation in South Africa since 1 October 1997 and it gives a summary of confidential enquiries into maternal deaths that occur in maternal obstetric institutions over a three year period (Pattinson et al., 2012). The NCCEMD was formulated as a response to the rising number of non-pregnancy related maternal mortality rates. In 2005-2007, HIV/AIDS (43.7%) was the leading cause of maternal deaths followed by: complications due to hypertension (15.7%), obstetric haemorrhage (12.4%), pregnancy-related sepsis (9.0%) and preceding maternal disease (6.0%). Task teams were formed to investigate the causes of maternal deaths and they identified a deficiency of essential skills among health professionals as one of the major contributing factors to the high maternal deaths. Several training programmes were recommended to empower health professionals. The institutional maternal mortality rate (iMMR) has shown a steady decrease since 2010 from 176.22/100 000 live births to 146.71 in 2012. The decrease in iMMR can mainly be attributed to the initiation and implementation of PMTCT programmes (Pattinson et al., 2012).

2.13 World Health Organization PMTCT Programmes

The World Health Organization first published the PMTCT guidelines in 2000. In 2006 the WHO improved their guidelines based on new evidence that became available and issued the second PMTCT guidelines that was referred to as "Option A" (WHO, 2006). This guideline included giving infants antiretroviral medication for seven days after birth, referred to as the "cover the tail". The importance of cover the tail is evidenced in the work of Six Week Extended-Dose Nevirapine (SWEN) Study Team (2008) where it was

found that extended use of ARV's can reduce infant mortality. The World Health Organization continued to update their PMTCT guidelines in 2010 and 2012 as new evidence became available (WHO, 2012b).

2.14 South Africa PMTCT Programmes

Activities relating to the prevention of mother-to-child transmission in South Africa can be traced back to 1999 and that was against the National Department of Health and the governance of the African National Congress. Initially the ANC government did not support legal dispensation of ARV medication to pregnant women. The Western Cape Province commenced a short course mono-therapy Zidovidine MTCT programme at two midwifery obstetrics units in January 1999 in Khayelitsha, with the aim to reduce the vertical transmission of the HIV from the mother to her child from 30% to less than 15% (Abdullah, Young, Bitalo, Coetzee & Myers, 2001). This programme was financially supported by Médecins Sans Frontières and the results showed that voluntary counselling and testing was acceptable in the community (Hodes & Naimak, 2011; Abdullah et al., 2001).

A pharmaceutical company, Boehringer-Ingelheim, sponsored a randomised controlled trial between May 1999 – February 2000, where single dose Nevirapine was evaluated against a combination of Zidovidine and Lamivudine in eleven public hospitals situated in Gauteng and KwaZulu Natal (Moodley et al., 2003). The aim was to reduce intrapartum and early postpartum HIV transmission from the mother to her child. The study showed that both Nevirapine and a combination of Zidovidine and Lamivudine were effective and safe to reduce MTCT in women who administered replacement feeds to their infants (Moodley et al., 2003).

Contrary to the success of MTCT reduction reported by Abdullah et al. (2001) and Moodley et al. (2003), Doherty, McCoy and Donohue (2005) reported on the poor effect of the routine national PMTCT programme that was rolled out in 2002 at 18 pilot sites, two from each province. The results of the pilot study showed poor implementation such

as unavailability of ARV medicine at the sites which seriously reduced the effectiveness of the implementation of PMTCT programme (Doherty et al., 2005).

In November 2003, the National Department of Health claimed to scale-up the availability of ART and issued the Operational Plan for Comprehensive HIV and AIDS care, management and Treatment for South Africa (National Department of Health [NDOH], 2003). The plan allowed for the provision of nevirapine (NVP) and the treatment to at least one ART site in every district. A further event that developed after the roll out of the National plan was health-care services, such as the voluntary counselling and testing programme.

In 2004 the National Department of Health introduced the "National Antiretroviral Treatment Guideline", which was an all-inclusive care management and treatment of HIV-infected individuals. The eligibility criteria included pregnant women with a CD_4 T-cell count < 200 cells/mm^3 (NDOH, 2008).

In 2008 the Minister of Health, Manto Tshabalala-Msimang, launched the National Strategic Plan (2007–2011), which enhanced "Option A" PMTCT programme. The paramount aim was to reduce mother-to-child transmission of HIV from 12% in 2008 to less than 5% by 2011 (Barron et al., 2013). In 2008 South Africa implemented dual therapy that included azidothymidine (zidovudine) and nevirapine. The Treatment Action Campaign (TAC) vehemently criticized the government for not giving the best available treatment to pregnant women, which would have included Lamivudine during labour and the postpartum period (Barron et al., 2013).

To scale up HIV testing in pregnant women, South African government formulated a new HIV counselling and testing (HCT) policy. The policy shifted from a voluntary counselling and testing approach to one that is seen as a "provider-initiated" approach. Pregnant women are now routinely tested and actively have to "opt out" if they refuse to be tested. This refusal should be recorded in their antenatal clinic card (National Department of Health [NDOH], 2009). Further counselling, advice and referral for the "opt outs" should

be done in a non-coercive manner to promote knowing one's HIV status and to offer them treatment to prevent transmission to their infant.

The main differences between WHO and Republic of South Africa 2010 regimens are as follows:

- The World Health Organization only mentions two categories of pregnant women i.e. those with CD_4 counts above and below 350 cells / mm^3. Contrary to this, the South African guidelines referred to women with CD_4 counts above and below 350 cells /mm^3 but also included women who were un-booked and those that present in labour not knowing their HIV status (NDOH & SANAC, 2010).
- The guidelines also differ with regard to the infant treatment recommendations, where South African guidelines include two additional categories that are eligible to receive ART: infants born from mothers who did not get any ARV therapy before or during delivery or born to mothers with unknown HIV status (NDOH & SANAC, 2010).
- Two options for breastfeeding mothers were recommended (i.e. Option A and Option B). In "Option A", NVP was administered to the infants during the period of breastfeeding (NDOH & SANAC, 2010; WHO, 2010).
- "Option B", HAART was recommended by WHO (2010) but not implemented at the time by South Africa. "Option B" promoted HAART to lactating mothers until breastfeeding was discontinued (WHO, 2010).

In relation to infant feeding options, the National Health Minister of South Africa (Minister A Motsoaledi), supported Tshwane declaration in 2011 that breastfeeding should be exclusively used at public health facilities and formula milk only be kept for medical indications and that the policy of free infant formula milk should be stopped immediately (News, 2011; Barron et al., 2013; du Plessis, 2013). The Department of Health established a national action framework for eliminating vertical transmission of HIV in line with a call from global agencies (Barron et al., 2013). Prohibition of the provision of free milk formula feeds also lessened the financial burden of provincial expenditure (Kouandaa et al., 2010. The Department of Public Service and Administration issued a

second draft for child care facilities in the Public Service further supporting the cessation of free formula milk dispensation to HIV-positive women (Department of Public Service and Administration [DPSA], 2012). To promote breastfeeding the guideline further encourages employers to allow women to nurse their infants at the work place (DPSA, 2012).

In 2012, WHO introduced a third option called “Option B+” (WHO, 2012b). Guideline “Option B+” recommends inclusion of pregnant women at all levels of CD_4 count that are eligible for HAART (WHO, 2012b). Okonji et al. (2012) stated that; for maximal benefits on PMTCT pregnant women should be initiated early to ARVs. “Option B+” not only provides the same triple ARV drugs to all HIV infected pregnant women beginning in the pre-birth clinic but also continuing this therapy for life (WHO, 2012b).

On the 8th of April 2013 the Minister of Health of South Africa, launched the fixed dose combination (FDC) treatment pill for people diagnosed with HIV/AIDS (NDOH, 2013a). The FDC is a combination of emtricitabine (FTC), efavirenz (EFV) and tenofovir (TDF) antiretroviral drugs (NDOH, 2013c). Expectant mothers were said to stay on treatment until they complete breastfeeding. They would continue on treatment should their CD_4 count be 350 cells / mm^3 or below, this policy was once again not compliant to the WHO guidelines as WHO recommends that pregnant women on “Option B+” should stay on antiretroviral medication for life (WHO, 2012b; NDOH, 2013c).

The latest amendment on ARV treatment for pregnant and breastfeeding women was announced by Minister A Motsoaledi on 23 July 2014 where he stated that as from January 2015 eligibility criteria for CD_4 would be increased from 350 to 500 cells / mm^3 and women that were on PMTCT would continue on ARV treatment for life. This conforms to WHO Option B+ guideline of 2012 (SAPA, 2014; The Presidency, 2014).

2.15 Better Births Initiative

The better births initiative began in South Africa in 2000. The aim was to improve the obstetric care in poor resource settings for women and to ensure that all women were treated with respect and received the treatment of care such as ART during pregnancy and birth (Smith & Garner, 2002).

2.16 Basic Antenatal Care (BANC)

The Basic antenatal care (BANC) training programme augments knowledge of healthcare professionals who work in primary health care facilities and was implemented in 2005. The difference in this guide is that, it actually provides evidence and reasons for why certain procedures should be implemented. In other words the guidelines are based on the most recent evidence available. It explains the rationale for why women should receive HIV counselling and testing during pregnancy to make informed decisions and to adequately care for their babies. If women understood the reasons for why infants are dying they would be better able to understand the implications of testing (Pattinson, 2005).

2.17 National Perinatal and Neonatal Morbidity and Mortality Committee

The late Minister of Health Dr Tshabalala-Msimang established the National Perinatal and Neonatal Morbidity and Mortality Committee (NaPeMMCo) in March 2008 to keep an audit of and to identify the pathological and health systems related causes of perinatal and neonatal deaths (Velaphi, 2009). This committee was tasked to provide interim annual and comprehensive triennial reports to the National Minister of Health. The committee recognised that comprehensive antenatal care and effective PMTCT programme could significantly reduce perinatal and neonatal deaths. Recommendations from the annual and the triennial reports support the importance of exclusive breastfeeding for HIV-positive women and infants who are on antiretroviral medication.

The report further recommends that all pregnant women should receive counselling and be encouraged to test for HIV in an effort to protect their infants against vertical transmission of HIV (Velaphi, 2009). The 2008-2010 report identified a vast gap in the health care system that about 37% of the infants which died in the hospitals were born to HIV-positive women. Moreover, in about 50% of all the deaths it was unknown whether infants were exposed to perinatal antiretroviral medication and nearly half of infants who were eligible to receive ARV's did not get them after birth (National Perinatal Morbidity and Mortality Committee [NaPeMMCo], 2011). The committee supports the stance that all HIV-positive women should get ARV treatment either through PMTCT or HAART and all infants who are HIV-exposed should receive ART prophylaxis (NaPeMMCo, 2011). Polymerase chain reaction (PCR) testing should be done on all infants at six weeks of age and HIV infection should be normalised as any other chronic disease (NaPeMMCo, 2011).

2.18 Emergency Steps in Managing Obstetric Care

The National Committee for the Confidential Enquiries into Maternal Deaths (NCCEMD) has made several recommendations regarding enhancement of training for health care professionals to reduce maternal and neonatal mortality rates. The Essential Steps in Managing Obstetric Emergencies (ESMOE) and Emergency Obstetric Scenario Training (EOST) was developed by the Royal College of Obstetricians and Gynaecologists and their International Office (Pattinson, 2010). South Africa has adapted this programme and formulated a training guide that was piloted at several sites since 2007. Frank, Lombaard, and Pattinson (2009) conducted an evaluation on interns who completed the ESMOE training programme and reported that the interns were better skilled and vigilant after completing the programme. The package does not only address emergency intervention but also strengthens the importance of the concept that women in labour who tested positive should be on ARV's and that every newborn infant born to an HIV-positive mother must get ARV treatment before the infant and mother leave the primary health care facility.

2.19 HIV Counselling and Testing (HCT) Drive

In April 2010, President Jacob Zuma and Dr. Aaron Motsoaledi the National Minister of Health launched the largest scale-up HIV counselling and testing campaign effort in the world by trying to test 15 million people before the end of June 2011. To achieve this goal many more primary health care facilities had been accredited to test, prevent, treat and care for people living with HIV/AIDS (The Presidency, 2011). Heywood (2011) reported that 1.7 million (16.6%) people tested HIV-positive out of 10.2 million people that voluntary opted to be tested, of these 1.4 million were put onto ARV medication (Health-e News, 2011).

2.20 Nurse Initiated Management of Antiretroviral Treatment (NIMART)

Nurse Initiated Management of Antiretroviral Treatment (NIMART) was established in 2010 (Crowley & Stellenberg, 2015). The NIMART followed the HIV Counselling and Testing (HCT) drive. The aim of NIMART was to decentralise ARV roll out to Primary Health Care (PHC) centres and professional nurses were to champion this programme. It was hoped that this programme would increase the uptake of antiretroviral medication and management of patients and decrease the workload of staff at secondary or tertiary hospitals. The NIMART programme allowed all pregnant women to be examined, diagnosed and be put on a PMTCT regime at their PHC clinics by a trained nurse practitioner. Tertiary referral was reserved for complicated cases (Nyasulu, Muchiri, Mazwi & Ratshefola, 2013).

2.21 Re-engineering of Primary Health Care clinics.

Pillay (2012) and Gray, Vawda and Jack (2013) refer to the re-engineering of Primary Health Care (PHC) facilities in South Africa as one of the key factors of the implementation of District Clinical Specialist Support team which includes: paediatricians, family physicians, obstetrician, anaesthetists, advanced midwives, advanced paediatric nurses and advanced PHC nurses. The support teams are to be deployed in each district to facilitate improved maternal and infant health concentrating on the availability of correct

implementation of PMTCT programmes and ensuring the availability of ARV treatment at PHC as primary health care clinics are easily accessible for pregnant women. Pillay (2012) furthermore emphasized the issue that school nurses should be re-introduced and educate school going children on the sexual and reproductive health issues that include HIV/AIDS and medical male circumcision.

2.22 Tshwane Declaration (2011)

A meeting of key stake holders took place on 22-23 August 2011 in Gauteng to review the policy of free dispensation of formula feeds to women who opt to formula feed their infants when HIV-positive (News, 2011). A resolution was taken that all free formula milk at primary health clinics and hospitals shall cease and that formula milk may only be prescribed for medical reasons. The resolution was based on evidence that MTCT of HIV can be reduced to less than 2% in HIV-positive mothers who receive antiretroviral medication during pregnancy, birth and who exclusively breastfeed their infants up to six months (Saloojee, Gray & McIntyre, 2011). Infants born to HIV positive mothers were also recommended to receive antiretroviral medication (News, 2011).

2.23 Voluntary Medical Male Circumcision

Male Medical Circumcision (MMC) was implemented according to WHO and UNAIDS 2007 recommendations as a key prevention strategy in preventing and promoting the reduction of vertical transmission of HIV from the mother to her infant (United Nations Children's Fund [UNICEF], 2010; World Health Organisation [WHO], 2016). The South African National Strategic Plan (NSP) for HIV, STI's and Tuberculosis (2012-2016) calls for the implementation of MMC as a comprehensive part of PMTCT of HIV (Heywood, 2011). It is claimed that voluntary MMC can reduce the risk of heterosexual vaginal transmission (Auvert, Taljaard, Lagarde, Sobngwi-Tambekou & Sitta 2005; Odendal 2013). The percentage is as much as 73% by five years (L'Engle, Lanham, Loolpapit & Oguma, 2014). The vigorous roll out of the MMC programmes in the country has accounted for more than 1.3 million medical male circumcisions performed since 2010, but this target is only about 31% of the 4.3 million target set for 2016 (Heywood, 2011).

2.24 Campaign for Accelerated Reduction in Maternal and Child Mortality in Africa

The Campaign for Accelerated Reduction in Maternal and Child Mortality in Africa (CARMMA) was launched on 4th May 2012 and promotes and advocates "for renewed and intensified implementation of the Maputo Plan of Action for Reduction of Maternal Mortality in Africa and for the attainment of MDG 5" (NDOH, n.d., p.8). The goal of CARMMA in South Africa is: "South Africa Cares: No woman should die while giving life" (Cadegan, English, Pillay & Barron, 2012, p. 3). The campaign has four key areas:

- Building on-going efforts particularly best practices;
- Generating and providing data on maternal and newborn deaths;
- Mobilizing political commitment and support of key stakeholders including national authorities and communities to mobilize additional domestic resources in support of maternal and newborn health and mobilizing communities to let them know that everyone has a role in improving maternal and child health and reduction of maternal and child deaths; and
- Accelerating actions aimed at the reduction of maternal, infant and child mortality in Africa. (NDOH, n.d. p.8).

The Campaign further encourages intensifying management for HIV–positive mothers and children by promoting treatment, improving management of co-morbidity and eliminating MTCT (NDOH, n.d).

2.25 The Maternal, Newborn, Child and Women's Health and Nutrition Strategic Plan 2012-2016

The Maternal, Newborn, Child and Women's Health and Nutrition Strategic Plan 2012-2016 was launched on the 4th May 2012. This programme applies a holistic approach that involves healthcare workers, mother child pair, families, and communities. The programme initiative upholds nutrition of pregnant women and breast feeding, including the promotion of breastfeeding for HIV-positive women. People are empowered on nutritional benefits to curb morbidity and mortality (NDOH, 2012; Cadegan et al., 2012)

2.26 The "Every Newborn Count" action plan was approved across the world in May 2014 at the World Health Assembly

The Every Newborn Action Plan (ENAP) is an action plan that was approved across the world in May 2014 at the World Health Assembly (World Health Organisation [WHO], 2014a). The main focus was to improve the survival of new-borns, enhance survival, development and health specifically of new-borns and their mothers and more specifically the "prevention of mother-to-child transmission of HIV" (WHO, 2014a). Programme managers and policy makers are urged to implement and champion the intervention on evidence based interventions.

2.27 MomConnect

MomConnect is one of the latest innovations by the National Department of Health implemented to improve maternal and infant health. Once pregnant women are registered they receive sms messages via cellular phones. MomConnect was launched by Dr A. Motsoaledi on the 21 August 2014 in Soshanguve. This innovation provides essential information about pregnancy and enhances the uptake of antiretroviral medication by mothers on PMTCT programmes (South African Government News Agency, 2014; Kotze, 2014).

2.28 Summary

An extensive history which can be traced back from 1930s and how HIV was transmitted from animals to people has been discussed. The ten celebrities that contracted HIV have been mentioned, the transmission route and emotions that accompanied the disclosure of their HIV statuses was explained. The intervention strategies discussed prove that the tide changed from an inactive response on the National government's side prior President Zuma's reign to the political back up that HIV is receiving in South Africa to date.

The research methodology will be described in chapter three.

Chapter Three
Research Methodology

3.1 Introduction

Research methodology is the theory of scientific decisions, which are taken within a specific framework and provides a method of logical reasoning when executing the research process (Saunders, Lewis & Thornhill, 2016; Creswell, 2014). The purpose of this dissertation was to execute a document review on the latest PMTCT policy guidelines to establish whether the PMTCT guidelines were formulated based on best evidence. A second objective was to systematically review literature that assessed the efficacy of ARV regimens to prevent mother-to-child transmission. It is important to describe the research methodology as the quality of the research findings is directly dependent on the rigorous execution of the research methodology (McGregor & Murnane, 2010).

Chapter three presents the research methodology used to collect, analyse and interpret the data in this project. The problem statement, aim and objectives of the study have been discussed in chapter one. Chapter three will commence with a theoretical grounding of the study. The detailed description of the research approach and the different research designs used to review the guidelines and to execute a meta-analysis of studies that assessed the efficacy of ARV regimens to prevent mother-to-child transmission will also be dealt with.

3.2 Theoretical framework

The study is based on Evidence Based Medicine (EBM) pioneered by Sackett et al. (1996). In this section the researcher will use Evidence Based Practice (EBP) instead of EBM which means individual clinical expertise is integrated with best available clinical evidence from a research that is systematically conducted (Polit & Beck, 2008). The EBP advocates for continuous training or capacitating personnel as new information becomes

available. The EBP does not put emphasis on expert opinion but on best evidence. Like any other theory EBP also has strengths and weaknesses which will be dealt with below:

Strengths

- Evidence based practice is a solution in improving quality of health care in cost constrained environment.
- An on-going learning is a prerequisite in the current technological advanced period.
- When there is not enough literature for a certain question posed a new research agenda can result. (Polit & Beck, 2008)

Weaknesses

- The EBP devalues patient inputs and individual clinical judgement.
- Less emphasis is put on qualitative research. (Polit & Beck, 2008)

This study counteracted the weaknesses by conducting both document analysis which is qualitative in nature and systematic review which is quantitative. Systematic reviews from randomised controlled trials are ranked the highest on the level of evidence (Polit & Beck, 2008). Below is a discussion regarding research design.

3.3 Research Approach and Design

Research approach refers to the “plans and the procedures for research that span the steps from broad assumptions to detailed methods of data collection, analysis, and interpretation” (Creswell, 2014, p.3). There are three main approaches to research: Quantitative approach (numbers related), qualitative approach (narratives) and mixed methods approach (Creswell, 2014; Saunders et al., 2016). Mixed methods is not merely referring to the combination of qualitative and quantitative data but the strategy of inquiry involves the collection, analysis and interpretation of information using specific research designs underpinned by philosophical assumptions. A mixed methods approach was used in this study as it is the most appropriate approach to qualitatively explore and

analyse PMTCT guidelines and to quantitatively describe the effectiveness of ARV regimens to prevent mother-to-child transmission systematically. A mixed method approach was used in this study as both the qualitative and quantitative method of analysis yield valuable information.

Lincoln, Lynham and Guba (2011) argued that research approaches are characterized by assumptions based on the researcher's distinctive typology, philosophical, ontology, epistemology, methodology and axiology position. A mixed methods approach is based on a post positivistic typology and uses a pragmatic philosophical position. Pragmatism is real-world orientated and proponents of pragmatism believe that "what works in practice and what promotes social justice" are important (Johnson & Christensen, 2012, p. 32).

The nature of reality (ontology) provides appreciation for subjective (individual), intersubjective (conversational or written) and objective reality (significant differences in effectiveness) (Johnson & Christensen, 2012). Ontologically, post positivists assert that reality exists, but it is influenced by social interactions. Post positivism recognizes that total objectivity is impossible but researchers strive to be as independent as possible from participants in order to reduce bias (Polit & Beck, 2008). The researcher therefore used a predesigned structure to systematically analyse the publications and review documents to prevent bias.

Assumptions about the theory of knowledge (epistemology) presume that what works in a specific context, thus evidence based PMTCT guidelines, would ultimately have social justice, and benefit to the community (HIV-positive pregnant women and their infants) specific needs. Pragmatic researchers acknowledge that qualitative and quantitative approaches have their own inherent limitations and therefore embarking on a variety of research designs complements each approach (Johnson & Christensen, 2012).

Document or content analysis was used to explore whether PMTCT policies were based on best evidence, whilst, a systematic meta-analysis of studies confirmed the efficacy of different PMTCT programmes. The ability to mix quantitative and qualitative approaches

has the advantage that results could be triangulated in an effort to strengthen the findings (Polit & Beck, 2008).

A concurrent triangulation research design was followed to execute this study (Kohlbacher, 2006; Creswell, 2014). Concurrent collection and analysis of quantitative and qualitative data took place and equal priority was given to both approaches (Creswell, 2014). Triangulation and integration took place during the analysis stage when the quantitative results from the systematic review of the publications were used to support recommendations stated in the PMTCT guidelines (Kitchenham et al., 2007; Creswell, 2014).

The methodology for qualitative document review is discussed first followed by the methodology used for the quantitative systematic review of literature.

3.4 Qualitative Phase

The next paragraphs will discuss the document analysis.

3.4.1 Review of PMTCT Guidelines

Policy guidelines contain powerful messages for the public and it is important that the messages are based on evidence and not on perceptions or idealistic concepts (Riffe, Lacy & Fico, 2014). Dukeshire and Thurlow (2002) suggested that policy makers need to engage in round table discussions together with academics and social scientists to ensure that guidelines are based on sound evidence. Countries including the United Kingdom and Canada recommend that a specific research strategy be used to assist policy-makers in ensuring that policy guidelines are built on a solid foundation of expertise and proven knowledge (Dukeshire & Thurlow, 2002).

Creating, revising or changing policy guidelines is usually a complex process and there are several factors that influence policy decisions (Zardo, Collie & Livingstone, 2014). Key people that influence PMTCT policy guidelines are government officials in the Health

Department, lobby or union groups and consumers (Zardo et al., 2014). Key influential people need to be targeted to ensure interventions aimed to improve policy guidelines are based on best evidence.

Document review refers to the process of collecting information by reviewing pre-specified documents using a systematic approach and making inferences to ensure that the information recommended by the decision-makers is based on best evidence available (Centers for Disease Control and Prevention [CDC], 2009). Riffe et al. (2014, p. 3) supported the previous view and claimed that document review refers to "the systematic assignment of communication [written] content to categories according to rules, and the analysis of relationships involving those categories using [scientific] methods".

The ultimate aim of a document review was to ensure that PMTCT policy guidelines were based on evidence that ensured the impact of the decisions that would affect the society in a favourable manner and that the policy implementers would implement the policy effectively (Bardach, 2012).

3.4.2 Qualitative Data Collection

A qualitative case study was chosen as the method to assess and evaluate whether PMTCT guidelines were based on best evidence (Kohlbacher, 2006). Using a case study to collect information fits well within a pragmatic philosophical viewpoint as the purpose was to assess and evaluate a single PMTCT programme and provide a detailed account on whether the programme was based on best evidence with the view to improve society (Baxter & Jack, 2008; Johnson & Christensen, 2012). A case study was chosen as a method of data collection because the focus is on why a specific statement was written in the PMTCT guidelines and on what basis was this statement written (Baxter & Jack, 2008). Furthermore, the written text (context) in the PMTCT guidelines cannot be manipulated, and text was assessed to evaluate whether statements in the guidelines were based on best evidence that would work in practice and promote social justice.

3.4.3 Unit of Analysis and Case Boundaries

The total population of documents consisted of twelve guidelines on PMTCT published by the World Health Organization and/or the National Department of Health, South Africa. Baxter and Jack (2008) and Miles, Huberman and Saldaña (2013) indicated that it is important to state the boundaries when a case study is used, because the scope could become too broad if boundaries were not set. In this study a single unit of analysis was selected namely the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015* (NDOH, 2015).

3.4.4 Content Analysis Method

Content analysis is an appropriate method to examine whether recommendations made in the PMTCT guidelines were based on evidence and aligned with the overall objectives of why the recommendations were made (Stemler, 2001; Kohlbacher, 2006). Kohlbacher (2006) asserted that content analysis should adopt a holistic approach and several definitions have been described since its inception. Stemler (2001) argued that content analysis is used to reduce information and could measure changes over time that evolved in documents, whilst Krippendorff (2004) stated that, content analysis is a scientific tool that allows replication of information and makes inferences that are valid from texts to contexts in which they are used.

Krippendorff (2004) mentioned six steps in undertaking content analysis:

- Unitising: Unitising refers to a systematic process where segments of texts are chosen because of the relatedness and interest to what needs to be analysed;
- Sampling: The total population was documents that reported on PMTCT guidelines published by the WHO and NDOH South Africa;
- Coding: Selecting words or sentences that needed to be based on evidence;
- Reducing: Reduction of codes was not applicable as only segments that needed to be based on evidences were selected;

- Inferring and narrating: The findings were recorded and the segments were supported with evidence from the literature.

The CDC (2009) recommended similar criteria as Krippendorff (2004) but added that, it is essential that one secures access to all the documents that need to be reviewed and that confidentiality is important when confidential documents are analysed. In this study only public published documents have been analysed, therefore there was no need for confidentiality. Another recommendation by CDC (2009, p. 2) was that the reviewer needed to have some insight into why the documents were produced and one of the major advantages of a document review is that it provides "behind-the scenes" or provides evidence in support of the recommendations, which is not always stated in the document. A disadvantage of the document review process is that it is time consuming and often evidence may not be found to substantiate the recommendations (Krippendorff, 2004; CDC, 2009).

3.4.5 Trustworthiness and Validity

Lincoln and Guba (1985) developed standards for trustworthiness of qualitative research in order to enhance quality and integrity for this type of methodology. The four criteria included: credibility, dependability, confirmability and transferability) (Lincoln & Guba, 1985). The researcher read and re-read the documents to ensure truth value and understanding of the guidelines. Consistency was kept by keeping a record and copies of all documents reviewed and notes that were written through the review process. Applicability was met through transferability in that selected text in the guideline was supported by best available evidence from accredited published literature.

Neutrality was met through confirmability in that the researcher was not bias to any of the evidence that was found to support the document review. Both the researcher and supervisor independently assessed the studies that support the excerpts from the guideline and then reached an agreement. Trustworthiness was ensured by giving direct quotations from published documents to support the recommendations made in the

PMTCT guidelines (Lincoln & Guba, 1985). Stability and reproducibility was ensured in that both the student and the supervisor independently read the supporting evidence before it was included in the review (Stemler, 2001). Neuendorf (2002) recommended that two coders should code the document during content analysis to ensure trustworthiness of the findings. The student coded the document and all findings were checked by the supervisor. Semantic validity is also important to ensure that correct interpretation is given to the written material (Neuendorf, 2002).

The qualitative phase of the review of the PMTCT guidelines has been dealt with above. The following paragraphs explain the quantitative process that was followed to execute the systematic review.

3.5 Quantitative Phase

Information technology has exponentially increased the availability of articles to more than two million per year, which makes keeping up with best evidence very difficult for clinicians and policy makers (Hemingway & Brereton, 2009). Policy makers need access to "good quality information on the effectiveness, meaningfulness, feasibility, and appropriateness" (Hemingway & Brereton, 2009, p. 1), to advocate for the use of antiretroviral therapy to prevent mother-to-child transmission of HIV, as insufficient information can potentially lead to devastating consequences. Moreover, evidence needs to be understood, translated and transferred, in other words, the knowledge from evidence based systematic reviews needs to be used for decision-making and be incorporated in guidelines to ensure that an individual can receive treatment based on best evidence (Hemingway & Brereton, 2009).

Best practice clinical guidelines are based on systematic reviews (Polit & Beck, 2008) and systematic reviews are often referred to as the "Gold Standard" to evaluate treatment interventions such as the use of antiretroviral therapy to prevent mother-to-child transmission of HIV (Boland, Cherry & Dickson, 2014). The following paragraphs deliberate on the definition of a systematic review, the difference between systematic and

traditional reviews and systematic review as a data collection method, Review Manager Computer program Version 5.3 (RevMan 5.3) as a tool of meta-analysis and as an analysis procedure for systematic reviews. Interpretation of findings and reporting results in forest plots as a method of presenting information for a systematic review is also discussed. Systematic reviews and meta-analysis comprise of specific terminology which may need some explanation as not all readers are acquainted with the terminology or conceptual definitions.

3.5.1 Conceptual Definitions

Conceptual definitions are explained in the following paragraphs.

3.5.1.1 Confidence Interval

The Confidence interval (CI) refers to the range of interval in which the population parameter of interest (i.e. the true mean of the population) is expected to lie at a specific probability (Schünemann et al., 2011). Confidence intervals can be computed at any degree of confidence but biomedical researchers doing systematic reviews usually use the 95% CI which means that the researchers are 95% confident (sure – not just a probability) that the true population mean falls within the given interval. Statistically, a 95% CI reflects a significance level of 0.05. If the 95% CI contain “0” then the difference between the groups population is not significant (Schünemann et al., 2011). The greater the interval or variance is, the less accurate is the estimate of the population parameter being tested. The narrower the confidence interval the more precise is the effect size. Wider intervals raise concern about uncertainty (Schünemann et al., 2011).

3.5.1.2 Fixed and Random Effects Models

Allison (2009, p.2) claimed that the fixed-effects model “treat unobserved differences between individual as a set of fixed parameters…[whilst in random-effects models] …unobserved differences are treated as random variables with a specified probability distribution”. Biostatisticians use fixed and random effects models to refer to the

population-mean and the subject specific effects (Snijders, 2005). Fixed-effects models weigh the extent of information in each individual study and concentrates on effects within the studies variability of the results (Borenstein, Hedges, Higgins & Rothstein, 2009).

Random-effects meta-analysis was used in this systematic review because the studies included did not all estimate the same intervention, thus there were variation across the studies as far as sample size and other parameters were concerned, therefore it was appropriate to use the random-effects model that estimated intervention effects across the studies (Snijders, 2005; Borenstein et al., 2009). If there is no heterogeneity amongst studies the fixed and random-effects model usually gives similar results. Studies included in this systematic review show some heterogeneity because the studies were not identical and this results in a slightly wider 95% CI with the statistical significance calculation being a bit more on the conservative side (Centre for Reviews and Dissemination [CRD], 2009; Borenstein et al., 2009).

3.5.1.3 Interpretation of the Forest Plot

Forest plots are also referred to as a “blobbograms” and can be generated using RevMan 5.3 to graphically depict the results of individual studies and meta-analysis (Lalkhen & McCluskey, 2008). Forest plots are used to graphically depict the relative strength of the treatment effect in the meta-analysis of randomised controlled trials that addresses the similar question or outcome (Bornman & Grigg, 2009). The forest plot can be presented in several ways and are commonly used to display the results of the meta-analysis both as a table and figure as displayed in Figure 3.1.

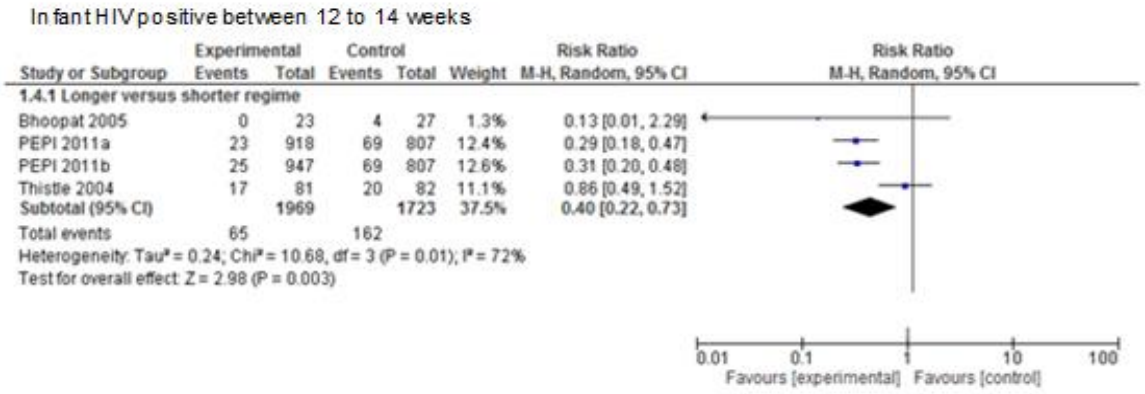

Figure 3.1 Example of a Forest plot

On the far left is the study identifier, consisting of first the author's name and year of publication (Holly, Salmond & Saimbert, 2012). The included studies can be arranged according to weight or size but commonly are presented in an alphabetical or chronological order (Holly et al., 2012). Next to the study identifier is the table that shows the number of events that occurred in the total population of the experimental group followed by the events that occurred in the control group (Holly et al., 2012). The proportion of weight or influence that each study contributes to the meta-analysis is then given in the next column (Bornman & Grigg, 2009; Holly et al., 2012).

The next column depicts a table that shows the measure of effect for each included study. On the far right the actual plot depicts the measure of effect. In this systematic review the Risk Ratio (RR) is represented by a block and 95% CI is represented by horizontal lines (Bornman & Grigg, 2009; Holly et al., 2012). The area of each block or square is proportional to the weight or size of the study. The overall measured effect is presented in the shape of a diamond, where the lateral points depict the 95% CI for the estimate effect (Bornman & Grigg, 2009; Holly et al., 2012). The vertical line on the graph represents "no treatment effect", thus if the 95% confidence intervals or the horizontal lines from the individual studies overlap the vertical line then it demonstrates that at 95% confidence there is no differences in the effect size between the two groups of the individual study (Bornman & Grigg, 2009; Holly et al., 2012). Thus if the CI includes "1" then the effect is not significant. Similarly if the diamond overlaps the vertical line it can

be stated that overall the meta-analysis of the included studies shows that there is no difference between the experimental group and the control group in the measured effect (Bornman & Grigg, 2009; Holly et al., 2012). Occasionally, some forest plots draw a dotted vertical line which shows the heterogeneity of the included studies. If the dotted vertical line includes all the studies then the studies are seen to be homogenous. Other forest plots depict the heterogeneity in a narrative on the left side under the study identifier and the I^2 is most often used as a percentage to state the heterogeneity, if the I^2 is equal or greater than 85% caution should be applied when interpreting the results as the studies differed extensively (Bornman & Grigg, 2009; Holly et al., 2012).

3.5.1.4 Homogeneity, Heterogeneity and I^2

Homogeneity refers to the similarity between studies (Holly et al., 2012). Clinical (participant, setting etc.), methodological (bias and quality of study), and statistical variability or heterogeneity always occurs to some extent when studies are combined and meta-analysis is applied to the same outcomes in a systematic review (Deeks, Higgins & Altman, 2011; Holly et al., 2012). What is important is to minimise the heterogeneity by setting strict inclusion and exclusion criteria before studies are included in the review. Furthermore, statistical tests can be applied to measure the inconsistency across studies to evaluate the impact that the heterogeneity has on the meta-analysis. The I^2 test is used to quantify inconsistency (Deeks et al., 2011). The I^2 test "describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)" (Deeks et al., 2011, p. 278). The percentage of variability for the purpose of this systematic review can be interpreted as follows:

- "0% to 40%: might not be important;
- 41% to 60%: moderate heterogeneity;
- 61% to 90%:substantial heterogeneity;
- 91% to 100%: considerable heterogeneity. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence

for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2)". (Deeks et al., 2011, p. 278).

3.5.1.5 PRISMA and PROSPERO

Researchers agreed that poor reporting and/or interpretation of systematic reviews weakens the value of systematic reviews that are used by clinicians, policy makers and users. A 27-item checklist was developed on how to report on systematic reviews (Moher, Liberati, Tetzlaff, Altman for the PRISMA Group, 2009). Researchers developed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement in order to provide guidelines to researchers on how to report on systematic reviews that evaluate health care interventions (Moher et al., 2009; Moher et al., 2015). The 27-item check list requires adherence to the characteristics as demonstrated in table 3.1.

Table 3.1 Checklist of Items to Include when Reporting Meta-analysis

(Moher et al., 2009).

Section/Topic	#	Checklist Item
Title		
Title	1	Identify the report as a systematic review, meta-analysis, or both
Abstract		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design.

Table 3.1 Checklist of Items to Include when Reporting Meta-analysis continued

Methods		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOT, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOT, funding sources) and any assumptions and simplifications made.
Methods		
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
Results		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOT, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

Table 3.1 Checklist of Items to Include when Reporting Meta-analysis continued

Discussion		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review

The development of the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) followed after the release of the PRISMA statement. The aim of PROSPERO is to promote prospective registration of systematic reviews and therefore prevent unintentional duplication of systematic reviews (Stewart, Moher & Shekelle, 2012). The PROSPERO database is an international database that offers free registration and free public access to prospective researchers who wish to embark on systematic reviews related to health issues (Booth et al., 2012; Stewart et al., 2012). The current systematic review was not registered as the main purpose of this systematic review was to identify evidence that supports the PMTCT guidelines and not to influence practice per se.

3.5.1.6 Meta-analysis

Meta-analysis comprises of specific statistical procedures where the results of independent randomised controlled trials are combined in an effort to increase the statistical power for the measured outcome and estimates of effect size and clinical effectiveness of health care interventions over individual studies (Borenstein et al., 2009; Crombie & Davies, 2009; Uman, 2011). Simply stated, meta-analysis can be seen as a summary of several studies that meet specific criteria where the effect size of the intervention and comparative group is presented giving cognisance to the weighted average of each independent study (Crombie & Davies, 2009; Uman, 2011).

The results of meta-analysis can be presented in relative risk and 95% CI and provide a detailed approximation of the treatment effect. The validity of the meta-analysis depends heavily on the quality of the results selected to be included in the systematic review, such as unpublished results, and the aim is to cover all the relevant studies that address the specific outcome (Borenstein et al., 2009). Sensitivity analysis and assessing heterogeneity amongst the studies further adds to the validity of the findings of the meta-analysis (Crombie & Davies, 2009; Uman, 2011).

Meta-analysis is mostly used to synthesise available evidence on effects of interventions or to support guidelines or policies to address practice (Borenstein et al., 2009). Meta-analysis is not applicable to all studies and there are times where meta-analysis is not appropriate:

- When studies are clinically heterogeneous;
- If studies are of poor quality meta-analysis can be misleading;
- Where publication or inclusion of articles bias is evident meta-analysis can create inappropriate summary (Alderson, Green & Higgins, 2004).

3.5.1.7 Primary and Secondary Studies

Primary studies according to Polit and Beck (2008) are first-hand reports detailing findings or facts in the original research. In other words: A primary source refers to the original source prepared by investigators who conducted the study. Secondary studies on the other hand refer to the accounts of facts or events done by a second person not the original investigator (Polit & Beck, 2008). The second person describes the accounts of a primary study. In this case a systematic review is referred to as a secondary source because it details information obtained from original primary studies, but the meta-analysis or the results of the systematic review are original and therefore a primary source of new information.

3.5.1.8 Relative Risk

Relative Risk (RR) is a measure of the influence of risk on disease and can be calculated as a ratio. Relative risk refers to the probability between two outcomes such as the incidence of HIV transmission to their infants between two groups of HIV-positive women, where the intervention group received treatment A and the control group received treatment B (Tripepi, Jager, Dekker, Wanner & Zoccali, 2007). In healthcare, risk usually refers to the probability of a bad outcome such as being HIV-positive infant in HIV exposed infants (women suffering with disease). There is likelihood that the intervention is superior when the RR is less than one in the case of a "bad" outcome. In other words if the RR is below one in the case of a bad outcome (HIV-positive infant), there is likelihood that the intervention (Group A treatment) is superior, thus favours the intervention group. If the RR is one or contains one then there is insufficient evidence to conclude that the groups are statistically significantly different, thus there is no difference in risk or in treatment received by group A and group B to prevent transmission of HIV to the infant (Kitchenham et al., 2007; Viera, 2008; Deeks et al., 2011).

3.5.1.9 Sensitivity Analysis

Sensitivity analysis is defined by Deeks et al. (2011) as a process of repeating meta-analysis of primary studies and substituting alternative decisions or decisions that were unclear or arbitrary or those that refer to ranges of values. Sensitivity analysis evaluates the robustness of processes taken to reach a certain decision. The questioning includes search methods, eligibility criteria and data analysis method. When uncertainties arise namely: Missing information that influences the results, it is therefore recommended that the primary investigators should be contacted (Deeks et al., 2011).

3.5.1.10 Risk of Bias Assessment

Determining the risk of bias is essential to evaluate the validity of the studies included in a meta-analysis (Higgins & Altman, 2011). Bias refers to a systematic error and in terms

of a meta-analysis “can lead to or underestimation or overestimation of the true intervention effect” (Higgins & Altman, 2011, p.188).

Potential sources of bias in clinical trials include:

- **Selection bias** – refers to the “systematic differences between baseline characteristics of the groups that are compared” (Higgins & Altman, 2011, p. 195). Selection bias may occur when adequate random sequence generation method such as a computerised random number generator was not used or when there is insufficient allocation concealment prior to assignment of the intervention is applied. Randomisation commonly prevents selection bias and ensures that there are no statistical significant differences in baseline data (data before randomisation) between the groups (Higgins & Altman, 2011). The implementation of allocation sequence concealment assists in preventing selection bias (Higgins & Altman, 2011). Low risk selection bias can be enhanced through central allocation or sequentially, sealed, numbered, opaque envelopes. Using date of birth or case record or open random allocation schedule can introduce a high selection bias (Higgins & Altman, 2011).
- **Performance bias** – refers to the “systematic differences between groups in the care that is provided” (Higgins & Altman, 2011, p.195). Blinding of personnel and study participants are implemented in randomised controlled trials to reduce the risk of performance bias (Higgins & Altman, 2011). Low risk of performance bias is judged when paricipants and researchers are not aware of treatment allocation or the outcome was not likely to be influenced by the lack of blinding.
- **Detection bias** – refers to “systematic differences between groups in how outcomes are determined” (Higgins & Altman, 2011, p.195). Evaluators that asses the outcomes need to be blinded to group allocation in an effort to reduce detection bias (Higgins & Altman, 2011).
- **Attrition bias** – refers to the “systematic differences between groups in withdrawals from the study” (Higgins & Altman, 2011, p.195). Attrition bias (absence of outcome data) occurs when there is a statistical significant difference between withdrawals after randomisation or loss to follow up between the groups

(Higgins & Altman, 2011). Good reporting on the nature and handling of incomplete data is important to prevent attrition bias.

3.5.2 Difference between Systematic and Traditional Reviews

It is claimed that a systematic review attempts to collate all relevant evidences that fit pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods to minimize bias in the identification, selection, synthesis, and summary of studies. Furthermore, it provides reliable findings from which conclusions can be drawn and decisions made (Moher et al., 2015, p. 3).

Systematic reviews have been described as a "high-level overview of primary research [several articles] on a particular research question that tries to identify, select, synthesize and appraise all high quality research evidence relevant to that question in order to answer it [the question]" (Cochrane Community (beta), 2015, para.2). Lefebvre, Manheimer and Glanville (2011, p. 97) argued that systematic reviews differ from traditional reviews in that "[s]ystematic reviews of interventions require a thorough, objective and reproducible search of a range of sources to identify as many relevant studies as possible. The scientific search for literature is a key element in differentiating systematic reviews from traditional narrative reviews and helps to reduce bias and therefore assists in attaining reliable estimates of effects (Lefebvre et al., 2011).

One of the core principles of conducting a systematic review is to identify relevant published and unpublished articles that meet pre-specified inclusion criteria (Lefebvre et al., 2011). Furthermore, each study is assessed for quality; the findings are synthesised in an unbiased way; statistical techniques are used to do the meta-analysis and results are presented in an impartial forest plot and summary description (Hemingway & Brereton, 2009; Uman, 2011). Systematic reviews not only report on clinical effectiveness (the difference is clinically meaningful), but examine the concerns of appropriateness and feasibility (Hemingway & Brereton, 2009).

Since the development of Cochrane Systematic Reviews in the late 1980's, published traditional reviews have increasingly been replaced by systematic reviews. Advocates for systematic reviews have exposed the short comings of traditional reviews such as insufficiencies in the process and the consequent bias in findings (Hemingway & Brereton, 2009). Hemingway and Brereton (2009) argued that the publication of two breakthrough manuscripts in 1992 by Antman, Lau, Kupelnick, Mosteller and Chalmers (1992) and Lau et al. (1992), highlighted the importance of systematic reviews and cautioned against the use of traditional reviews:

- Firstly, if a systematic review was employed in the original studies regarding the benefits of clot dissolving medications for patients who suffered heart attacks, it would have been evident that clot dissolving medications could save lives as early as the mid-1970's (Hemingway & Brereton, 2009).
- Secondly, although indisputable evidence was there to be compared, narrative reviews employed were not adequate in giving a summary on existing knowledge. The narrative reviews did not mention the effectiveness or suggest that treatment be incorporated in the ongoing investigation (Hemingway & Brereton, 2009).
- Lau et al. (1992) suggested that, there was a need for cumulative meta-analyses that incorporate results from small trials.

The above highlighted the shortcomings in the findings of traditional reviews. Traditional reviews report narratively on individual articles and are commonly referred to as: Literature reviews, narrative reviews or critical review of literature (Uman, 2011). Articles that report on individual studies offer little understanding of the greater problem because traditional reviews report on grouped information "according to the class of treatment, the end point of interest …descending order of quality…The pooled differences between treatment and control groups are then presented as a summation of the results of the individual trials…" (Lau et al., 1992, p. 248). Traditional reviews are not preceded with a detailed peer-reviewed protocol which clearly states the review method and therefore it is not easy to replicate the findings (Hemingway & Brereton, 2009; Uman, 2011). A systematic search of literature is not followed and selection bias is prevalent (Uman, 2011). Statistical methods are not applied to present the synthesis of the literature

(Uman, 2011). Low quality articles are included such as non-random comparative studies (Uman, 2011).

Moreover, traditional reviews look at p-values from individual studies and there is no statistical method currently available to synthesise p-values, whereas systematic reviews synthesise the effect sizes of each individual study (Borenstein et al., 2009). Traditional reviews then make recommendations on p-values that could be misleading whilst systematic reviews make recommendation based on the effect size to recommend the employment of treatment or not (Borenstein et al., 2009).

The purpose of this systematic review was to combine professional and social judgment to provide evidence based answers to the question what is the best evidence available to prevent mother-to-child transmission of the HIV and to use this information to assess whether the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015* (NDOH, 2015), was based on the best evidence available. The systematic review was based on the Centre for Reviews and Dissemination (CRD) guidance on how to undertake systematic reviews in healthcare but was not registered with the International Prospective Register of Systematic Reviews (PROSPERO) as the systematic review was done for the sole purpose of assessing whether the national PMTCT guideline was based on best evidence (Moher et al., 2015).

Table 3.2 gives a succinct summary of the comparison between systematic and traditional reviews (Table 3.2).

Table 3.2 Comparison between Systematic and Traditional Reviews

Outcome	Systematic Review	Traditional Review
Characteristics	The scope of the review is identified in advance through a peer-reviewed protocol.	No protocol required and studies included are at random.
	Pre-determined search strategy is followed to identify relevant published and unpublished evidence.	The method of studies included is often not described and the search is not replicable.
	Literature search is documented and established standards are used to critically appraise studies quality.	Quality of studies is not appraised. Selection bias present or evident.
	Inclusion and exclusion criteria are applied and explicit methods of extracting and synthesizing study findings are used.	Data extracted according to the class of treatment, the end point of interest or year of publication not according to pre-determined outcomes.
	Statistical techniques are used to do the meta-analysis and results are presented in an impartial forest plot and summary description.	Pooled differences between treatment and control groups are narratively summarised.
	Systematic reviews report on clinical appropriateness and feasibility.	Findings are reported on individual studies and offer little understanding of the greater problem.
Uses	Systematic reviews are used to identify any gaps in current research and propose future research.	Provide background reading for information.
	Used by researchers to show evidence that primary studies are required and then used to apply for grant funding for research.	
Outcome	Systematic Review	Traditional Review
Uses	Systematic reviews are increasingly part of student dissertations or postgraduate theses.	Mostly used to validate new research.
	Systematic reviews are used to summarise the empirical evidence and inform policy makers and health care users of best evidence.	
Limitations	Systematic reviews with narrowly defined review questions provide specific answers to specific questions.	Biases that occur in selecting and assessing the literature are unknown and the review cannot be replicated.

3.5.3 Benefits and Limitations of Systematic Reviews

The CRD (2009) asserted that systematic reviews provide comprehensive overviews of a specific problem and they are a means of evaluating and integrating critical information about a particular research question that assists health care workers in decision-making. Systematic reviews combine results of primary studies to produce an impartial and balanced summary of existing literature, which enables researchers to recommend interventions that are likely to be effective in specific settings (Kitchenham et al., 2007). The rigorous data collection and analysis methodology reduces bias but unfortunately does not protect against publication bias of primary studies by editors of journals, therefore all efforts must be done to seek unpublished studies as well (Li et al., 2015). Meta-analysis of studies increases the probability of detecting real effects that were not detectable in individual studies that used small sample sizes (Li et al., 2015).

Systematic reviews are trustworthy and can be used for decision making policies as a rigorous research methodology is applied to select, reduce, and synthesise evidence (Hemingway & Brereton, 2009). The results of systematic reviews can be generalised to a larger population and are critical tools for clinicians and policy makers to keep themselves up to date with best evidence as it is seen as the gold standard for decision making (Uman, 2011).

The preparation of systematic reviews requires substantially more rigour and effort than preparing traditional reviews and therefore is respectable for reducing bias (Li et al., 2015). Depending on the research question, there may be a requirement to consult large volumes of literature which can take a long time to read and could be financially costly (Kitchenham et al., 2007). Systematic reviews aim to give the best possible appraisal of any true effect but as with any other research project caution must be applied before accepting the reliability of the findings as some people may not adhere to the rigorous methodology of a systematic review (Hemingway & Brereton, 2009).

Systematic reviews provide balance between conflicting findings as the findings of a meta-analysis may occasionally be the opposite of the findings of a primary, single large

randomised control trial. In this case it would be appropriate to ensure that the meta-analysis aggregated appropriate studies using similar interventions (Hemingway & Brereton, 2009).

It is important that systematic reviews be scrutinised as to whether a rigorous methodology was applied before the recommendations of the review are blindly followed. The reader always needs to apply judgement in assessing any report as any studies or systematic review may have shortcomings despite the fact that it may carry very important information (Hemingway & Brereton, 2009). Another limitation is that systematic reviews may have to develop over a long period and this could result in an expensive budget (Kitchenham, 2004).

3.5.4 Systematic Review as a Data Collection Method

Polit and Beck (2008) and RCSI Library (2014) stated that when developing a protocol the researcher must clearly mention the predetermined selection criterion that adheres to the following: Population, Intervention, Comparison, Outcome and Types of study designs to include in the review (PICOT acronym). When PICOT is identified during the protocol stage it helps to prevent bias. Li et al. (2015) recommended that the following principles be adhered to in order to ensure high quality extraction of data; comprehensiveness, completeness, accuracy, consistency, transparency, efficiency, and accessibility.

The procedure and instrument to collect and analyse systematic reviews are described in the following paragraphs. Information was extracted independently by the researcher and the supervisor on a standard data extraction form. Thereafter the data was independently captured onto a software analysis programme namely Review Manager Computer program Version 5.3. The findings were compared between the two capturers to ensure accuracy of captured information (Welsh, Normansell & Cates, 2015). The final decision making power rested with the supervisor after motivation was given of why an article should be included or not and how data should be captured (Li et al., 2015). There was no third reviewer required as there were no disagreements between the supervisor and

the researcher. The researcher adhered to the recommended principles as extraction of pre-specified outcomes from the studies is vital to make appropriate conclusions and recommendations for practice and further research (Li et al., 2015).

The review process involves several distinct actions that can be divided into three main phases; planning, conducting and reporting (Kitchenham et al., 2007). The use of standardised guidelines is recommended to ensure the quality of systematic reviews on clinical effectiveness that can be evaluated (CRD, 2009). The recommended standardised guidelines consisted of a framework of statements or questions that needed to be answered to ensure that the findings are reliable and valid (CRD, 2009; Hemingway & Brereton, 2009; Uman, 2011: Li et al., 2015; Moher et al., 2015). The following process was adhered to:

Phase One: Planning the Review

Step One: Identification of the Need for a Review

- Kitchenham et al. (2007) recommended that researchers should confirm the need to undertake a systematic review before embarking on the project and to assess whether a systematic review that answers the question has not been published yet. The researcher followed the recommended CRD checklist to establish whether there was a need for the review (CRD, 2009). An extensive literature search then followed examining: The Cochrane Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR) and CENTRAL were accessed through University of Fort Hare Library Services to identify potential randomised controlled trials on the selected topic. One complete systematic review authored by Siegfried, van der Merwe, Brocklehurst and Sint, (2011) namely *Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection* had been identified. The review was critically appraised according to the Centre for Reviews and Dissemination's guidelines (CRD, 2009). The following questions were asked:
- Was the review question clearly defined in terms of population, interventions, comparators, outcomes and type of study designs (PICOT)?

- Was the search strategy adequate and appropriate?
- Were there any restrictions on language, publication status or publication dates?
- Were preventative steps taken to minimize bias and errors in the study selection process?
- Was the appropriate criterion used to assess the quality of the primary studies, and were preventative steps taken to minimize bias and errors in the quality assessment process?
- Were preventative steps taken to minimize bias and errors in the data extraction process?
- Were adequate details presented for each of the primary studies?
- Were appropriate methods used for data synthesis?
- Were differences between studies assessed?
- Were the studies pooled, and if so was it appropriate and meaningful to do so?
- Did the authors' conclusions accurately reflect the evidence that was reviewed? (CRD, 2009, p. 4).

The published systematic review (*Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection*) met all above criteria but the challenge was that review was last updated in 2011 and the researcher was aware of new randomised controlled trials that met the inclusion and exclusion criteria, which should be included in the new review. There was thus justification to embark on a new systematic review to include randomised controlled trials that were published after 2011. The need was identified to systematically review literature that reports on the efficacy of ARV regimens to prevent mother-to-child transmission of the HIV. This was in an effort to determine whether, and to what extent, PMTCT programmes decrease HIV transmission to the infant and to include data that became available after 2011.

The reason for embarking on a new review was to obtain the latest and best evidence in an effort to support excerpts from the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015* (NDOH, 2015).

Step Two: Establishing a Review Team

It was a mandatory requirement to present the research proposal to faculty members and to scrutinise whether the minimum academic and ethical requirements for a Master degree was met. The systematic review protocol was part of the master proposal presentation. Recommendations for modifications of the research proposal from faculty members were included and the proposal was submitted to the Higher Degrees Committee for registration of the title. The supervisor is experienced in Cochrane Systematic Reviews and assisted the student through the whole review process, thus the review team consisted of the student and the supervisor (Welsh et al., 2015). There was no conflict of interest from either of the team members that could influence the research findings.

Step three: Specifying the Research Question, Objective, Inclusion Criteria and Writing a Proposal

Stating the research question is one of the most important parts of the systematic review as the question drives the research methodology (Hemingway & Brereton, 2009; Boland et al., 2014). The research question was framed using the PICOT elements namely: Population; Intervention (test treatment/routine treatment); Comparison (intervention group or control group); Outcomes, and Types of study design (Petticrew & Roberts, 2006; CRD, 2009).

Population or Type of Participants:

Population or participants refers to specific characteristics that participants met at randomisation of the original study, of which the reviewer is interested to include in the review (Li et al., 2015). Inclusion criteria for the population of interest in this study were pregnant women and their infants. Studies were included if the population included HIV-positive women during pregnancy, labour and the postpartum period or infants born to HIV-positive women.

Types of Intervention and Comparison

Chandler, Churchill, Higgins, Lasserson and Tovey (2013) emphasized that it is highly desirable when conducting a systematic review to explicitly mention the comparative and intervention when interpreting results. In the current study the randomised controlled trials were included that compared PMTCT programmes. Polit and Beck (2008) stated that intervention refers to the use of treatment or anything to modify the desired outcome. The interventions of interest in this study were: ARV's administered to pregnant women during pregnancy, labour, and delivery post-partum and feeding options so as to reduce mother-to-child transmission of HIV. The comparison group received a different type of antiretroviral medication or there were differences in the duration or the period for example, ARV's were only taken in the antenatal period.

Type of Outcomes

Outcomes should be clarified in advance and only essential outcomes that address the research question should be reported on (Chandler et al., 2013). Chandler et al. (2013) recommended that seven or fewer outcomes should be sufficient for a systematic review. Primary outcomes measured in this review were HIV infection status at:

- Birth;
- two weeks;
- four to eight weeks;
- 12 to 14 weeks;
- As well as at six and 12 months.

Secondary outcomes of interest included:

- Maternal deaths any time post randomisation
- Stillbirths before labour after randomisation
- Infant adverse events up to 18 months after birth
- Infant deaths at or before six months after birth
- Infant deaths up to 18 months after birth
- Any maternal adverse events

Types of studies

Randomised controlled trials comparing any antiretroviral treatment regime that concentrated on reducing the risk of transmitting HIV from the mother to the infant during pregnancy, labour and the while breastfeeding. Placebo controlled trials were not included as there is sufficient evidence that all women should receive antiretroviral therapy.

3.5.5 Search Strategy

An electronic search of several databases that contain electronic journals with articles reporting on randomised controlled trials reporting on the use of antiretroviral medication to prevent mother-to-child transmission was conducted through the University of Fort Hare, Library services. The databases searched were: BioMed Central, Cochrane Library, EBSCOhost, ERIC, Health Source: Consumer Edition, Health source: Nursing/Academic Edition, Masterfile (EBSCOhost), MEDLINE, Nursing Reference Center, PubMed, PsycINFO, Science Online and Science Classic, ScienceDirect, and SocIndex with fulltext, Taylor and Francis and Wiley InterScience.

The search was conducted during 2015. Restriction criteria for the search included: English articles that contained full text and that were published between 1 January 2001 and 30 November 2015.

Polanin, Tanner-Smith and Hennessy (2015) emphasised the threat to the validity of systematic reviews due to publication bias by editors, who prefer to publish studies with significant effects and do not accept studies that show null effects. The importance of additional search strategies to identify results from unpublished randomised control trials are important as the inclusion of only published studies showed greater treatment effect yields or larger effect sizes (Bornman & Grigg, 2009; Stern, Jordan & McArthur, 2014; Polanin et al., 2015). It is acknowledged that a very well executed randomised control trial contributes to the effect size of the meta-analysis in a systematic review; therefore results from conference abstracts were included in this systematic review (Kwon,

Powelson, Wong, Ghali, & Conly, 2014). Authors were not contacted to identify more articles.

3.5.6 Keyword Search

The electronic search was done using several combinations of key words. The combinations included:

- HIV OR Random* OR PMTCT OR Prevention of mother-to-child transmission OR vertical transmission
- Vertical transmission OR PMTCT OR Prevention of mother-to-child transmission OR random* OR mother-to-child transmission
- Vertical transmission AND PMTCT OR Prevention of mother-to-child transmission AND random* OR mother-to-child transmission
- Vertical transmission AND random* controlled trials OR PMTCT AND Prevention of mother-to-child transmission
- TX Vertical transmission AND TX random* controlled trials AND TX PMTCT AND TX mother-to-child transmission

3.5.7 Study selection

Titles were screened and abstracts of selected studies were read. If the study was relevant the complete article was evaluated for inclusion in the review or not. Record was kept of the excluded studies and reasons why the studies were excluded. Clearly pre-stipulated selection criteria as stated above (PICOT) was used to select the studies for inclusion in the review. Studies were critically appraised for methodological quality (randomised controlled trial), bias, and concealment of allocation, blinding and attrition rate by the supervisor and the researcher.

3.5.8 Data Collection

Data was then extracted independently by the researcher and the supervisor. The supervisor and researcher independently entered the data into RevMan 5.3 for analysis (Boland et al., 2014).

3.5.9 Data Analysis

Review Manager (RevMan 5.3) was used to analyse and synthesize the studies and forest plots were used to present the information.

3.5.10 Review Manager

Review Manager (RevMan 5.3) is a review writing software computer programme developed and maintained by The Cochrane Collaboration, The Nordic Cochrane Centre in Copenhagen in collaboration with users and methodologists (Deeks et al., 2011). RevMan is a required tool to be used by reviewers when preparing Cochrane systematic reviews but it is also available for use by academic institutions as well (Deeks et al., 2011,). RevMan uses a specific format and information. The information is captured into the programme and the reviewer can choose to present information in odds ratios or relative risks and 95% CI (Deeks et al., 2011). RevMan was set to use the Mantel and Haenszel random effects model in an effort to be on the conservative side, leading to wider confidence intervals when heterogeneity in treatment effect was observed. Statistical methods used were the relative risks and confidence intervals set at 95%. Forest plots were used to present the results graphically.

3.6 Summary

This chapter justified the use of document and systematic review. The processes of embarking on document review as explained by Krippendorff were discussed extensively. Limitations and benefits of document review were explained together with steps used so as to enhance the scientific rigor in qualitative research.

Terminology used in systematic reviews was discussed so as to familiarize the reader. The use of Review Manager was also explained and terms used to interpret results in this project were detailed. Chapter four articulates the results of document analysis.

Chapter Four
Document Review

4.1 Introduction

Chapter four presents the results of the document review. The researcher analysed the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April, 2015* (National Department of Health [NDOH], 2015). The document was reviewed according to the principles described in chapter three. Supporting evidence was sourced from accredited journals and when evidence was found the researcher extracted the evidence and rated the information based on the National Health and Medical Research Council [NHMRC] (1999) and NHMRC (2009) of Australia published levels of evidence and grades.

4.2 Levels of Evidence

The National Health and Medical Research Council of Australia has published levels of evidence and grades that can be used by developers in the development of guidelines to ensure that recommendations for implementations are based on best clinical practice (NHMRC, 1999; NHMRC, 2009). Table 4.1 explains the levels of evidence according to the scale used to measure the evidence.

Table 4.1 Levels of Evidence

Level	Definition
1a	Systematic review and meta-analysis of randomised controlled trial
1b	At least one randomised controlled trial
2a	At least one well designed controlled study without randomisation
2b	At least well designed controlled quasi-experimental study
3	Well-designed non-experimental descriptive studies such as comparative, correlation or case studies
4	Expert committee reports, opinions, clinical experience of respected authorities

4.3 Comparison of guidelines

Twelve guidelines were originally sampled (table 4.2). These guidelines were read and the evolution in treatment options given to pregnant women and infants including the feeding options was noted.

Table 4.2 Guidelines

Identifier	Reference
WHO 2001	New data on the prevention of mother-to-child transmission of HIV and their policy implications. Conclusions and recommendations. WHO Technical Consultation on Behalf of the UNFPA/UNICEF/WHO/ UNAIDS Inter-Agency Task Team on Mother-to-Child Transmission of HIV (WHO, 2001).
RSA 2001	Protocol for providing a comprehensive package of care for the prevention of mother-to-child transmission of HIV (PMTCT) in South Africa (NDOH, 2001).
RSA 2003	Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa (NDOH, 2003)
WHO 2006	Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Towards universal access: Recommendations for a public health approach (WHO, 2006).
RSA 2008	Policy and guidelines for the implementation of the PMTCT programme (NDOH, 2008).
WHO 2010	Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Recommendations for a public health approach 2010 version (WHO, 2010).
RSA 2010	Clinical guidelines prevention of mother-to-child transmission (NDOH & SANAC, 2010).
WHO 2012	Programmatic update: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants (WHO, 2012b).
WHO 2013	Global update on HIV treatment 2013: Results, impact and opportunities (WHO, 2013).
RSA 2013	The South African antiretroviral treatment guidelines 2013 PMTCT guidelines: Revised March 2013 (NDOH, 2013c).
RSA 2014	National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults 24 December 2014 (NDOH, 2014).
RSA 2015	National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015 (NDOH, 2015).

The essential differential criteria of the twelve guidelines evaluated are compared in table 4.3.

Table 4.3 Essential Differential Criteria of the Guidelines

Monotherapy Identifier	Regimen administered to pregnant women	Treatment for infants according to feeding option
WHO 2001	Pregnancy: N/A Labour: sd-NVP Postpartum: N/A	All infants NVP syrup according to weight < 2.5kg: 10mg >2.5kg: 15mg
RSA 2001	Pregnancy: N/A Labour: Sd-NVP 200mg At onset of labour, repeat once after 24 hours if not delivered yet. Postpartum: N/A	All infants born to HIV infected women received a single dose of Nevirapine (0, 2ml/kg if <2000 gram and 0.6 ml if > 2000 gram) between 72 hours after birth.
RSA 2003	Pregnancy: If CD_4 cells/mm3 from 200-350, pregnant women received d4T/3TC/NVP for life after the first trimester for life. Labour: Sd-NVP then Folate, iron, vitamin B, C and multivitamin supplement throughout pregnancy. Postpartum: Those eligible for ART continued and the not eligible recieved vitamins.	Single dose nevirapine within 72 hours of birth and cotrimoxazole prophylaxis from 6 weeks. Formula was freely available from clinics for those mothers who opted for formula feeding.
Dual therapy		
WH0 2006	ART for pregnant women was therefore recommended for: all women in clinical stage 4 irrespective of the CD_4 cell count; women in clinical stage 3, with the CD_4 <350 cells/mm3 count, if available; if the CD_4 cell count is not available, all women in stage III should be treated; women in clinical stage I and 2 with a cell count of CD_4 <200 cells/mm3 Pregnancy: AZT 300mg twice a day starting at 28 weeks of pregnancy or as soon as feasible thereafter. Labour: Sd-NVP 200mg+ AZT 300mg / 3TC 150mg AZT 300 mg at onset of labour and every 3 hours until delivery Postpartum: AZT/3TC × 7 Days	All infants NVP syrup according to weight < 2.5kg: 10mg >2.5kg: 15mg + AZT x 7 days If the mother received less than four weeks of ART during pregnancy, then four weeks, instead of one week, of infant AZT was recommended
RSA 2008	CD4 cell count >200 Pregnancy: AZT started from 28 weeks Onwards Labour: sd-NVP + AZT at onset of labour and then 3-hourly	Sd-NVP (within 72 hrs) + AZT for 7 days AZT for 28 days.

Identifier Triple therapy	Regimen administered to pregnant women	Treatment for infants according to feeding option
WHO 2010	Two options were recommended for HIV-infected pregnant women who were not eligible for ART: Option A: Not eligible for ART Pregnancy: Started from 14 weeks gestation. AZT 300 mg twice daily Labour: sd-NVP 200mg at onset of labour + AZT 300 mg + 3TC 150 mg twice daily Postpartum: AZT 300 mg + 3TC 150 mg twice daily for 1 week.	In breastfed infants, daily administration of NVP to the infant from birth until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding stopped before 6 weeks (but at least 1 week after the early cessation of breastfeeding), was recommended. In infants receiving only replacement feeding, daily administration of NVP from birth or sd-NVP at birth plus twice-daily AZT from birth until 4 to 6 weeks of age was recommended.
	Option B: Eligible for lifelong AZT + 3TC + LPV/r, AZT + 3TC + ABC, AZT + 3TC + EFV, or TDF + 3TC (or FTC) + EFV. NVP 200 mg twice daily Eligible for ART. AZT + 3TC + NVP or TDF + 3TC (or FTC) + NVP or AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV Labour: Continue ART Postpartum: Continue during postpartum period.	Option B In infants, regardless of infant feeding practices (breastfeeding or replacement feeding), the maternal triple ARV prophylaxis was combined with the daily administration of NVP or twice daily AZT to the infant from birth until 4 to 6 weeks of age.
RSA 2010	Eligible for lifelong ART (i.e. CD_4 < 350 or WHO clinical stage 3 or 4). Pregnancy: TDF + 3TC/FTC + NVP (start ART within 2 weeks) Continue with ART; substitute EFV with NVP if was in first 12 weeks of pregnancy. Labour: Continued during labour	NVP at birth and then daily for 6 weeks irrespective of infant feeding choice.
	Not eligible for ART i.e. CD_4 > 350 and WHO stage 1 or 2. Pregnancy: AZT from 14 weeks Labour: Sd-NVP + AZT 3hrly Postpartum: TDF + FTC single dose (stat) after delivery	NVP at birth and then daily for 6 weeks continued as long as breastfeeding.

Identifier **Option B+**	Regimen administered to pregnant women	Treatment for infants according to feeding option
WHO 2012	Same for treatment and prophylaxis Regardless of CD_4 count, triple ARVs started 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 1 week after cessation of all breastfeeding.	Daily NVP from birth until 1 week after cessation of all breastfeeding; or, if not breastfeeding or if mother was on treatment, through age 4–6 weeks.
WHO 2013	Fixed combination TDF + 3TC or FTC + EFV soon after diagnosis and continued for life.	Daily NVP from birth until 1 week after cessation of all breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4–6 weeks.
RSA 2013	$CD_4 \leq 350$ or stage 3 or 4. Continued FDC as lifelong treatment. $CD_4 > 350$ or stage 1 or 2. Continued with FDC as prophylaxis through antenatal, labour and delivery postnatal till one week after complete antenatal cessation of breastfeeding.	Start NVP as soon after birth as possible (within 72 hours post-delivery) and continue for 6 weeks. If breast fed continued after 1 week of cessation of breastfeeding.
RSA 2014	Pregnancy: Immediate initiation of lifelong FDC/ART for all HIV-positive women who are pregnant, breastfeeding or within 1 year post-partum, regardless of CD_4 cell count.	NVP at birth and then daily for 6 weeks continued as long as any breastfeeding.
RSA 2015	Do VL for all pregnant and breastfeeding women at first visit regardless of when the last VL was done. Women who are put on a FDC (TDF+3TC (FTC) +EFV) in their pregnancy should be monitored and managed, where possible, by the same provider in the same facility through the antenatal and postnatal periods until the end of breastfeeding. They should then be referred to appropriate services to continue lifelong ART as part of the general adult ART population.	If mother viral load < 1000 copies/ml. Then Infant requires prophylaxis with AZT plus NVP and birth PCR testing. Emphasise exclusive breastfeeding for the first 6 months, with complementary feeding only from 6 months and breastfeeding continued until 12 months.

Identifier	Regimen administered to pregnant women	Treatment for infants according to feeding option
	All unbooked women who test positive during labour should be given prophylactic ART during labour and initiated on lifelong ART before being discharged.	Patients with confirmed 2nd or 3rd line regimen failure should not breastfeed their infants
	All pregnant women not on ART (any gestational age) = FDC. If there is a contraindication to the FDC then TDF + 3TC (or FTC) + EFV.	NVP at birth and then daily for 6 weeks
	Pregnant women currently on ART should continued current ART regimen. Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done. Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC and Creatinine ≤85µmol/l and any CD_4 cell count. If Creatinine >85 µmol/l. Stop FDC, initiate AZT if Hb ≥7g/dl. Creatinine >85 µmol/l High-risk pregnancy: Refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction. Contraindication to EFV (active psychiatric Illness then change with AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r. Refer urgently for alternate triple therapy CD_4 <250cells/µl: NVP 200mg daily for 2 weeks, then 200mg BD CD_4 ≥250cells/µl LPV/r 2 tablets 12 hourly.	All HIV-exposed infants not on ART should have a rapid test at 18 months of age to confirm HIV status conferred by the birth, 10-week HIV PCR test, or the 18-week HIV PCR performed 6 weeks post the 12-week NVP prophylaxis, or 6 weeks post-cessation of breastfeeding test ALL HIV-exposed infants must be tested for HIV at birth. Infants born to HIV-positive women should receive daily NVP for 6 weeks, unless there are circumstances that warrant 12 weeks of NVP or NVP plus AZT. Ensure that the birth PCR results have been documented for all the HIV exposed neonates.
	Labour Unbooked and presents in labour and tests HIV positive - sdNVP + sd Truvada and AZT 3 hourly in labour- Woman qualifies for lifelong ART. Do creatinine and CD_4 testing. Woman should get results at the 3-6 days visit. Emergency caesarean section in unbooked woman with no ART start sdNVP + sd Truvada for C/S and start FDC next day regardless of CD_4 cell count.	NVP as soon as possible and daily for 12 weeks (if infant is breastfed). An additional HIV PCR test is required 4 weeks after NVP is discontinued.

Identifier	Regimen administered to pregnant women	Treatment for infants according to feeding option
	Mother did not get any ART before or during delivery and tests HIV-positive >72hours post-delivery OR Mother newly diagnosed HIV-positive within 72 hours of delivery OR Mother started ART less than 4 weeks prior to delivery. Postpartum Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year Lifelong FDC initiated immediately Breastfeeding mother diagnosed with HIV. Start mother on a FDC immediately Mothers of unknown HIV status or who are HIV-negative should be tested 3-monthly, throughout pregnancy, at labour/delivery, at the 6-week EPI visit and 3-monthly throughout breastfeeding. Maternal CD_4 at initiation of ART, at 12 months, then annually if clinically indicated. Non-breastfeeding mother diagnosed with HIV. To ensure women who conceive on ART are fully suppressed to minimise risk of MTCT. Do maternal VL at confirmation of pregnancy if already on ART>3 months, do VL at months 3, 6, 12, 18, 24 throughout pregnancy and breastfeeding	NVP and AZT immediately If infant tests HIV PCR negative: stop AZT and continue NVP for 12 weeks. If mother has received 12 weeks of ART then infant NVP can be stopped. Give NVP immediately and test infant with rapid HIV test. If positive continue NVP for 6 weeks and if negative discontinue NVP. If rapid test is positive do an HIV PCR. If negative, repeat HIV PCR at 10 weeks. If HIV PCR positive, initiate baby on triple ART immediately and send confirmatory HIV PCR. If more than 72 hours since delivery, no infant NVP. Perform an HIV PCR, if positive initiate ART. Infant HIV testing 6 weeks post-cessation of breastfeeding (either HIV PCR or ELISA, depending on age) Infant PCR positive • Confirm with a second PCR • Start cotrimoxazole • Initiate ART while waiting for the confirmatory PCR result All women should: •Be given at least 8 week's supply of ART and 6 or 12 week supply for infant prophylaxis on discharge •Follow-up at a health facility within 3-6 days and again 6 weeks post-partum •Have a correctly completed RTH booklet

The main changes for pregnant/breastfeeding women, paediatrics, adolescents and adults are:
Immediate initiation of lifelong ART for all HIV-positive women who are pregnant, breastfeeding or within 1 year post-partum, regardless of CD_4 cell count.
Use of EFV as part of the first-line regimen, regardless of the gestation of the pregnancy.
Use of maternal lifelong ART throughout pregnancy and breastfeeding to reduce MTCT.
Viral load testing for women on ART≥3 months at confirmation of pregnancy to direct management.
Repeat HIV testing for HIV-negative women 3-monthly during pregnancy, at labour/delivery, at the 6 week Expanded Programme on Immunisation (EPI) visit and 3-monthly throughout breastfeeding.
This should be done during routine antenatal care, postnatal care and EPI/child health follow-up visits
Women with contraindications to FDC should be considered high-risk pregnancies. They should be initiated on AZT immediately and referred urgently for initiation on to three single ART drugs.
Provision of birth HIV PCR for all HIV exposed neonates.
Use of extended 12 weeks NVP or dual post-exposure prophylaxis with NVP and AZT for infants where maternal viral load suppression may be inadequate. (NDOH, 2015 p.14).
Changes specific to infants and early adolescents:
Provision of ART for all children under 5 years, regardless of their CD4 cell count or clinical staging.
ART initiation for children ≥5 years now starts at CD_4 count ≤500 cells/µl regardless of clinical staging.
Immediate initiation of infant ART with first positive HIV PCR, whilst waiting for confirmatory test results.
Use of second HIV PCR test as a confirmatory for positive HIV PCR test.
No longer use viral load as part of baseline asessment for ART initiation in children.
Birth PCR HIV testing of all HIV-exposed neonates, repeated at 10 weeks and Rapid HIV test at 18 months. For those on extended 12 week NVP, the PCR will be repeated at 18 weeks and a Rapid HIV test at 18 months. (NDOH, 2015 p.15).

4.4 Findings of Document Review

Document review was done on the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015* (NDOH, 2015). The document was reviewed and supporting evidence in support of PMTCT treatment regimens were sourced from accredited publications. The results will be presented as follows: The boxes that contain italics are excerpts from the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April 2015.*

The following paragraph presents results: The left side contains the level of evidence as depicted in table 4.1 followed by supporting evidence and a source where the supporting evidence were obtained from.

> *"In 2013, the fixed-dose combination pill (FDC) was introduced, made up of the regular three drugs used in the first-line regimen (TDF, FTC/3TC and EFV) to improve adherence and retention" (NDOH, 2015, p. 14).*

[1b] "Over 96 weeks, the combination of TDF, FTC, and EFV was superior to fixed-dose ZDV/3TC + EFV for achieving and maintaining an HIV RNA level of 400 copies/mL and an increase in CD_4 cells" (Pozniak et al., 2006, p.535).

[1b] "Through 144 weeks, the combination of tenofovir DF, lamivudine, and efavirenz was highly effective and comparable with stavudine, lamivudine, and efavirenz in antiretroviral-naive patients. However, tenofovir DF appeared to be associated with better lipid profiles and less lipodystrophy" (Gallant et al., 2004, p.191).

[1b] Through week 48, the combination of tenofovir DF and emtricitabine plus efavirenz fulfilled the criteria for non-inferiority to a fixed dose of zidovudine and lamivudine plus efavirenz and proved superior in terms of virologic suppression, CD_4 response and adverse events resulting in discontinuation of the study drugs. (Gallant et al., 2006, p.251).

[3] The principal factors associated with non-adherence appear to be patient-related, including substance and alcohol abuse. However, other factors may also contribute, such as inconvenient dosing frequency, dietary restrictions, pill burden, and side effects; patient–health-care provider relationships; and the system of care. (Chesney, 2000, p.S171).

[3] “ART consisting of a single pill per day was associated with significantly better adherence and lower risk of hospitalization in patients with HIV compared to patients receiving three or more pills per day” (Sax, Meyers, Mugavero & Davis, 2012, p.1).

[3] “Self-reported adherence is better among patients with less complex ART regimens. This is in part because patients’ understanding of regimen dosing decreases as regimen complexity increases. Therefore, simplifying antiretroviral regimens may have an important role in improving patients’ adherence (Stone et al., 2001, p.124).

“On 23 July 2014, the Minister of Health, Dr. Aaron Motsoaledi announced that the threshold for initiation of ART will rise to CD_4 count ≤500/µl and…” (NDOH, 2015, p. 14).

[2a] Consequently, many antiretroviral guidelines from around the world now recommend routine initiation of ART when the CD_4 cell count decreases to 350 cells/mL or at higher CD_4 cell counts for certain subgroups of HIV-infected individuals, such as pregnant and/or breast-feeding women and persons with HIV-related nephropathy or hepatitis virus coinfection. (Wilkin & Gulick, 2008, p.1580).

[1a] This review may only be used to provide supportive and not definitive evidence because the difference between study groups was not significant for two of the studies in the 500 referent group and one study did not have a similar subgroup to compare. More studies that look at >500 cells/μL or 350–500 cells/μL as referent groups are needed for firm clarification of the benefits or risk. Overall, this review suggests that, whenever possible, therapy should be started when CD_4 counts are at or above 500 cells/μL rather than waiting for the CD_4 to fall to lower counts or the old recommended guidelines (350 cells/μL) in order to prevent mortality and morbidity due to AIDS progression. (Olubajo, Mitchell-Fearon & Ogunmoroti, 2014, p.4).

[1b] In this study involving 1763 serodiscordant couples in which HIV-1 infected participants had a CD_4 count of 350 to 550 cells per cubic millimeter, there was a relative

reduction of 96% in the number of linked HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy . There was a relative reduction of 89% in the total number of HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, regardless of viral linkage with the infected partner. The sustained suppression of HIV-1 in genital secretions resulting from antiretroviral therapy is the most likely mechanism for the prevention of HIV-1 transmission that we observed. (Cohen et al., 2011, p.503).

> *"…the PMTCT Programme will now adopt the B+ approach, which entitles every pregnant and breastfeeding woman to lifelong ART regardless of CD_4 count or clinical staging. This will be effected on January 2015" (NDOH, 2015, p. 14).*

[1b] Option B+ represents a substantial change in the approach to PMTCT that holds promise for not only effectively reducing new HIV infections in children, but also improving the health of their mothers. This approach has been endorsed by WHO and is being rapidly implemented in many countries. We took advantage of EGPAF's presence supporting MOH in 11 countries that have adopted Option B+ to analyse their early experience implementing Option B+. This review found that most countries quickly adopted and began scale up of Option B+, some even before the formal WHO guidelines were released. This scale up resulted in substantial increases in percentages of HIV+ pregnant women in ANC who started on ART. (Kieffer et al., 2014, p.S193).

> *"The guidelines reinforce family-centred care and one-stop-shop approaches to service provision" (NDOH, 2015, p.15).*

[1a] The family-centred model of care addresses many needs of infected patients and other household members. Major reported obstacles involved recruiting one or more types of family members into care, early diagnosis and treatment of infected children, preventing mortality during children's first six months of highly active antiretroviral therapy, and staffing and infrastructural limitations. (Leeper, Montague, Friedman & Flanigan, 2010, p.1).

[1a] There are many challenges to increase male involvement/participation in PMTCT services. So far, few interventions addressing these challenges have been evaluated and reported. It is clear however that improvement of antenatal care services by making them more male friendly, and health education campaigns to change beliefs and attitudes of men are absolutely needed. (Ditekemena et al., 2012, p.1).

> *The main purpose of these guidelines is to improve the clinical outcomes of people living with HIV, reduce morbidity due to TB/HIV co-infection, reduce HIV incidence and avert AIDS-related deaths in the most cost-efficient manner by ensuring that people living with HIV start with the right therapy at the right time. (NDOH, 2015, p. 16)*

[4] "One of the vision and goals of the National Strategic Plan [NSP] on HIV, STI and TB 2012-2016 is Zero new HIV and TB infections and Zero preventable deaths associated with HIV and TB" (Heywood, 2011, p.21).

[4] "South Africa currently ranks the third highest in the world in terms of TB burden, with an incidence that has increased by 400% over the past 15 years" (Heywood, 2011, p.13).

[4] The TB infection rate places South Africa as the third country with the highest level of TB in the world after India and China. South Africa recorded 970 new infections per 100, 000 people in 2009. The number grew to 981 people newly-infected with TB out of every 100 000 in 2010 and 993 new infections per 100 000 in 2011. (The South African National AIDS Council, 2013, p.1).

> *"Simplify guidance for health workers to improve the quality of HIV care for all people living with HIV and HIV-exposed infants" (NDOH, 2015, p.16).*

[3] The continuously changing recommendations on PMTCT stress the need for a much simpler and effective approach…but Option B+ would help to overcome many barriers that prevent guidelines to be implemented in order to increase coverage and ultimately

achieve the goal of 'virtual elimination' of mother-to-child transmission in sub-Saharan Africa. (Gamell et al., 2013, p.1).

> *"Prevent new infections and reduce AIDS-related deaths among children, adolescents, and adults" (NDOH, 2015, p. 16).*

[4] "Zero preventable deaths associated with HIV and TB" (Heywood, 2011, p.21).

> *" viral load testing as a preferred approach for monitoring ART success and diagnosing treatment failure" (NDOH, 2015, p.16).*

[4] "Viral load is the best gauge of the level of HIV in the body" (Healthline, 2015, para.5).

[4] "Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. Measurement of CD_4 count is particularly useful before initiation of ART" (AIDS info, 2014, c5).

> *"Provide lifelong ART for all pregnant and breastfeeding women living with HIV" (NDOH, 2015, p. 16).*

[1a] High baseline VL and short exposure to ARVs for PMTCT are risk factors for failing to achieve undetectable VL. These findings support the new WHO guidelines for early initiation of ARV prophylaxis for PMTCT for maximal reduction of maternal VL. (Okonji et al., 2012, p.249).

[1a] "The findings of this review support reducing or stopping routine CD_4 monitoring for patients who are immunologically stable on ART in settings where routine viral load monitoring is provided" (Ford et al., 2015, p.1).

> *"Initiate ART earlier at a CD_4 count threshold of 500 cells/µl" (NDOH, 2015, p. 16).*

[1a] This systematic review provides an evidence-based comparison of starting treatment at >500 cells/μL with starting treatment at the range between 350 cells/μL and 500 cells/μL. An 11% increase in risk was detected from initiation therapy at the 350–500 cells/μL range (0.37 [0.26, 0.53]), when compared with starting treatment before 500 cells/μL (0.33 [0.22, 0.48]). Most individual study comparisons showed a benefit for starting treatment at 500 cells/μL in comparison with starting at the 350–500 cells/μL range with risks ranging from 19% to 300%, though a number of comparisons were not statistically significant. (Olubajo et al., 2014, p.1).

[1b] "The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy" (Cohen et al., 2011, p.493).

"Prioritise initiation of patients with CD_4 count of <200 cells/μl, severe HIV disease and HIV/TB co-infection" (NDOH, 2015, p.16).

[1b] …median time delay between starting TB treatment and starting ART was 51 days However, this study found delays to starting ART were substantial, and a fifth of eligible patients did not start ART at all. These data show that the co-location of services alone is insufficient to permit timely initiation of ART, and further measures must be implemented to facilitate integrated treatment" (Nglazi et al., 2012, p. 939).

[1a] The results of several randomised controlled trials addressing when to start ART in TB, with a primary endpoint of survival, have indicated that immediate ART (within 2 weeks) improves survival in patients with advanced AIDS (CD_4 <50). Despite increased risk of IRIS, there is still a survival benefit to immediate therapy. In those patients with CD_4 >50, then early ART (within 2 months) provides a good balance of competing risks of death/AIDS v. IRIS. It is important to recognise that time delays between the onset of TB symptoms and starting ART in those eligible for ART are associated with potentially preventable HIV-related mortality and that all delays should be minimised. (Bekker & Wood, 2011, p.7).

"Strengthen retention in care and adherence to ART" (NDOH, 2015, p.16).

[3] Nonadherence in the management of chronic illness is a pervasive clinical challenge…Specifically; baseline data indicated social support was associated with less negative affect and greater spirituality, which, in turn, were associated with self-efficacy to adhere. Self-efficacy to adhere at baseline predicted self-reported adherence at 3 months, which predicted chart-extracted viral load at 6 months. (Simoni, Frick & Huang, 2006, p. 74).

[3] Individuals living with HIV encounter many barriers to access and adherence to treatment. This non-systematic review revealed few effective evidence-based strategies to guide clinicians, public health practitioners, and other health care providers. These findings make a compelling case for more data on improving delivery of ART in LMIC. (Scanlon & Vreeman, 2013, p.17).

"Reinforce phasing out of d4T in first-line regimens" (NDOH, 2015, p.16).

[4] However; d4T has fallen out of favour as a drug for use in first-line therapy due to the increased risk of body fat side-effec ts. In June 2003, the British HIV Association recommended against the use of d4T in an initial anti-HIV drug regimen. In 2009, the World Health Organization recommended against the use of d4T because of its long-term, irreversible side-effects. (NAM Publications, 2015, para.3).

[3] "Stavudine-based treatment regimens in low-income countries are associated with significant long-term toxicities, predominantly lipoatrophy. Close clinical monitoring for toxicity with timely D4T substitution is recommended. Phasing-out of stavudine should be implemented, as costs allows" (Phan, Thai, Choun, Lynen & van Griensven, 2012, p.1).

"Ensure that HIV and TB services are provided as part of integrated maternal and child health, and sexual and reproductive health services" (NDOH, 2015, p.16).

[2b] The importance of integrating the two services that are vertically run is expected to improve access to and uptake of key essential services and extend coverage to

underserved and vulnerable populations and thus minimizing missed opportunities. Experts around the world recognize the central role of Sexual and Reproductive Health (SRH) services in preventing HIV infection. Evidence suggests that improving access to contraception for women to prevent pregnancy is an important and cost-effective way to prevent HIV-positive births. Integrating SRH and HIV services therefore verifies its importance for improving maternal and child health as well as leading to prevention of HIV infection. (Mutalemwa et al., 2013, p.1).

[4] Countries will prioritise integration between HIV services for pregnant women and maternal, new-born and child health, family planning, orphans and vulnerable children and other relevant programmes and services in order to expand the coverage of HIV services, increase access, strengthen linkages and referrals, improve quality and optimize the use of resources. Countries will do this in particular by integrating the provision of HIV testing and counselling antiretroviral prophylaxis and treatment into antenatal care and maternal new-born and child health services. In addition, the provision of family planning will be integrated into HIV programmes for women living with HIV. Depending on the national context, countries may seek to strengthen maternal, new-born and child health and antenatal care platforms. (The Joint United Nations Programme on HIV/AIDS [UNAIDS], 2011, p.26).

> *"Managing HIV as a chronic health condition" (NDOH, 2015, p.18).*

[4] The success of antiretroviral therapy has led some people to now ask whether the end of AIDS is possible. For patients who are motivated to take therapy and who have access to lifelong treatment, AIDS-related illnesses are no longer the primary threat, but a new set of HIV-associated complications have emerged, resulting in a novel chronic disease that for many will span several decades of life. (Deeks, Lewin & Havlir, 2013, p. 1525).

> *"HCT should be offered to all pregnant and breastfeeding women with unknown HIV status or those who tested HIV-negative 3 or more months previously" (NDOH, 2014, p.22).*

> *All women who test negative should be offered repeat HIV testing every 3 months throughout pregnancy, at labour/delivery, at the 6-week EPI visit and 3 monthly throughout breastfeeding (NDOH, 2015, p.23).*

[3] In studies in Botswana and SA, new mothers with negative HIV test results or of unknown HIV status were tested immediately post-partum or at infant immunisation visits. The results demonstrated a seroconversion rate of 2.4 - 7.9% during pregnancy and post-partum. These women are at high risk of vertical transmission. Repeat HIV testing of mothers during late pregnancy, at delivery or at the clinic immunisation visits, would identify women who acquire HIV during pregnancy and in the early post-partum period. The HIV diagnosis of infants whose mothers tested negative during pregnancy is often delayed, with significant implications for morbidity and mortality. Most SA women deliver at a healthcare facility and 99% attend the 6-week vaccination visit. Moreover, testing at these time-points shows high uptake, while offering HIV tests to both partners may identify discordant couples and allow counselling on HIV prevention. (Kalk et al., 2013, p.92).

> *All pregnant women should be encouraged to book into antenatal care early, as soon as they believe they are or are confirmed to be pregnant. They should be offered HCT at their first antenatal visit (NDOH, 2015, p.22).*

[3] Women were interviewed in the labour wards post-delivery about their ANC experience. Gestational age at first clinic visit was compared to gestational age at booking (ANC service provided). ANC attendance was high (97.0%) with 46.0% seeking care before 20 weeks gestation (early). Among the 198 women who sought care, 19.2% were asked to return more than a month later, resulting in a 3-month delay in being booked into the clinic for these women. Additionally 49.0% of women reported no antenatal screening being conducted when they first sought care at the clinic. Delay in recognizing pregnancy (21.7%) and lack of time (20.8%) were among the reasons women gave for late attendance. Clinic booking procedures and delays in diagnosing pregnancy are important factors causing women to access antenatal care late. In a country where

a third of pregnant women are HIV infected, early ANC is vital in order to optimise ART initiation and thereby reduce maternal mortality and paediatric HIV infection. It is therefore imperative that existing antenatal care policies are implemented and reinforced and that women are empowered to demand better services. (Solarin & Black, 2013, p. 359).

[3]…the percentage using antenatal care, the number of antenatal visits and the timing of the first antenatal visit during the pregnancy of the youngest child were analysed.78.2% of the mothers had received antenatal care services, but only12.9% had at least five antenatal visits. (Ren, 2011, e260).

"They must also be counselled on safe infant feeding, be assisted in making appropriate feeding choices, be informed and counselled that exclusive breastfeeding for the first six months is the best option" (NDOH, 2015, p.23).

[4] In settings where formula feeding is not affordable, HIV infected women were counselled to exclusively breastfeed their infants up to age six months and then to wean the infant. However, post-weaning, the infant can acquire serious gastroenteritis and/or malnutrition and both conditions could lead to death of the child. (Taha, 2010, p.919)

[4] Comprehensive services are provided to ensure that all mothers are supported to exclusively breastfeed their infants for six months, and thereafter to give appropriate complementary foods, and continue breastfeeding up to two years of age and beyond. Mothers with HIV should breastfeed for 12 months according to national guidelines. They should also be informed and counselled that complementary foods should only be introduced from 6 months of age, with continued breastfeeding up to 12 months. (News, 2011, p.214).

"All pregnant women are encouraged to involve partners or spouses during HCT and in caring for the pregnancy. Condom use during pregnancy should be encouraged" (NDOH, 2015, p.23).

[4] Duty and responsibility of ALL health care personnel: It is the duty and responsibility of ALL health care workers to identify HIV-positive men, women and their partners, HIV exposed and HIV-positive infants, children and youth so that they can access HIV care. Practised within a human and child rights framework, this critical intervention should prolong life and optimise maternal and child survival. (National Department of Health [NDOH], 2009, p.24).

> *"All pregnant women are encouraged to be registered on MomConnect" (NDOH, 2015, p.23).*

[4] The Department of Health will this Women's month launch a project which seeks to register all pregnant women in the country for an sms service which provides information and advice on pregnancy as well as a channel to notify them about poor service. (South African Government Agency, 2014, para.1).

Women who test HIV-positive on the initial screening test should have their HIV status confirmed using a second rapid HIV test with another test type in compliance with HCT policy as in Algorithm 1. Discordant results should be confirmed with an ELISA test. (NDOH, 2015, p.23).

[4] If the first rapid HIV test is positive (reactive), a confirmatory HIV test (second rapid test) should immediately be performed from a second finger prick utilising a different rapid test kit product. A client is considered to be HIV-positive if the second rapid test is also positive. A record should be kept and updated on all identified relevant indicators. (NDOH, 2009, p.49).

> *"All confirmed HIV-positive women are eligible for immediate initiation with lifelong ART, preferably FDC" (NDOH, 2015, p.23).*

[3] Discontinuing ART during pregnancy increases the rate of mother-to-child transmission of HIV-1, either when ART is stopped in the first trimester and subsequently restarted or when it is interrupted in the third trimester. This finding supports

recommendations to continue ART in pregnant women who are already receiving treatment for their health. (Galli et al., 2009, p.1310).

> *All women who test negative should be offered repeat HIV testing every 3 months throughout pregnancy, at labour/delivery, at the 6-week EPI visit and 3 monthly throughout breastfeeding. They should also be provided with a TB symptom screen with each visit. (NDOH, 2015, p.23).*

[4] South Africa ranks the third highest in the world in terms of TB burden (0.4–0.59 million), after India (2.0–2.5 million) and China (0.9–1.2 million). HIV is fuelling the TB epidemic with more than 70% of TB patients also living with HIV. (Heywood, 2011, p. 23).

> *“All HIV tests performed and results obtained must be documented in the Road-to-Health (RTH) booklet, including the laboratory tracking barcode" (NDOH, 2015, p.28).*

[4] Health care workers providing care and follow-up to the mother or the infant can use health cards that specify infection status and HIV exposure. Health cards can contain the following information:

• HIV status of the mother and interventions given
• Postnatal recording of delivery interventions given
• Feeding option initiated
• Interventions given to baby, including feeding, cotrimoxazole, early diagnostic testing, and ARV prophylaxis
• Antiretroviral drugs provided to the mother and/or infant
• HIV testing status for the infant. (AIDS Star, n.d., para.1).

[4] “Therefore, to minimize the real risk of significant loss to follow-up, strong links and referral mechanisms must be assured to support the transition from ANC to ART services (WHO, 2012a, p.44).

> *Barriers include having to travel long distances to the clinic, long waiting times at the clinic, clinic staff shortages, inability to take time off work, lack of full understanding of the treatment plan, and fear of stigma and discrimination. However, when effectively linked to prevention, treatment and care services, HCT enables those being tested to make positive health-related decisions. (NDOH, 2015, p. 36).*

[4] "Long queues, shortage of doctors and nurses, scarcity of female condoms, lack of proper infection control, lengthy walks in order to access ARVs, lack of adherence clubs, shortage of medicines and integration of TB/HIV" (Okunande, 2011, p.7).

[4] "Challenges facing: Refugees, Asylum Seekers and Migrants are; racism and xenophobic attitude, management inabilities and language barriers" (Okunande, 2011, p.9).

> *"TB symptom screening at every visit: test all who have a positive symptom screen; initiate INH prophylaxis if eligible and give TB treatment if tested positive for TB" (NDOH, 2015, p.37).*

[3] The feasibility of INH prophylaxis in TST-positive patients in this setting is possible. However, the long-term advantage of INH prophylaxis in terms of TB prevention, especially in HIV-1-infected patients on highly active antiretroviral therapy (HAART), is still an issue that needs more research. (Khongphatthanayothin et al., 2012, p. 270).

> *"An annual cervical cancer screening (Pap smear) for all HIV-positive women" (NDOH, 2015, p. 37).*

[3] In multivariate analysis, high viral signal, but not viral risk category, was independently associated with persistence among HIV-positive subjects (odds ratio [OR], 2.5; 95% confidence interval [CI], 2.1–2.9). Furthermore, persistence was 1.9 (95% CI, 1.5–2.3) times greater if the subject had a CD_4 cell count <200 cells/mL (vs 1500

cells/mL). Thus, HIV infection and immunosuppression play an important role in modulating the natural history of HPV infection. (Ahdieh et al., 2001, p.682).

> *"At the first ANC visit/HIV diagnosis, the patient should have a CD_4 cell count test and serum creatinine taken and be staged clinically" (NDOH, 2015, p. 38).*

[4] "Creatinine has been found to be a fairly reliable indicator of kidney function. Elevated creatinine level signifies impaired kidney function or kidney disease" (Davis, 2015, p.1).

[4] "Note: it is not possible to assess the eGFR accurately in people with abnormal amounts of muscle and in people who have conditions that can affect the level of creatinine" (Patient.co.uk, 2012, para.10).

[3] "The physiologic increase in GFR during pregnancy normally results in a decrease in concentration of serum creatinine, which falls by an average of 0.4 mg/dl to a pregnancy range of 0.4 to 0.8 mg/dl"(Maynard & Thadhani, 2009, p.14).

> *"Patients should be screened and swiftly treated for syphilis and other STIs, in line with basic antenatal care" (NDOH, 2015, p. 38).*

[1b] "The high seroconversion rates for both syphilis and HIV infection in pregnancy justifies re-screening for these conditions in endemic areas such as ours" (Qolohle, Hoosen, Moodley, Smith & Mlisana, 1995, p.65).

> *"Encourage disclosure to family or friends" (NDOH, 2015, p.39).*

[4] "Serodiscordant couples who are aware of each other's HIV status may be able to support, access and adherence to treatment, to give each other emotional support, and to support uptake of and adherence to PMTCT interventions" (WHO, 2012a, p.14).

> *Monitor and offer ongoing adherence support. Be supportive and non-judgmental to encourage open and honest patient communication. Adherence goal is >95% of doses taken. Patients with adherence <80% require more adherence support. Missed appointments for prescription pick-ups are a powerful predictor of poor adherence, and should trigger immediate questions about issues that may affect attendance and adherence. Routine adherence discussion/education with adherence counsellors is valuable. (NDOH, 2015, p.39).*

[3] "Non-adherence in the management of chronic illness is a pervasive clinical challenge" (Simoni et al., 2006, p.1).

> *"Address adverse events, interim illness and issues around stigma and disclosure" (NDOH, 2015, p. 39).*

[3] "Beyond the difficult medical prognosis, knowledge of HIV-positive status is of great social consequence, and stigma and violence are still actual threats for African women"(Audureau, Kahn, Besson, Saba & Ladner, 2013, p.5).

> *"The goal of ART treatment is to reduce the patient's VL to an undetectable level and ensure that it remains undetectable, as well as to improve the immunological status with the CD_4 count rising and remaining above the baseline" (NDOH, 2015, p. 44).*

[4] "Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. Measurement of CD_4 count is particularly useful before initiation of ART" (AIDS info, 2014, c5).

[4] "Keeping your CD_4 count high can reduce complications of HIV disease and extend your life" (WebMD, 2015, para 2).

[4] CD_4 cells, also called T-cells, are like the alarm bells of the immune system. They alert the immune system to invading viruses and bacteria. Certain receptors on the CD_4

cell make them a prime target for HIV infection. Infection lowers CD_4 count. Lower CD_4 count means a weaker immune system. (Healthline, 2015, para.2).

"All HIV-positive women require management and care during the antenatal, labour, delivery and postnatal phases" (NDOH, 2015, p.44).

[3] Among 69 HIV-infected children (26% of the cohort), 23% (95% confidence interval [Cl], 14%-35%) were estimated to have had intrauterine, 65% (CI, 53%-76%) intrapartum/ early postpartum, and 12% (Cl, 5%-22%) late postpartum transmission. The estimated risks for intrauterine, intrapartum/early postpartum, and late postpartum infection, respectively, were 6% (16/261; CI, 4%-10%), 18% (45/245; CI, 14%-24%), and 4% (8/189; CI, 2%-8%). These results support earlier studies indicating that most transmission occurs during labor and delivery or in the early postpartum period and that the risk of HIV transmission through breast-feeding during the postpartum period is substantial (Bertolli et al., 1996, p.722).

"This includes iron" (NDOH, 2015, p.44).

[3] "Pregnancy further increases iron requirements" (Beaufrère et al., 1995, p.1209).

"…folate…" (NDOH, 2015, p. 44).

[4] All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs. Because the effects of high intakes are not well known but include complicating the diagnosis of vitamin B12 deficiency, care should be taken to keep total folate consumption at <1 mg per day, except under the supervision of a physician. Women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice. (U.S. Department of Health and Human Services, 1992, p.5).

"…and calcium supplementation…" (NDOH, 2015, p.44).

[1b] "Calcium supplementation appears to be beneficial for women at high risk of gestational hypertension and in communities with low dietary calcium intake" (Atallah, Hofmeyr & Duley, 2000, para.7).

"the provision of ARVs; the diagnosis, prevention and management of opportunistic infections," (NDOH, 2015, p. 44).

[4] "One of the vision and goals of the National Strategic Plan [NSP] on HIV, STI and TB 2012-2016 is "Zero new HIV and TB infections" and "Zero preventable deaths associated with HIV and TB" (Heywood, 2011, p.21).

"…including TB…" (NDOH, 2015, p.44).

[4] "South Africa currently ranks the third highest in the world in terms of TB burden, with an incidence that has increased by 400% over the past 15 years" (Heywood, 2011, p.12).

[3] …the modification of obstetric practices, especially during labour and delivery; and counselling on infant feeding, safer sex, family planning and contraception. "Among 69 HIV-infected children (26% of the cohort), 23% (95% confidence interval [CI], 14%-35%) were estimated to have had intrauterine, 65% (CI, 53%-76%) intrapartum/early postpartum, and 12% (CI, 5%-22%) late postpartum transmission. The estimated risks for intrauterine, intrapartum/early postpartum, and late postpartum infection, respectively, were 6% (16/261; CI, 4%-10%), 18% (45/245; CI, 14%-24%), and 4% (8/189; CI, 2%-8%). These results support earlier studies indicating that most transmission occurs during labor and delivery or in the early postpartum period and that the risk of HIV transmission through breast-feeding during the postpartum period is substantial. (Bertolli et al., 1996, p.722).

"All HIV-positive pregnant women should receive ART with appropriate counselling from their first antenatal visit regardless of gestational age" (NDOH, 2015, p.44).

[3] …the percentage using antenatal care, the number of antenatal visits and the timing of the first antenatal visit during the pregnancy of the youngest child were analysed.78.2% of the mothers had received antenatal care services, but only12.9% had at least five antenatal visits and 35.2% had their initial visit in the first trimester. Only 9.0% whose first antenatal visit took place during the first trimester had at least five antenatal visits. (Ren, 2011, c260).

[1b] "Over 96 weeks, the combination of TDF, FTC, and EFV was superior to fixed-dose ZDV/3TC + EFV for achieving and maintaining an HIV RNA level ,400 copies/mL and an increase in CD_4 cells" (Pozniak et al., 2006, p.535).

[1b] "Through 144 weeks, the combination of tenofovir DF, lamivudine, and efavirenz was highly effective and comparable with stavudine, lamivudine, and efavirenz in antiretroviral-naive patients. However, tenofovir DF appeared to be associated with better lipid profiles and less lipodystrophy" (Gallant et al., 2004, p.191).

[1b] Through week 48, the combination of tenofovir DF and emtricitabine plus efavirenz fulfilled the criteria for non-inferiority to a fixed dose of zidovudine and lamivudine plus efavirenz and proved superior in terms of virologic suppression, CD_4 response and adverse events resulting in discontinuation of the study drugs. (Gallant et al., 2006, p.251).

"All women should start this regimen at the first antenatal clinic visit" (NDOH, 2014, p. 44).

[4] "Triple ARVs starting as soon as diagnosed, continued for life" (WHO, 2012b, p.2).

"All unbooked women who test positive during labour should be given prophylactic ART during Labour" (NDOH, 2015, p.44).

[1b] "A single dose of tenofovir and emtricitabine at delivery reduced resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery by half; therefore this treatment should be considered as an adjuvant to intrapartum nevirapine" (Chi et al., 2007, p.1698).

[1b] "Postexposure prophylaxis can offer protection against HIV infection to babies of women who missed opportunities to be counselled and tested before or during pregnancy. The nevirapine and zidovudine regimen is safe and easy to implement" (Taha et al., 2003, p.1711).

[1b] A maternal short-course zidovudine regimen reduces MTCT of HIV-1 at age 24 months, despite prolonged breastfeeding. However, efficacy was observed only among women with CD_4 cell counts > or =500/ml. New interventions should be considered to prevent MTCT, especially for African women with advanced HIV-1 immunodeficiency. (Leroy et al., 2002, p.631).

"Emphasise exclusive breastfeeding for the first 6 months" (NDOH, 2015, p. 44).

[4] Comprehensive services are provided to ensure that all mothers are supported to exclusively breastfeed their infants for six months, and thereafter to give appropriate complementary foods, and continue breastfeeding up to two years of age and beyond. Mothers with HIV should breastfeed for 12 months according to national guidelines. They should also be informed and counselled that complementary foods should only be introduced from 6 months of age, with continued breastfeeding up to 12 months. (News, 2011, p.214).

> *"Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done. Pregnant women Creatinine ≤85µmol/l and any CD_4 cell count" (NDOH, 2015, p.45).*

[4] "Creatinine has been found to be a fairly reliable indicator of kidney function. Elevated creatinine level signifies impaired kidney function or kidney disease" (Davis, 2015, para.3).

[4] "Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. Measurement of CD_4 count is particularly useful before initiation of ART" (AIDS info, 2014, c-5).

> *"Contraindication to EFV (active psychiatric illness)" (NDOH, 2015, p. 45).*

[4] If you are allergic to efavirenz or any other medicines. If you have ever had liver problems, including hepatitis B or C infection. If you have ever had mental illness. If you have ever used drugs or large amounts of alcohol. If you have ever had seizures or are taking medicine for seizures. If you have any other medical conditions. (Bristol-Myers Squibb, 2014 para.9).

> *"sdNVP + sd Truvada and AZT 3-hourly in labour" (NDOH, 2015, p. 45).*

[1b] "A single dose of tenofovir and emtricitabine at delivery reduced resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery by half; therefore this treatment should be considered as an adjuvant to intrapartum nevirapine" (Chi et al., 2007, p.1698).

> *When determining renal function in pregnancy, it is important to note that other methods of estimating renal function, including estimated glomerular filtration rate (GFR) from the Cockroft- Gault equation, are inaccurate in pregnancy. The use of serum creatinine and not the GFR should be used (NDOH, 2015, p. 48).*

[4] “Note: it is not possible to assess the GFR accurately in people with abnormal amounts of muscle and in people who have conditions that can affect the level of creatinine” (Patient.co.uk, 2012, para.9).

“Do VL for all pregnant and breastfeeding women at first visit regardless of when the last VL was done” (NDOH, 2015, p.48).

[4] “Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. Measurement of CD_4 count is particularly useful before initiation of ART” (AIDS info, 2014, c5).

“To identify eligibility for CrAg or CLAT (CD_4<100)” (NDOH, 2015, p. 48).

[3] Despite access to antiretroviral therapy, mortality from cryptococcal meningitis (CM) is high among persons with advanced HIV infection in sub-Saharan Africa. Cryptococcal antigen (CrAg) is present several weeks to months before the onset of symptoms of meningitis and can be screened to prevent life threatening meningitis. Recently, the World Health Organisation recommended that a new rapid CrAg lateral flow “dipstick” assay (LFA) is to be used to screen HIV-infected persons with CD_4 counts of less than 100 cells/μL. In this paper, we describe two cases of cryptococcosis with differing outcomes. In the first case, the new CrAg LFA was used as part of a screen and preemptive treatment strategy to prevent CM. In the second case, our patient had no access to the CrAg LFA and subsequently developed life threatening meningitis. (Dhana, 2013, p.1).

“Screening for STIs and syphilis” (NDOH, 2015, p. 48).

[1b] “The high seroconversion rates for both syphilis and HIV infection in pregnancy justifies re-screening for these conditions in endemic areas such as ours”. (Qolohle et al.,1995, p.65).

> *"Do VL at confirmation of pregnancy if already on ART>3 months. VL at months 3, 6, 12, 18, 24 throughout pregnancy and breastfeeding" (NDOH, 2015, p.49).*

[4] "Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. Measurement of CD_4 count is particularly useful before initiation of ART" (AIDS info, 2014, c5).

> *"Assess adherence carefully" (NDOH, 2015, p.50).*

[3] "Non adherence in the management of chronic illness is a pervasive clinical challenge" (Simoni et al., 2006, p.1).

> *"Mothers are encouraged to exclusively breastfeed their infants during the first 6 months of life, with appropriate complementary foods being introduced from 6 months and breastfeeding continuing for up to 2 years and beyond" (NDOH, 2014, p.51).*

[3] "HAART while breastfeeding could be a promising alternative strategy in resource-limited countries" (Peltier et al., 2009, p.2415).

[4 Comprehensive services are provided to ensure that all mothers are supported to exclusively breastfeed their infants for six months, and thereafter to give appropriate complementary foods, and continue breastfeeding up to two years of age and beyond. Mothers with HIV should breastfeed for 12 months according to national guidelines. They should also be informed and counselled that complementary foods should only be introduced from 6 months of age, with continued breastfeeding up to 12 months. (News, 2011, p.214).

> *"All HIV-exposed infants not on ART should have a rapid test at 18 months of age to confirm HIV status conferred by the 6-week HIV PCR test" (NDOH, 2015, p.52).*

[4] “Early infant diagnosis…is performed by an HIV polymerase chain reaction (PCR) test recommended at ~6 weeks of age” (Sherman et al., 2014, p. 235).

> *“Mothers of unknown HIV status or who are HIV-negative should be tested 3-monthly” (NDOH, 2015, p.52).*

[4] However, there is still a possibility of being infected, since it can take up to three months for your immune system to produce enough antibodies to show infection in a blood test. It is advisable to be re-tested at a later date, and to take appropriate precautions in the meantime. During the window period, a person is highly infectious, and should therefore take measures to prevent any possible transmission. (AIDS Foundation of South Africa, 2014, para.10).

> *…”throughout pregnancy, at labour/delivery”… (NDOH, 2015, p.52)*

[3] This study is the first to show in West Africa that HIV testing in a labour room is feasible and well accepted by pregnant women. HIV screening in labour rooms needs to be routinely implemented to reduce missed opportunities for intervention aimed at HIV care and prevention, especially PMTCT (Ekouevi et al., 2012, p.1).

> *“All HIV-positive women who started FDC (TDF+FTC(3TC)+EFV) or another triple-drug regimen during the antenatal period should continue to receive this regimen throughout labour and delivery ” (NDOH, 2015, p.47).*

[3] Discontinuing ART during pregnancy increases the rate of mother-to-child transmission of HIV-1, either when ART is stopped in the first trimester and subsequently restarted or when it is interrupted in the third trimester. This finding supports recommendations to continue ART in pregnant women who are already receiving treatment for their health. (Galli et al., 2009, p. 1310).

> *"Infants born to HIV-positive women should receive skin-to-skin contact with their mothers almost immediately, regardless of the mother's infant feeding choice" (NDOH, 2015, p.53).*

[1a] "Significant between-group differences favouring Skin to Skin Contact mothers were noted in summary scores of affectionate love/touch, contact behavior early postpartum, and holding the infant positively and affectionate touch at one year" (Moore, Anderson & Bergman, 2009, p.10).

> *"Infants born to HIV-positive women should receive daily NVP for 6 weeks" (NDOH, 2015, p. 54).*

[1b] Although a 6-week regimen of daily nevirapine might be associated with a reduction in the risk of HIV transmission at 6 weeks of age, the lack of a significant reduction in the primary endpoint—risk of HIV transmission at 6 months—suggests that a longer course of daily infant nevirapine to prevent HIV transmission via breast milk might be more effective where access to affordable and safe replacement feeding is not yet available and where the risks of replacement feeding are high. (Six Week Extended-Dose Nevirapine (SWEN) Study Team, 2008, p.300).

> *"A transfer or referral letter must at the minimum stipulate when ART was initiated, record baseline and monitoring blood results and outline the management plan for both mother and infant" (NDOH, 2015, p. 54).*

[4] "Therefore, to minimize the real risk of significant loss to follow-up, strong links and referral mechanisms must be assured to support the transition from ANC to ART services" (WHO, 2012a, p. 44).

> *"IRIS occurs when improving immune function unmasks a previously occult opportunistic infection which subsequently presents with an unusually aggressive*

> *inflammatory presentation, or causes paradoxical deterioration of an existing opportunistic disease" (NDOH, 2015, p. 71).*

[3] Soon after HAART initiation, a marked inflammatory reaction can occur, triggered by restoration of pathogen-specific immunity. IRIS may be targeted by various infective antigens, dead or dying infective antigens, host antigens, tumor antigens and other antigens, giving rise to a heterogeneous range of clinical manifestations. Treatment should be optimized for the associated condition and initiated immediately. Glucocorticoids should be used in patients who are severely affected by IRIS. (Wagner, 2008. p.286).

> *"Known hepatitis B viral (HBV) co-infection" (NDOH, 2014, p. 71).*

[4] Liver cancer is almost always fatal and often develops in people at an age when they are most productive and have family responsibilities. In developing countries, most people with liver cancer die within months of diagnosis. In high-income countries, surgery and chemotherapy can prolong life for up to a few years. (WHO, 2015, para. 23)

> *"Mothers must be counselled about the risks of mixed feeding their infants during their first 6 months of life, as exclusive breastfeeding reduces the risk of HIV transmission and improves child survival" (NDOH, 2015, p.87).*

[4] Comprehensive services are provided to ensure that all mothers are supported to exclusively breastfeed their infants for six months, and thereafter to give appropriate complementary foods, and continue breastfeeding up to two years of age and beyond. Mothers with HIV should breastfeed for 12 months according to national guidelines. They should also be informed and counselled that complementary foods should only be introduced from 6 months of age, with continued breastfeeding up to 12 months. (News, 2011, p.214).

> *"HIV-positive mothers who decide not to breastfeed their infants (after appropriate counselling and education) should understand that formula is not routinely provided as part of the PMTCT programme at public health facilities and be counselled on appropriate exclusive formula feeding in amount and frequency for optimal growth and development. They should be able to provide adequate formula for their infant as a replacement feed to their HIV uninfected infants when specific conditions are met. (NDOH, 2015, p.87).*

[4] "Formula feeds will no longer be provided at public health facilities, with the following exceptions: Nutritional supplements, including formula feeds, will be available on prescription by appropriate healthcare professionals for mothers, infants and children with approved medical conditions" (News, 2011, p.214).

> *"All pregnant women should receive Ferrous sulphate (FeSO4)1 tablet daily" (NDOH, 2015, p. 90).*

[4] "Weekly iron (60 mg of ferrous sulphate) and folic acid (3 mg) supplementation (WIFS) for WRA, including adolescent girls between 10–19 years could be an effective strategy to achieve good iron stores before a woman becomes pregnant" (Goonewardene, Shehata & Hamad, 2012, p.7).

> *…and folic acid 5 mg (1tablet) daily throughout their pregnancy. All women should be given nutritional advice and counselled on the importance of taking their tablets (NDOH, 2015, p.90).*

[4] Anaemia in pregnancy, defined as a haemoglobin concentration (Hb) < 110 g/L, affects more than 56 million women globally, two thirds of them being from Asia. Multiple factors lead to anaemia in pregnancy, nutritional iron deficiency anaemia (IDA) being the commonest. Underlying inflammatory conditions, physiological haemodilution and several factors affecting Hb and iron status in pregnancy lead to difficulties in establishing a definitive diagnosis. IDA is associated with increased maternal and perinatal morbidity

and mortality, and long-term adverse effects in the new born. Strategies to prevent anaemia in pregnancy and its adverse effects include treatment of underlying conditions, iron and folate supplementation given weekly for all menstruating women including adolescents and daily for women during pregnancy and the post partum period, and delayed clamping of the umbilical cord at delivery. Oral iron is preferable to intravenous therapy for treatment of IDA. B12 and folate deficiencies in pregnancy are rare and may be due to inadequate dietary intake with the latter being more common. These vitamins play an important role in embryo genesis and hence any relative deficiencies may result in congenital abnormalities. Finding the underlying cause are crucial to the management of these deficiencies. Haemolytic anaemias rare also rare in pregnancy, but may have life-threatening complications if the diagnosis is not made in good time and acted upon appropriately. (Goonewardene et al., 2012, p.3).

> *"Cryptococcus is usually only a problem if CD_4 count drops to below 100 cells/µl. Smokers and people who work outdoors have higher risk of Cryptococcus" (NDOH, 2015, p. 99).*

[3] Despite access to antiretroviral therapy, mortality from cryptococcal meningitis (CM) is high among persons with advanced HIV infection in sub-Saharan Africa. Cryptococcal antigen (CrAg) is present several weeks to months before the onset of symptoms of meningitis and can be screened to prevent life threatening meningitis. Recently, the World Health Organisation recommended that a new rapid CrAg lateral flow "dipstick" assay (LFA) is to be used to screen HIV-infected persons with CD_4 counts of less than 100 cells/μL. In this paper, we describe two cases of cryptococcosis with differing outcomes. In the first case, the new CrAg LFA was used as part of a screen and preemptive treatment strategy to prevent CM. In the second case, our patient had no access to the CrAg LFA and subsequently developed life threatening meningitis. (Dhana, 2013, p.1).

4.5 Summary

A total of twelve guidelines were sampled by WHO and Department of Health South Africa published between 2001 to 2015. The document analysis was only based on the *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults April, 2015.* The comparison detailing treatment received by women in pregnancy, labour and postpartum including the infant regimen irrespective of feeding choice was conducted from the twelve guidelines. Extraction from NDOH, 2015 was supported with evidence from accredited resources. The scaling was done according to National Health and Medical Research Council [NHMRC] Guidelines, (2009). Some findings were supported with good evidence whereas other finding had low levels of support.

The results of the systematic review will be presented in Chapter five.

Chapter Five
Systematic Review

5.1 Introduction

A total of 25 primary studies that assessed the efficacy of ARV regimens to prevent mother-to-child transmission of the HIV during pregnancy, birth, and the postnatal period were systematically reviewed. Therefore were included in a meta-analysis using the RevMan 5.3 computer software. A short summary description of each included study is discussed. Chapter five presents the interpretation of the meta-analysis and the results are depicted as forest plots.

5.2 Inclusion criteria

Specific predetermined criteria were used to evaluate studies for inclusion in the systematic review.

5.2.1 Types of Studies

Randomised controlled trials (RCT) of antiretroviral regimens intended to reduce the risk of mother-to-child transmission (MTCT) of HIV infection comparing different types of antiretroviral medication or different durations of treatment.

5.2.2 Types of Participants

Participants were pregnant women on any PMTCT programme and/or infants born from HIV-positive women.

5.2.3 Types of Interventions

Antiretroviral therapy intended to explicitly reduce the risk of mother-to-child transmission of HIV infection.

5.2.4 Search Strategy

The researcher and supervisor independently reviewed the articles to ensure the inclusion criteria were met. University of Fort Hare librarians were requested to assist with the initial search strategy. The titles of the search strategy were examined and abstracts of 237 studies were requested and evaluated. After reading the abstracts of the 237 articles, 198 articles were excluded as they were not relevant or did not meet all the inclusion criteria. Full texts of 39 articles were studied and the methodology assessed. Out of the 39 studies a further 14 were excluded due to methodological shortcomings. This systematic review is based on 25 studies that met the inclusion criteria (Figure 5.1).

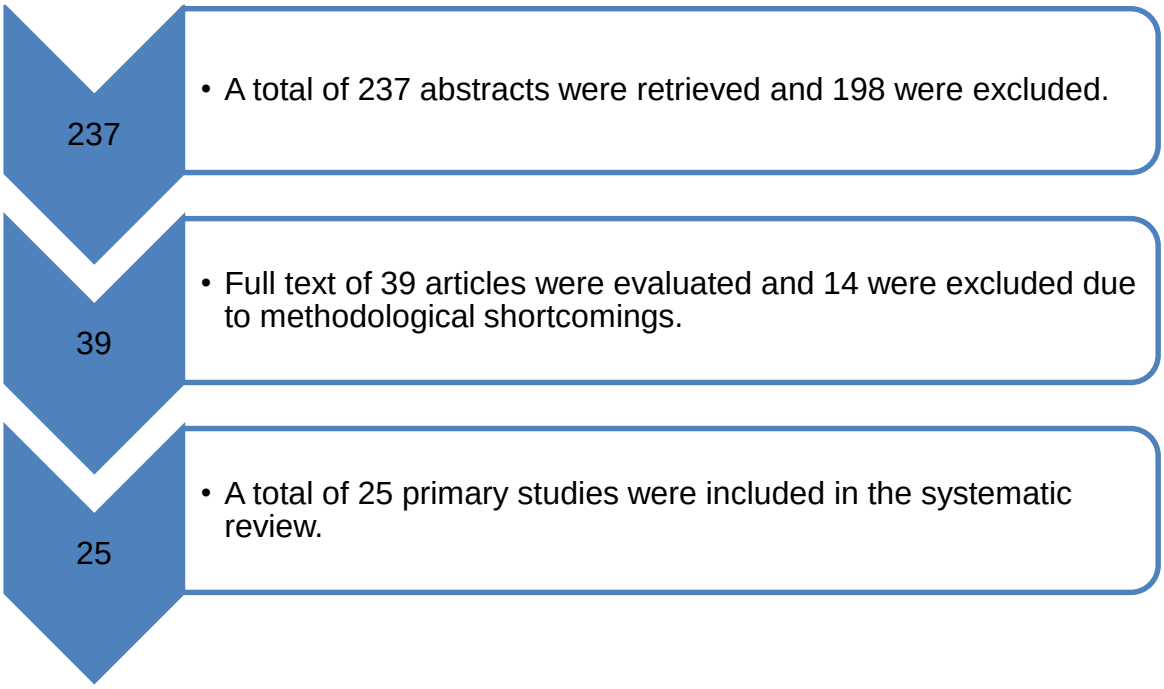

Figure 5.1 Search Strategy

5.3 Excluded Studies after Full Evaluation

The following fourteen studies were excluded after full evaluation of the published articles (Table 5.1).

Table 5.1 References of Excluded Studies

#	Reference
1	Bhadrakom, C., Simonds, R. J., Mei, J.V., Asavapiriyanont, S., Sangtaweesin, V., Vanprapar, N., Moore, K.H.P., Young, N.L., Hannon, W.H., Mastro, T.D., & Shaffer, N., for the Bangkok Collaborative Perinatal HIV Transmission. (2000). Oral zidovudine during labour to prevent perinatal transmission, Bangkok: Tolerance and zidovudine concentration in cord blood. *AIDS*, *14(*5), 509–516.
2	Chi, B.H., Chintu, N., Cantrell, R.A., Kankasa, C., Kruse, G., Mbewe, F., Sinkala, M., Smith, P.J., Stringer, E.M., & Stringer, J.S.A. (2008). Addition of single-dose tenofovir and emitricitabine to intrapartum nevirapine to reduce perinatal HIV transmission. *Journal Of Acquired Immune Deficiency Syndromes*, *48*(2), 220–3.
3	Chotpitayasunondh, T., Vanprapar, N., Simonds, R. J., Chokephaibulkit, K., Waranawat, N., Mock, P., Chuachoowong,R., Young, N., Mastro, T.D., & Shaffer, N., for the Bangkok Collaborative Perinatal HIV transmission Study Group. (2001). Safety of late in utero exposure to zidovudine in infants born to Human Immunodeficiency Virus infected mothers: Bangkok. *American Academy of Pediatrics. 107*(1), 1–6.
4	Connor, E.M., Sperling, R.S., Gelber, R., Kiseley, P., Scott, G., O'Sullivan, M.J., Bey, M., Van Dyke, R., Shearer, W., Jacobson, R.L., Jimenez, E., O'Niel, E., Bazin, B., Delfraissy, J.F., Culnane, M.,Coombs, R., Elkins, M, Moye, J., Stratton, P., & Balsley, J. (1994). Reduction of maternal-infant transmission of Human Immunodeficiency Virus Type 1 with zidovudine treatment. *The New England Journal of Medicine*, *331*(18), 1174–1180.
5	Dabis, F., Elenga, N., Meda, N., Leroy, V., Viho, I., Manigart, O., Dequae-Merchadou, L., Msellati, P., & Sombie, I., for the DITRAME Study Group. (2001). 18 Month mortality and perinatal exposure to zidovudine in West Africa. *AIDS*, *15(*6), 771–779.
6	Dabis, F., Msellati, P., Meda, N., Welffens-Ekra, C., You, B., Manigart, O., Leroy, V., Simonon, A, Cartoux, M., Combe, P., Ouangre, A., Ramon, R., Ky-Zerbo, O., Montcho, C., Salamon, R., Rouzioux,C., van de Perre, P. & Mandelbrot, L., for DITRAME Study Group. (1999). 6-month efficacy, tolerance and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: A double-blind placebo-controlled multicentre trial. *The Lancet*, *353*(9155), 786–792. doi:10.1016/S0140-6736(98)11046-2.

#	Reference
7	Dorenbaum, A., Cunningham C.K., Gelber, R. D., Culnane, M., Mofenson, L., Britto, P., Rekacewicz, C., Newell, M.L., Francois-Delfraissy, J. Cunningham-Schrader, B., Mirochnick, M.,& Sullivan, J.L., for the International PACTG 316 Team. (2002). Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission. *American Medical Association*, *288*(2), 189–198.
8	Kilewo, C., Karlsson, K., Ngarina, M., Massawe, A., Lyamuya, E., Swai, A., Lipyoga, R., Mhalu, F., & Biberfeld, G., for the Mitra Plus Study Team. (2009). Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: The Mitra Plus Study. *Journal Of Acquired Immune Deficiency Syndromes*, *52*(3), 406–416.
9	Leroy, V., Karon, J.M., Alioum, A., Ekpini, E.R., Meda, N., Greenberg, A.E., Msellati, P., Hudgens, M., Dabis, F., &Wiktor, S.Z., for the West Africa PMTCT Study Group. (2002). Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS*, *16*(4), 631–41.
10	Limpongsanurak, S., Thaithumyanon, P., Chaithongwongwatthana, S., Thisyakorn, U., Ruxrungtham, K., Kongsin, P., Tarounotai, U., Chatentheptaewan, T., Triratwerapong, T., Ubolyam, S., Phanuphak, P., Virutamasen, P., Hanwanich, M., Hawanon, P. & Chulasugondha, P. (2001). Short course zidovudine maternal treatment in HIV-1 vertical randomized controlled multicentre trial. *Journal of the Medical Association of Thailand*, *84*, S338–45.
11	Shaffer, N., Chuachoowong, R., Mock, P.A., Bhadrakom, C., Siriwasin, W., Young, N.L., Chotpitayasunondh, T., Chearskul, S., Roongpisuthipong, A., Chinayon, P., Mastro, T.D., & Simonds, R.J., on behalf of the Collaborative Perinatal HIV Transmission Study Group. (1999). Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet*, *353*, 773–80.
12	Thior, I., Lockman, S., Smeaton, L.M., Shapiro, R.L., Wester, C., Heymann, S.J., Gilbert, P.B., Stevens, L., Peter, T., Kim, S, van Widenfelt, E., Moffat, C., Ndase, P., Arimi, P., Kebaabetswe, P., Mazonde, P., Makhema, J., McIntosh, K., Novitsky, V., Lee, T.H., Marlink, R., Lagakos, S. & Essex, M., for the Mashi Study Team. (2006). Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana. A randomized trial: The Mashi Study. *American Medical Association*, *296*(7), 794–805.
13	Thomas, T.K., Masaba, R., Borkowf, C.B., Ndivo, R., Zeh, C., Misore, A., Otieno, J., Jamieson, D., Thigpen, M.C., Bulterys, M., Slutsker, L., De Cock, K.M., Armornkul, P.N., Greenberg, A.E., F., & Fowler, M.G., for KiBS Study Team. (2011). Triple-antiretroviral prophylaxis to prevent mother-to- child HIV transmission through breastfeeding-The Kisumu Breastfeeding Study, Kenya: A clinical trial. *PLoS Medicine*, *8*(3), e1001015.

#	Reference
14	Wiktor, S.Z., Ekpini, E., Karon, J.M., Nkengasong, J., Maurice, C., Severin, S.T., Roels, T.H., Kouassi, M.K., Lackritz, E.M., Coulibaly, I.M. & Greenberg, A.E. (1999). Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: A randomised trial. Lancet, 353, 781–85.

The reasons for exclusion are given in table 5.2.

Table 5.2 Reasons for Exclusion of Studies

	Author	Reason for exclusion
1	Bhadrakom 2000	Control group got placebo
2	Chi 2008	No intervention during labour
3	Chotpitayasunondh 2001	Control group got placebo
4	Connor 1994	Control group got placebo
5	Dabis 2001	Control group got placebo
6	Dabis 1999	Control group got placebo
7	Dorenbaum 2002	Control group got placebo
8	Kilewo 2009	Non randomised prospective cohort study
9	Leroy 2002	Control group got placebo
10	Limpongsanurak 2001	Control group got placebo
11	Shaffer 1999	Control group got placebo
12	Thior 2006	Control group got placebo
13	Thomas 2011	Results are combined no control or experimental group
14	Wiktor 1999	Control group got placebo

5.4 References of Studies Included in the Meta-analysis

A Study Identification code was allocated to each of the primary studies included in the meta-analysis. Study Identification codes were allocated alphabetically according to first author name or where appropriate the name of the consortium that published the article, followed by the year of publication. Studies that compared different treatments within the same trial, the same Study Identification code was used followed with an alphabetical letter (e.g. Gray 2006a, 2006b and 2006c). The Study ID allocated to each study as well as the full reference of the primary studies included in the meta-analysis is described below in table 5.3.

Table 5.3 Study ID and Reference of Included Studies

#	Study ID	Reference
1	BAN 2010	Chasela, C., Hudgens, M.G., Jamieson, D.J., Kayira, D., Hosseinipour, M.C., Kourtis, A.P., Martinson, F., Tegha, G., Knight, R.J., Ahmed, Y.I., Kamwendo, D.D., Hofman, I.F., Ellington, S.R., Kacheche, Z., Soko, A., Weiner, J.B., Fiscus, S.A., Kazembe, P., Mofolo, I.A. Chigwenembe, M., Sichali, D.S., & van der Horst, C., for the BAN Study Group. (2010). Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. The New England Journal of Medicine, 362(24), 2271–2281.
2	Bhoopat 2005	Bhoopat, L., Khunamornpong, S., Lerdsrimongkol, P., Sirivatanapa, P., Sethavanich, S., Limtrakul, A., Limtrakul, A., Gomutbhuthra, V., Kajanavanich, S., Thorner, P.S. & Bhoopat, T. (2005). Effectiveness of short-term and long-term zidovudine prophylaxis on detection of HIV-1 subtype E in human placenta and vertical transmission. *Journal Of Acquired Immune Deficiency Syndromes*, *40*(5), 545–50.
3	Chi 2007	Chi, B.H., Sinkala, M., Mbewe, F., Cantrell, R.A., Kruse, G., Chintu, N., Aldrovandi, G.M., Stringer, E.M., Kankasa, C., Safrit, J.T & Stringer, J.S.A. (2007). Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: An open-label randomised trial. *Lancet*, *370*, 1698–705. doi:10.1016/S0140- 6736(07)61605-5.
4	Chung 2005	Chung, M.H., Kiarie, J.N, Richardson, B.A., Lehman, D.A., Overbaugh, J. & John-Stewart, G.C. (2005). Breast-milk HIV-1 suppression and decreased transmission: A randomized trial comparing HIVNET 012 nevirapine versus short course zidovudine. *AIDS*, *19*(13), 1415–22. doi:PUBMED:18077838
5	Chung 2008	Chung, M.H., Kiarie, J.N, Richardson, B.A., Lehman, D.A., Overbaugh, J., Kinuthia, J., Njiri, F. & John-Stewart, G.C. (2008). Highly Active Antiretroviral Therapy (HAART) versus zidovudine/ nevirapine effects on early breast milk HIV Type-1 RNA: A phase II randomised clinical trial. *Antiviral Therapy*, *13*(6), 799–807.
6	Gray 2005	Gray, G.E, Urban, M, Chersich, M.F., Bolton, C., van Niekerk R, Violari, A., Stevens, W. & McIntyre, J.A., for the PEP Study Group. (2005). A randomized trial of two post exposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS*, *19*(12), 1289–1297.

#	Study ID	Reference
7	Gray 2006a Gray 2006b Gray 2006c	Gray, G., Violari, A., McIntyre, J., Jivkov, B., Schnittman, S., Reynolds, L. & Ledeine, J. (2006). Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: Its role in preventing HIV infection in infants. *Journal Of Acquired Immune Deficiency Syndromes*, *42*(2), 169-176.
8	HIVNET 012 1999	Guay, L., Musoke, P., Fleming, T., Bagenda, D., Allen, M., Nakabiito, C., Sherman, J., Bakaki, P., Ducar, C., Deseyve, M., Emel, L., Mirochnick, M., Fowler, M.G., Mofenson, L., Miotti, P., Dransfield, K., Bray, D., Mmiro, F. & Jackson, B.J. (1999). Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*, *354*, 795–802.
9	HPTN040 2012a HPTN040 2012b	Nielsen-Saines, K., Watts, H., Veloso, V.G., Bryson, Y.J, Joao, E.C., Pilotto,J.H., Gray, G., Theron, G., Santos, B., Fonseca, R., Kreitchmann, R., Pinto, J., Mussi-Pinhata, M.M., Ceriotto, M., Machado, D., Bethel, J., Margado, M.G., Dickover, R., Camarca, M., Mirochnick, M., Siberry, G., Grinsztejn, B., Moreira, R.I,, Bastos, F.I., Xu, J., Moye, J. & Mofenson, L.M., for the NICHD HPTN 040/PACTG 043 Protocol. (2012). Three postpartum antiretroviral regimens to prevent intrapartum HIV Infection, *366*(25), 2368–2379. doi:10.1056/NEJMoa 1108275.
10	HPTN046 2012	Coovadia, H.M., Brown, E.R., Fowler, M.G., Chipato, T., Moodley, D., Manji, K., Musoke, P., Stranix-Chibanda, L. Chetty, V., Fawzi, W., Nakabiito, C., Msweli, L. Kisenge, R., Guay, L., Mwatha, A.,Lynn, D.J., Eshleman, S. H., Richardson, P., George, K., Andrew, P., Mofenson, L.M., Zwerski, S. & Maldonado, Y., for the HPTN 046 protocol team. (2012). Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): A randomised, double-blind, placebo-controlled trial. *Lancet*, *379*(9812), 221–228. doi:10.1016/S0140-6736(11)61653-X.
11	Kesho Bora 2011	The Kesho Bora Study Group. (2011). Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): A randomised controlled trial. *Lancet Infectious Diseases*, *11*, 171–80.

#	Study ID	Reference
12	Kiarie 2003	Kiarie, J.N, Kreiss, J.K., Richardson, B.A. & John-Stewart, G.C. (2003). Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. *AIDS*, *17*(1), 65–71. doi:10.1097/01.
13	Mashi 2006a	Shapiro, R.L., Thior, I., Gilbert, P.B., Lockman, S., Wester, C., Smeaton, L.M., Stevens, L., Heymann, S.J., Ndung'u, T., Gaseitsiwe, S., Novitsky, V., Makhema, J., Lagakos, S. & Essex, M. (2006). Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS*, *20*(9), 1281–8.
	Mashi 2006b	Thior, I., Lockman, S., Smeaton, L.M., Wester, C., Heymann, S.J., Gilbert, P.B., Stevens, L., Peter, T., Kim, S., van Widenfelt, E., Moffat, C., Ndase, P., Arimi, P., Kebaabetse, P., Mazonde, P., Makhema, J., McIntosh, K., Novitsky, V., Lee, T-H., Marlink, R., Lagakos, S., Essex, M., for Mashi Study team. (2006). Breastfeeding Plus Infant Zidovudine Prophylaxis for 6 Months vs Formula Feeding Plus Infant Zidovudine for 1 Month to Reduce Mother-to-Child HIV Transmission in Botswana A Randomized Trial: The Mashi Study. *JAMA*, 296 (7), 794-805.
14	Mma Bana 2010	Shapiro,R.L., Hughes M.D., Ogwu, A., Kitch, D., Lockman,S., Moffat, C., Makhema, J., Moyo, S., Thior, I., McIntosh, K., van Widenfelt, E., Leidner, J., Powis, K., Asmelash, A., Tumbare, E., Zwerski, S., Sharma, U., Handelsman, E., Mburu, K., Jayeoba, O.,Moko, E., Souda, S.,Lubega, E.,Akhtar, M., Wester, C., Tuomola, R.,Snowden, W., Martinez-Tristani, M., Mazhani,L. & Essex, M. (2010). Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *The New England Journal of Medicine*, *362*(24), 2282–94.
15	PEPI 2011a PEPI 2011b	Kumwenda, N. I., Hoover, D.R., Mofenson, L.M., Thigpen, M.C., Kafulafula, G., Li,Q., Mipando, L., Nkanaunena, K., Mebrahtu, T., Bulterys, M., Fowler, M.G. &Taha, T.E. (2008). Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *The New England Journal of Medicine*, *359*(2), 119–129. Taha, T.E., Li,Q., Hoover, D.R., Mipando, L., Nkanaunena, K., Thigpen, M.C. Taylor, A., Kumwenda, J., Fowler, M.G., Mofenson, L.M. & Kumwenda, N. I. (2011). Post exposure prophylaxis of breastfeeding HIV-exposed infants with antiretroviral drugs to age 14 weeks: Updated efficacy results of the PEPI-Malawi Trial. *Journal Of Acquired Immune Deficiency Syndromes*, *57*(4), 319–325.

#	Study ID	Reference
16	PETRA 2002a	The PETRA study team*. (2002). Efficacy of three-short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother-to-child in Tanzania, South Africa and Uganda (Petra study): A randomised double blind, placebo controlled trial. *Lancet*, *359*, 1178–86.
	PETRA 2002b	As above
17	PHPT 2000a	Lallemant, M., Jourdain, G., LeCouer, S., Kim, S., Koetsawang, S., Comeau, A.M., Phoolcharoen, W., Essex, M., McIntosh, K. & Vithayasai, V., for the Perinatal HIV prevention Trial (Thailand) Investigators. (2000). A trial of shortened zidovudine regimens to prevent mother-to-child transmission of Human Immunodeficiency virus Type 1. *The New England Journal of Medicine*, *343*(14), 982-991.
	PHPT 2000b	As above
18	PHPT-2 2004	Lallemant, M., Jourdain, G., Le Coeur, S., Mary, J.Y., Ngo-Giang-Huong, N., Koetsawang, S., Kanshana, S., McIntosh, K. & Thaineua, V., for the Perinatal HIV Prevention Trial (Thailand) Investigators. (2004). Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *The New England Journal of Medicine [NEJM]*, *351*(3), 217-227.
19	Promise PEP 2015	Nagot, N., Kankasa, C., Meda, N., Hofmeyr, J., Nikodem, C., Tumwine, J.K., Karamagi, C., Somerfelt, H., Neveu, D., Tylleskär, T. & Van de Perre, P. for the PROMISE-PEP group. (2012). Lopinavir/Ritonavir versus Lamivudine peri-exposure prophylaxis to prevent HIV-1 transmission by breastfeeding: The PROMISE-PEP trial Protocol ANRS 12174. *BMC Infectious Diseases*, *12*(246), 1–11. Nagot, N., Kankasa, C.,Tumwine, J.K., Meda, N., Hofmeyr, G.J., Vallo, R., Mwiya, M., Kwagala, M., Traore, H., Sunday, A., Singata, M., Siuluta, C., Some, E., Rutagwera, D., Neboua, D., Ndeezi, G., Jackson, D., Maréchal, V., Neveu, D., Engebretsen, I.M.S., Lombard, C., Blanche, S., Sommerfelt, H., Rekacewicz, C., Tylleskär, T., Van de Perre, P. for the ANRS 12174 Trial Group. (2015). Extended pre-exposure prophylaxis with lopinavir–ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *The Lancet* www.thelancet.com Published online November 18, 2015 http://dx.doi.org/ 10.1016/S0140-6736(15)00984-8.

#	Study ID	Reference
20	SAINT 2003	Moodley, D., Moodley, J., Coovadia, H., Gray, G., McIntyre, J., Hofmyer, J., Nikodem, C., Hall, D., Gigliotti, M., Robinson, P., Boshoff, L., & Sullivan, J. L. for the South African Intrapartum Nevirapine Trial (SAINT) investigators. (2003). A multicenter randomised controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of Human Immunodeficiency virus type 1. *Journal of Infectious Diseases.*, *187*, 725–35.
21	SWEN 2008	Six Week Extended-Dose Nevirapine (SWEN) Study Team. (2008). Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: An analysis of three randomised controlled trials. *Lancet*, *372*, 300–13.
22	Taha 2003	Taha, T.E., Kumwenda, N. I., Gibbons, A., Broadhead, R.L., Fiscus, S., Lema, V., Liomba, G., Nkhoma, C., Miotti, P.G. & Hoover, D.R. (2003). Short post exposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet 2003; 362: 1171–77*, *362*, 1171–77. Retrieved from http://www.thelancet.com.
23	Taha 2004	Taha, T.E., Kumwenda, N.I., Hoover, D.R., Fiscus, S.A., Kafulafula, G., Nkhoma, C., Nour, S., Chen, S., Liomba, G. Miotti, P.G. & Broadhead, R.L. (2004). Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: A randomised controlled trial. *The Journal of the American Medical Association*, *292*, 202–9.
24	Thistle 2004	Thistle, P., Gottesman, M., Pilon, R., Glazier, R.H., Arbess, G., Philips, E., Wald, R.L., Chitsike, I., Simor, A., Chipato, T. & Silverman, M. (2004). A randomized control trial of an Ultra-short zidovudine regimen in the prevention of perinatal HIV transmission in rural Zimbabwe. *The Central African Journal of Medicine*, *50*(9-10), 79–84.
25	Thistle 2007	Thistle, P., Spitzer, R.F., Glazier, R.H., Pilon, R., Arbess, G., Simor, A., Boyle, E., Chitsike, I., Chipato, T., Gottesman, M. & Silverman, M. (2007). A randomized double-blind, placebo-controlled trial of combined nevirapine and zidovudine compared with nevirapine alone in the prevention of perinatal transmission of HIV in Zimbabwe. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *44*(1), 111–9. http://doi.org/1058-4838/2007/4401-0020

5.5 Characteristics of Studies Included in the Meta-analysis

Characteristics of the included studies are presented according to the Study Identification code, followed by the characteristics of each study. Acknowledgement is given, that content of characteristics are taken mostly **verbatim** from the studies included, without using quotation marks.

5.5.1 Characteristics of Study One: BAN 2010

Study Identifier	BAN 2010
Country and location	Bwaila Hospital, Lilongwe, Malawi.
Duration	BAN began enrolling participants in April 2004. End date of enrolment not mentioned.
Type of study	Randomised Factorial Controlled Trial. Randomising occurred at
Randomisation	antenatal and within 36 hours post-delivery. Permuted block method was used to randomise participants.
Sample size	A total of 2369 mother–infant pairs were randomised.
Type of participant	Primary eligibility criteria include: • HIV-positive pregnant women; • ≤30 weeks gestation; • At least 18 years of age (or 14 years of age if married); • Haemoglobin >7 g/dL; • CD_4+ lymphocyte count of at least 250 cells per cubic millimeter (≥200 cells per cubic millimeter before July 24, 2006); • No prior antiretroviral medication use; • Normal liver function tests (2.5 upper limit of normal); • No serious complications of pregnancy; • Not previously enrolled in the BAN study;

- Based on clinical assessment, no maternal condition which would preclude start of study drug.

Infant criteria:

- Infant birth weight ≥2000 grams;
- No severe congenital malformations or other conditions incompatible with life;
- Infants found to be perinatally HIV-infected at birth or at two weeks of life, and their mothers, were subsequently disenrolled from the study and referred for recommended antiretroviral treatment.

Type of intervention

After delivery, mother infant pairs were randomly assigned to a two-group nutritional intervention to promote maternal health and a three- group antiretroviral intervention, thus a one in six chance of treatment.

Maternal-regimen group (N=849):

Women in the maternal-regimen group initially received Combivir twice daily and nevirapine at a dose of 200 mg once daily for two weeks and twice daily thereafter until 28 weeks. After the first 39 women were randomly assigned to the maternal-regimen group, nevirapine was replaced with twice-daily nelfinavir at a dose of 1250 mg for the next 146 women; nelfinavir was replaced with twice-daily lopinavir plus ritonavir, (Kaletra), a combination of 400 mg of lopinavir and 100 mg of ritonavir, for the remaining women.

Infant-regimen group (N= 852):

Infants received a dose of nevirapine that increased according to age, ranging from 10 mg daily in the first two weeks to 30 mg daily for weeks 19 through 28.

Control group (N= 668):

Neither the mother nor the infant received additional ARV’s.

	All women in labour and their newborn infants received a single dose of oral nevirapine. In addition, all mothers received zidovudine and lamivudine as a single tablet (Combivir) containing 300 mg of zidovudine and 150 mg of lamivudine every 12 hours from the onset of labor to seven days after birth. All infants received twice-daily zidovudine (2 mg per kilogram of body weight) and lamivudine (4 mg per kilogram) for seven days. The interventions for both mothers and infants began after delivery and were continued until the cessation of breastfeeding but no longer than 28 weeks.
Type of outcome	BAN had three primary study outcomes: • HIV transmission to infants. The primary efficacy end point was the rate of detection of HIV-1 infection at 28 weeks among infants who were uninfected at two weeks and among all infants who underwent randomisation. Infants were tested for HIV-1 infection at birth and at two, 12, 28, and 48 weeks with the use of the Amplicor 1.5 DNA polymerase-chain-reaction (PCR) assay; • Maternal depletion assessing weight loss; • Feasibility of exclusive breastfeeding for 24 weeks followed by rapid weaning.
Follow up visits	Mother–infant pairs were followed at one, two, four, six, eight, 12, 18, 21, 24, 28, 32, 36, 42, and 48 weeks after birth.
Infant feeding mode	All women were counselled to exclusively breastfeed followed by rapid weaning between 24 and 28 weeks postnatally.
Random sequence generation (selection bias)	Low risk as sequence allocation used a permuted block design.
Allocation concealment	Allocation concealment is unclear as it is not mentioned in the study.

Performance bias and detection bias	High risk as both personnel and participants knew what treatment was allocated after randomisation.
Incomplete outcome data (attrition bias)	High risk of bias as loss to follow-up before 28 weeks was >10% with an attrition rate of 12% of mother–infant pairs in each study group.
Notes	The control group was terminated after recommendation by the data and safety monitoring committee on 26 March 2008, after 668 of the planned 806 mother–infant pairs had been assigned to the control group.

5.5.2 Characteristics of Study Two: Bhoopat 2005

Study Identifier	Bhoopat 2005
Country and location	Maharaj Nakorn Chiang Mai University Hospital or Health Promotion Center Region 10 at Nakornping Hospital, Thailand.
Duration	Period not reported.
Type of study	Randomised controlled trial. Pregnant women who met the inclusion criteria were antenataly randomised.
Randomisation	
Sample size	Fifty HIV-seropositive pregnant women on at least two weeks ZDV prophylaxis.
Type of participant	HIV seropositive pregnant women who met the inclusion. Mother and infants were followed. Inclusion crtieria: • HIV positive pregnant women; • At least ZDV received for two weeks; • Mother chose not to breastfeed; • Laboratory values within acceptable limits: Hb>8g/dL, absolute neutrophil count >750 cell/cubic mm, SGPT <5x ULN, creatinine <1.5mg/dL. Exclusion criteria:

	• Did not meet the above criteria, either due to the condition of the mother or foetus or treatment that contraindicates ZDV use; • Oligohydramnios; • Medical need for TRIPLE ARV's; • Inexplicable polyhydramnios or in utero anaemia.
Type of intervention	Short-term ZDV arm (14 – 36 days of ARV's before delivery): • Mothers (27) were randomised to receive ZDV 300mg twice a day for at least two weeks before onset of labour; • Therafter 300mg ZDV three hourly during labour until birth. Long-term ZDV arm (62-92 days of ARVs): • Mothers (23) were randomised to receive ZDV 300mg twice a day for at least 62 days before the onset of labour; • Therafter 300mg ZDV three hourly during labour until birth.
Type of outcome	Infant, HIV-1 (subype E) status at birth, ten days, six weeks and four, six, nine and twelve months. For infant HIV diagnosis, peripheral blood drawn at birth and at six weeks and four and six months after birth was spotted onto filter papers, dried, and stored at 220 °C until tested by HIV DNA polymerase chain reaction (PCR) using the AMPLICOR HIV-1 DNA version 1.5 assay (Roche Molecular Systems, Alameda, CA). Infants were considered infected if two samples obtained on separate occasions were HIV-positive by PCR and uninfected based on two negative DNA PCR tests obtained after one month of age. For HIV-infected neonates, transmission was labeled ‘‘in utero’’ if the DNA PCR test obtained within three days of birth was positive.
Follow up visits	Women were monitored every two weeks until delivery and then at ten days, six weeks, and four months postpartum.

	Infants were monitored at birth, ten days, six weeks and four, six, nine and 12 months after birth.
Infant feeding mode	Breastfeeding was not promoted.
Random sequence generation (selection bias)	Unclear method and is not stated
Allocation concealment	Unclear "…participants were randomised"
Performance bias and detection bias	Unclear, not reported.
Incomplete outcome data (attrition bias)	Low risk as exclusions overall were 0% (0/50); Short course ZDV - 0% (0/27); Long course ZDV -0% (0/23).
Notes	A secondary outcome was to measure HIV-1 in the placenta.

5.5.3 Characteristics of Study Three: Chi 2007

Study Identifier	Chi 2007
Country and location	The data was collected in two public healthcare facilities, located in Lusaka, Zambia.
Duration	16 March 2005 up to the 13 February 2007.
Type of study	Open-label Randomised Controlled Trial and randomising occurred prenatally. Computer-generated block randomisation, with variable block sizes was used to allocate random sequence. Sequentially numbered, opaque envelopes were used to conceal allocation.
Randomisation	
Sample size	Four hundred women were randomised in labor but one was excluded because the envelope was incorrectly opened. A total of 200 women were randomly assigned to the intervention group and 199 to the control group.

Type of participant	Primary eligibility criteria included: • HIV-positive pregnant women; • Between 28 to 38 weeks pregnant; • Routine short-course zidovudine; • Self administered NVP 200mg at onset of labour; • Active labour before randomisation. Exclusion criteria: • Women who were on ARV's or reported previous use of ARVs; • Indications to be referred to a tertiary birthing facility.
Type of intervention	Intervention group (N=200 women) received: • ZDV 300mg BD from 32 weeks until labour; • sdNVP 200mg at onset of labour and; • Oral tenofovir 300 mg and emtricitabine 200mg (coformulated as Truvada by Gilead Sciences, Foster City, CA, USA). The dose was given under direct observation orally during labour. Control group (N=199 women) received standard routine care which included: • ZDV 300mg BD from 32 weeks until labour; • sdNVP 200mg at onset of labour; All infants received NVP 2mg/kg administered once within 72 hours of delivery; ZDV 4mg/kg orally BD for seven days post delivery.
Type of outcome	The primary outcome was maternal resistance to non-nucleoside reverse transcriptase inhibitor drugs at six weeks postpartum. Secondary outcomes were maternal non-nucleoside reverse transcriptase inhibitor drug resistance at two weeks postpartum, other maternal drug resistance (specifically to tenofovir,

	emtricitabine, or zidovudine) at two and six weeks postpartum, perinatal HIV transmission rates, and drug safety.
Follow up visits	Mother–infant pairs were followed at birth, two and eight weeks postpartum. Maternal non-nucleoside reverse transcriptase inhibitor resistance was assessed by sequencing the reverse transcriptase gene from maternal plasma specimens obtained at six weeks (primary outcome) and two weeks (secondary outcome) after childbirth. Dried-blood spot specimens from infants on filter paper and tested them with a commercial test (Amplicor HIV-1 DNA, Version 1・5, Roche Molecular Systems, Branchburg, NJ, USA). Two consecutive DNA PCR tests were required for diagnosis of HIV. Transmission was regarded as intrauterine if results at birth and six weeks were both positive, and as intrapartum or early postpartum if an infant tested HIV-negative at birth, but positive at six weeks (with a confirmatory positive result at least four weeks later).
Infant feeding mode	All women were counselled to breastfeed.
Random sequence generation (selection bias)	Low risk as computer-generated block randomisation scheme, with variable block sizes was used.
Allocation concealment	Low risk, an independent research pharmacist prepared a set of sequentially numbered opaque envelopes before study activation and envelopes were opened in a consecutive order for each participant.
Performance bias and detection bias (blinding)	Low risk, it was an open labelled study so the participants and staff knew the allocation but the laboratory personnel were unaware of each participant's allocated treatment.
Incomplete outcome data (attrition bias)	Low risk, of the 397 infants born to mothers in the intervention and control groups, 355 (89%) remained in the study at six weeks of life. Three fetuses (1%) died before delivery, nine infants (2%)

died in the first six weeks of life, and 30 (8%) were lost to follow-up.

5.5.4 Characteristics of Study Four: Chung 2005

Study Identifier	Chung 2005
Country and location	Pregnant women attending antenatal clinic at the Mathare North City Council Clinic in Nairobi, Kenya.
Duration	From 5 March to 31 October 2003
Type of study Randomisation	Randomised Controlled Trial. Women were randomised at 32 weeks gestation.
Sample size	A total of 66 women were randomised, 34 were randomised to the nevirapine regimen (HIVNET 012), and 32 were randomised to the zidovudine regimen (Thai-CDC).
Type of participant	Women were eligible to participate in the study if: • They were above 18 years of age; • Had no previous exposure to antiretroviral medications; • Had haemoglobin concentrations ≥8 g/dl; • Agreed to home visits; • Resided in the clinic catchment area.
Type of intervention	One regimen (HIVNET 012) was the oral administration of 200 mg of nevirapine to the mother at the onset of labour, and a single 2 mg/kg (6 mg if birthweight > 2.5 kg) oral dose of nevirapine suspension administered to the infant within 72 hours of delivery. The second regimen (Thai-CDC) was the oral administration of 300 mg of zidovudine twice daily to the mother from 34 weeks' gestation until the onset of labour and 300 mg orally every three hours from the onset of labour until delivery.
Type of outcome	Infant HIV status between three days and two weeks of birth and at six weeks.

	Primary outcome was breast milk HIV-1 RNA viral load at six weeks post-partum. Secondary outcome was PCR for HIV-1 DNA at six weeks to diagnose HIV infection status.
Follow up visits	After randomisation, participants were seen weekly in the clinic until delivery. At or within three days of delivery, maternal blood was obtained for CD_4 cell count and HIV-1 RNA virus levels. Infant blood was collected on filter paper for HIV-1 DNA. For mothers and infants in whom early collection was not achieved, specimen blood collection was performed within two weeks of delivery during a home visit. Mothers and their infants were followed for six weeks after delivery.
Infant feeding mode	Exclusive breastfeeding was promoted.
Random sequence generation (selection bias)	Low risk as computer-generated block randomisation was done and randomisation was concealed until time of randomisation. Unclear risk as randomisation was revealed through numbered envelopes by the study physician who assigned the treatment regimens.
Allocation concealment	Unclear as Study investigators and participants were not blinded to the interventions, but it is not stated whether the statistician was blinded.
Performance bias and detection bias	Unclear
Incomplete outcome data (attrition bias)	Low, all 60 infants who were born had HIV-1 assessment performed within two weeks of delivery. At the six week study endpoint, 56 mothers and 55 infants were assessed and analyzed. In the zidovudine arm, one mother moved away from the study site, one mother died, and two infants died prior to six weeks. In the nevirapine arm, one mother decided to formula

feed exclusively and chose not to participate further in the study. Overall, in the zidovudine arm 27 mothers (90%) and 26 (87%) infants were assessed while in the nevirapine arm 29 (97%) mothers and 29 (97%) infants were assessed at six weeks.

5.5.5 Characteristics of Study Five: Chung 2008

Study Identifier	Chung 2008
Country and location	Mathare North City Council Clinic in Nairobi, Kenya.
Duration	3 November 2003 and 20 April 2006.
Type of study Randomisation	Randomised Controlled Trial. Women were randomised at 34 weeks gestation.
Sample size	A total of 58 women were randomised at 34 weeks gestation, 30 women were randomised to the HAART regimen, and 28 women were randomised to the ZDV/NVP regimen.
Type of participant	Inclusion criteria: Pregnant women: • Who elected to breastfeed; • Were ≤ 32 weeks gestation; • Had a haemoglobin ≥ 8g/dl; • Had no previous exposure to antiretrovirals; • Who were ≥ 18 years; • Agreed to home visits; • Resided in the clinic catchment area. Exclusion criteria: • If the CD_4 count was < 200 cells/mm3 or > 500 cells/mm3, the subject was in eligible for randomization.
Type of intervention	In the HAART arm, 300 mg of zidovudine (ZDV), 150 mg of lamivudine, and 200 mg nevirapine (NVP) was given twice daily from 34 weeks gestation until six months after delivery.

	In the ZDV/NVP arm, 300 mg of ZDV was given twice daily from 34 weeks gestation until labour then every three hours until delivery; 200 mg of NVP was given as a single oral dose at the onset of labour and a single 2 mg/kg (6 mg if birthweight > 2.5 kg) oral dose of NVP suspension was administered to the infant within 72 hours of delivery.
Type of outcome	Primary outcome: HIV-RNA levels in breast milk. HIV-1 specific immune responses in breast milk and in infants. Secondary outcomes: Infant HIV-1 was determined by HIV-1 filter paper PCR for HIV-1 DNA, it was performed at birth, one month and 12 months postpartum. Infant and maternal deaths
Follow up visits	Mothers and their infants attended study clinic at two weeks and one month postpartum and then every three months after delivery until 12 months postpartum.
Infant feeding mode	Exclusive breastfeeding was promoted.
Random sequence generation (selection bias)	Low risk as randomization was performed using computer-generated block randomization.
Allocation concealment	Is unclear
Performance bias and detection bias	High risk as the study investigators and participants were not blinded to the interventions.
Incomplete outcome data (attrition bias)	Low risk as the attrition rate was similar and small, of the 58 randomized women, four mothers were lost to follow-up prior to delivery (2 in the HAART arm and 2 in the ZDV/NVP arm), three women had stillbirths (2 in the HAART arm and 1 in the ZDV/NVP arm), and 51 mothers gave birth: 26 mothers in the HAART arm and 25 mothers in the ZDV/NVP arm with one year follow up of 2/16 in HAART and 4/25 ZDV/sdNVP arm.

Notes	Further enrollment of mother-infant pairs was stopped after preliminary analyses indicated the size of the cohort was adequate to detect significant differences in breast milk viral load between the two arms.

5.5.6 Characteristics of Study Six: Gray 2005

Study Identifier	Gray 2005
Country and location	Three Public hospitals in South Africa, Mowbray, Coronation and Chris Hani Baragwanath hospital.
Duration	October 2000 to September 2002.
Type of study Randomisation	Multicentre two arm randomised open label controlled trial.
Sample size	1051 infants
Type of participant	Inclusion criteria: • HIV-1 exposed infants. Exclusion criteria: • Infant presented with congenital abnormalities; • Unable to take oral medication; • Preterm or a weight of <1200g; • Infant that required ventilation.
Type of intervention	NVP arm (518): INFANT - NVP suspension 10mg/ml as a single oral dose at 2mg/kg within 24 hours of delivery ZDV arm (533): INFANT - zidovudine syrup 10mg/ml as an oral dose at 4mg/kg within 24 hours of delivery, then 12 hourly for six weeks after birth.
Type of outcome	Intrapartum and early postpartum HIV transmission to infants. Infant HIV status at birth, six and 12 weeks. HIV-1 DNA PCR was used to confirm HIV infection. Adverse events. Effect of breastfeeding.

Follow up visits	Birth, six and 12 weeks
Infant feeding mode	Mixed feeding, formula and breast from there to six months.
Random sequence generation (selection bias)	Low risk, computer generated. Non-transparent and sequentially numbered envelopes were used.
Allocation concealment	Low risk as allocation was provided to study nurses in sequentially numbered, non-transparent envelopes.
Performance bias and detection bias	Unclear, participants and providers were not blinded and no details given about blinding of assessors.
Incomplete outcome data (attrition bias)	High risk as there was a large attrition rate although the attrition rates were similar. There were an attrition percentage of 31.1% (166/533) in the ZDV group and 32.2% (167/518) in the NVP group

5.5.7 Characteristics of Study Seven: Gray 2006a, b, c

Study Identifier	Gray 2006a, Gray 2006b, Gray 2006c
Country and location	Chris Hani Baragwanath Hospital in Soweto, South Africa.
Duration	May 1999 to May 2000
Type of study Randomisation	Prospective open-label, randomised 4-arm study single center study.
Sample size	A total of 373 pregnant women were enrolled. The sample size of this study was determined considering that a 19% or higher MTCT rate in any of the treatment groups is unacceptable.
Type of participant	Inclusion criteria: • HIV-1 infected; • Antiretroviral-naïve;

- Serum creatinine ≤1.5 times the upper limit of normal (ULN);
- Total serum lipase ≤1.4 times ULN;
- Liver enzymes (aspartate aminotransferase and alanine aminotransferase) ≤ 5 times ULN;
- 18 years of age or older;
- Between 34 to 36 weeks of gestation;
- Prepared to formula feed their infants;
- Willing to have their infant followed for six months after birth.

Exclusion criteria:

- Severe foetal abnormalities;
- Presence of three or more foetuses;
- Occurrence of a newly diagnosed hiv-related opportunistic infection;
- Malignancy condition requiring acute therapy at the time of enrolment;
- Active drug abuse;
- A history of pancreatitis;
- Past or present symptoms of grade 2 or greater bilateral peripheral neuropathy.

Type of intervention

Women were randomized to receive one of four study treatments during the remainder of their pregnancy and throughout labour and delivery:

Arm 1- d4T arm (N=93):

- Mother received d4T 40mg (or 30mg if wt <60kg) twice daily (BD) during pregnancy through labour and delivery plus an additional dose about one hour before delivery.
- Infant received d4T syrup suspension 1mg/kg BD within 36 hours of birth to six weeks after birth.

	Arm 2- ddI arm (N=95): • Mother received a 200mg (or 125 mg if wt <60 kg) ddI dose BD during pregnancy through labour and delivery plus an additional dose about one hour before delivery. • Infants received ddI in liquid form 120mg/m^2 BD within 36 hours of birth to six weeks after birth. Arm 3- combination d4T/ddI (N=93): • Mother combination of d4T and ddI as above. • Infants received a combination of d4T and ddI as above. Arm 4- ZDV arm (N=92) • Mother received ZDV 300mg BD during pregnancy through labour and delivery plus an additional dose about one hour before delivery. • Infants received ZDV 4mg/kg BD within 36hrs of birth to six weeks after birth. Infants were weighed and measured to determine the dosage.
Type of outcome	HIV-1 infection in infant at birth, six, 12 and 24 weeks. Measured by DNA PCR. Adverse events in infant and mother.
Follow up visits	Mothers were followed for six weeks and infants at birth, three, six, 12, and 24 weeks of age.
Infant feeding mode	Breast feeding was discouraged, mothers needed to agree to exclusively formula feed. Infant formula was provided for six months postdelivery.
Random sequence generation (selection bias)	Unclear, reported as 'randomised' but no further details given.
Allocation concealment	Unclear, not mentioned.
Performance bias and detection bias	Unclear risk as participants and providers were not blinded and no details given about blinding of assessors.

Incomplete outcome data (attrition bias)	Low risk as attrition was < 10% at 2.9% (11/373) overall. In the d4T group attrition was 2% (2/93); in the ddI group attrition was 1.1% (2/95); in the d4T plus ddI group it was 5.4% (5/95) and in the ZDV group it was 3.4% (3/89).

5.5.8 Characteristics of Study Eight: HIVNET 012 1999

Study Identifier	HIVNET 012 1999
Country and location	Mulago Hospital in Kampala, Uganda.
Duration	Enrolment began November 1997 and ended on 30 April 1999
Type of study	Double blind Randomised Controlled Trial and randomisation
Randomisation	took place antenatally.
Sample size	626 pregnant women were randomly assigned.
Type of participant	Inclusion criteria: • HIV-1 positive women; • Aged $\geq$ 18 years; • > 32 weeks gestation; • Lived near the study hospital. Exclusion criteria: • Current antiretroviral theraphy; • Uncontrolled hypertension; • Haemoglobin <75g/L; • Blood creatinine >1.5 mg/dl; • Alanine transaminase concentration >3x ULN; • Chronic alcohol or drug use; • Benzodiazepine use; • Anticoagulant therapy; • Magnesium sulphate within two weeks of enrolment or likely to be needed during labour or delivery.

Type of intervention	NVP arm (N=313): • Mother received a single oral 200mg tablet of NVP at onset of labour. • Infant received a single oral dose 2mg/kg 72 hours after birth or at hospital discharge (whichever was soonest). ZDV arm (N=313): • The zidovudine regimen included administration of two 300 mg tablets at onset of labour, followed by one 300 mg tablet every three hours during labour. • Infants received zidovudine syrup, 4mg/kg twice daily for seven days after birth. Placebo arm (N=19) was discontinued after the results of the Thailand trial found that a short course of ZDV given in antepartum and intrapartum period was effective. The first dose of each drug for mothers was given to women to take home with them at about 36 weeks' gestation; were asked to take the study drug at onset of labour pains and to come to the hospital to deliver their babies.
Type of outcome	HIV infection and HIV-1 free survival (i.e. time to death or first positive HIV-1 RNA assay) at birth, 6-8 weeks, 14-16 weeks and 18 months. HIV infection confirmed by HIV-1 RNA PCR or culture Adverse events in mother at six weeks postpartum Adverse events in infant up to 18 months
Follow up visits	Mothers during pregnancy and infants at birth six to eight weeks, 14-16 weeks and 18 months.
Infant feeding mode	Breastfeeding was encouraged.
Random sequence generation (selection bias)	Low risk as randomisation was computer generated in blocks of 12.

Allocation concealment	Low risk as sequentially numbered treatment packs were prepared by a study pharmacist, according to allocation schedule.
Performance bias and detection bias	High risk, participants and assessors knew treatment allocation after randomisation.
Incomplete outcome data (attrition bias)	Low risk the overall attrition was 2.6% (17/645); 3.5% (11/313) in ZDV group, 1.6% (5/313) in NVP group and 5.2% (1/19) in placebo group before the arm was discontinued.

5.5.9 Characteristics of Study Nine: HPTN040 2012a HPTN040 2012b

Study Identifier	HPTN040 2012a, HPTN040 2012b
Country and location	Enrollment occurred at 17 sites in Brazil, South Africa, Argentina, and the United States.
Duration	Randomisation took place from April 2004 through July 2010.
Type of study Randomisation	Randomised controlled trial.
Sample size	The primary efficacy analysis included 1684 infants.
Type of participant	Inclusion criteria: Women: • HIV-1–infected mothers who had not received ART before labour. Infants: • HIV exposed infants; • No more than 48 hours old; • Gestational age of at least 32 weeks; • Weighed at least 1.5 kg; • Had no life-threatening conditions; • Were able to take oral medication.
Type of intervention	Infants exposed to HIV-1 were randomly assigned to one of three ART regimens within 48 hours after birth. All infants received zidovudine for six weeks, at a dose of 12 mg (for infants with a

birth weight >2.0 kg) or 8 mg (for those with a birth weight ≤2.0 kg) twice daily.

Group 1 (N=566)

- Zidovudine for six weeks.

Group 2 (N=562)

- The second group received the zidovudine regimen plus
- Three doses of nevirapine: the first within 48 hours after birth, the second 48 hours after the first dose, and the third 96 hours after the second dose. The nevirapine dose was 12 mg (birth weight >2.0 kg) or 8 mg (birth weight ≤2.0 kg) once daily.

Group 3 (N=556)

- Received the zidovudine regimen
- Nelfinavir 200 mg (birth weight >3.0 kg), 150 mg (birth weight >2.0 kg and ≤3.0 kg), or 100 mg (birth weight ≤2.0 kg) twice daily for two weeks.
- Lamivudine dose was 6 mg (birth weight >2.0 kg) or 4 mg (birth weight ≤2.0 kg) twice daily for two weeks.

Fixed dosing based on weight categories was used for drug administration.

Type of outcome

The primary study end point was intrapartum HIV-1 transmission at three months of age.

Secondary end points included transmission at additional time points, infant deaths, and risk factors for HIV-1 transmission, including maternal HIV RNA level and CD_4+ T-cell count at delivery, status with respect to maternal syphilis, demographic characteristics, obstetrical factors, and status with respect to zidovudine receipt during labour.

Follow up visits	Study visits occurred at birth, four to seven days,10 to 14 days, four to six weeks, and three and six months of age.
Infant feeding mode	Formula feeding was promoted.
Random sequence generation (selection bias)	Unclear risk as it is only reported that infants were randomly assigned to a treatment group in blocks of 12.
Allocation concealment	Unclear risk; not stated
Performance bias and detection bias	Unclear risk; not stated
Incomplete outcome data (attrition bias)	Low risk as overall attrition was low. Reasons for study discontinuation (97 infants) included death (21), withdrawal of consent (37), loss to follow-up (32), relocation (6), and other reasons (1).

5.5.10 Characteristics of Study 10: HPTN046 2012

Study Identifier	HPTN046 2012
Country and location	Women were recruited from antenatal clinics in Durban in South Africa, Dar es Salaam in Tanzania, Kampala in Uganda and Chitungwiza in Zimbabwe.
Duration	19 June 2008 until 12 March 2010.
Type of study Randomisation	A randomised, double-blind, placebo-controlled trial.
Sample size	1527 infants were randomised 762 extended NVP and 765 placebo.
Type of participant	Primary eligibility criteria included: • Maternal age (≥18 years); • Infants had to be HIV-1 DNA PCR negative on a specimen obtained within 21 days before randomisation or infant

	HIV-1 DNA PCR negative from a specimen obtained within seven days of birth; • Breastfeeding at time of randomisation and the mother's intention to continue breastfeeding; • Infant birthweight of 2000 g or more; • Women receiving antiretroviral drugs for HIV-1 treatment or for PMTCT were eligible. Exclusion criteria: • Women and infants if either had a serious medical disorder that would interfere with study participation.
Type of intervention	All enrolled infants received once-daily open-label nevirapine (10 mg/mL oral suspension) for the first six weeks of life. Group 1 (N=761 started placebo). Infants in the extended NVP group started masked study drug and continued a once-daily dosing regimen until six months of age or until cessation of breastfeeding, whichever came first. The nevirapine dose was increased with age, ranging from 20 mg once-daily after six to eight weeks of age to 28 mg once-daily after 5‑6 months of age. Group 2 (N=763) Placebo - no extended NVP.
Type of outcome	The primary efficacy endpoint was HIV-1 infection at age six months in infants who were uninfected at age six weeks in each study group. Primary safety endpoints were frequency and severity of adverse reactions in randomly allocated infants until age six months in each group for all infants who received at least one dose of study intervention. Secondary endpoints included HIV-1- free survival, relative rates of HIV-1 infection, and infant

	survival rates (mortality irrespective of HIV-1 infection) in the two study groups.
Follow up visits	Infant study visits were undertaken within seven days postpartum, at two, five, six and eight weeks, and at three, six, nine, 12, and 18 months. Infants who developed HIV-1 infection were taken off the study drug and referred for additional care and treatment.
Infant feeding mode	Women were counselled to exclusively breastfeed for six months.
Random sequence generation (selection bias)	Low risk as infants were stratified by maternal antiretroviral treatment status at randomisation and randomly allocated in a one-to-one ratio according to computer-generated permutated block algorithms by site with random block sizes.
Allocation concealment	An independent contractor in the USA provided identical, sealed, individual study drug kits, which were prepared and labelled centrally according to the random allocation assignment generated by the HPTN Statistical and Data Management Center.
Performance bias and detection bias	Low risk as study staff and participants were masked to the study drug.
Incomplete outcome data (attrition bias)	Low risk as overall attrition rate was low 21 in NVP group and 24 in placebo group.

5.5.11 Characteristics of Study 11: Kesho Bora 2011

Study Identifier	Kesho Bora 2011
Country and location	Five sites in three countries. Centre Muraz, Bobo-Dioulasso, Burkina Faso; International Centre for Reproductive Health, Mombasa, Kenya; Kenyatta National Hospital, Nairobi, Kenya; University of KwaZulu-Natal, Durban, South Africa; and Africa Centre, University of KwaZulu-Natal, Somkhele, South Africa.

Duration	Randomisation took place from June 2005 until August 2008.
Type of study	Multicentre, randomised controlled trial.
Randomisation	
Sample size	A total of 824 women were randomised.
Type of participant	Inclusion criteria: • Between 28 and 32 weeks' gestation; • WHO clinical stage 1, 2, or 3 HIV infection; • CD_4 cell count of 200–500 cells per μL. Exclusion criteria: • With contraindications to rapid initiation of antiretrovirals; • With a known allergy to antiretrovirals or benzodiazepines; • Women being treated with drugs that interact with antiretrovirals; • With severe anaemia, neutropenia (grade 2 or above); • Liver or renal failure.
Type of intervention	As soon as possible from 34 weeks, but not after 36 weeks, gestation, women were randomly assigned (1:1) to start either triple antiretroviral prophylaxis (triple antiretroviral group) or standard MTCT prophylaxis (zidovudine and single-dose nevirapine group). Group 1 (N=412) Women received 300 mg zidovudine, 150 mg lamivudine, and 400 mg lopinavir plus 100 mg ritonavir twice daily until cessation of breastfeeding (to a maximum of six and a half months post partum). Group 2 (N=412) Women received 300 mg zidovudine twice daily until delivery and a dose of 600 mg zidovudine plus 200 mg nevirapine (single-dose nevirapine) at onset of labour.

Type of outcome	The primary endpoints were HIV-free infant survival at six weeks and 12 months; HIV-free survival at 12 months in infants who were ever breastfed; AIDS-free survival in infants at 18 months; and serious adverse events in mothers and babies.
Follow up visits	Women visited the antenatal clinics every two weeks from enrolment until delivery. Mothers and their babies attended antenatal clinics at two, four, six and eight weeks after delivery and then monthly until one year and every three months thereafter.
Infant feeding mode	Women who opted for replacement feeding from birth received free formula up to six months and those who opted for breastfeeding were supported and counselled to exclusively breastfeed and rapidly wean over a two weeks period with complete cessation before the infant reached six months of age.
Random sequence generation (selection bias)	Low risk as randomisation was stratified by centre and planned infant feeding mode balanced in blocks of six or eight by a computer generated random sequence.
Allocation concealment	Low risk as sealed envelopes containing the group assignment were prepared at the study coordinating centre and were marked externally only with the randomisation sequence number. The assigned envelope was opened only once all enrolment procedures had been completed.
Performance bias and detection bias	High risk as participants and study investigators were not masked to treatment allocation.
Incomplete outcome data (attrition bias)	Low risk as survival analysis was used to address attrition and similar percentage of infants were lost to follow up with 27/401 (6%) infants lost to follow-up at 12 months in the Tripple arm and 36/404 (9%) infants were lost follow-up at 12 months in the short arm.
Notes	From December 2006, after WHO recommendations were updated, the study protocol was amended and prophylaxis was

initiated from 28 weeks' gestation for all patients enrolled after this date; and one week of zidovudine 300 mg twice daily plus lamivudine 150 mg twice daily post partum was added for women randomised to the zidovudine and single-dose nevirapine group. All infants received a dose of 0, 6 ml oral nevirapine suspension (about 2 mg/kg), preferably within 72 hrs of birth (no later than 7 days after birth). They also received co-trimoxazole prophylaxis from age six weeks to 12 months unless they were not infected with HIV after complete cessation of breastfeeding. From December, 2006, after the protocol amendment, they also received one week of zidovudine (4 mg/kg twice daily) from birth.

5.5.12 Characteristics of Study 12: Kiarie 2003

Study Identifier	Kiarie 2003
Country and location	Tertiary hospital in Nairobi, Kenya.
Duration	November 1999 and clinical follow-up was completed in January 2001.
Type of study Randomisation	Randomised Controlled Trial.
Sample size	A total of 139 women were randomized (70 to the Thai-CDC and 69 to the HIVNET-012 regimen).
Type of participant	Inclusion criteria: • Women at ≤ 35 weeks gestation; • Planned to remain in the city until six weeks after delivery; • Had no contraindication to taking antiretroviral drugs.
Type of intervention	Group 1 (N=70) • Women randomized to the Thai-CDC regimen were given 20 tablets of zidovudine in an electronic medication bottle. Group 2 (N=69)

	• Women randomized to the HIVNET-012 regimen were given one 200 mg tablet of nevirapine and 6 mg of nevirapine syrup for her infant.
Type of outcome	Infant HIV status at six weeks. Adherence to therapy. Adverse events.
Follow up visits	Women were seen every two weeks until randomization at 36 weeks, after which they were seen weekly until delivery and again at one week after delivery.
Infant feeding mode	Breastfeeding was encouraged.
Random sequence generation (selection bias)	Unclear as it was only reported as using block randomisation.
Allocation concealment	Unclear as it is only reported as sealed envelopes were used.
Performance bias and detection bias	High risk as participants and care providers were not blinded.
Incomplete outcome data (attrition bias)	High risk as the overall attrition was greater than 10% with 21.4% (15/70) attrition in the Thai CDC group and 20.3% (14/69 in the HIVNET 012 group.

5.5.13 Characteristics of Study 13: Mashi 2006a, b

Study Identifier	Mashi 2006a Mashi 2006b
Country and location	Study took place at district hospitals in the southern region of Botswana. One city Gaborone, one town Lobatse and two large villages, Molepolole and Mochudi in Botswana [i.e in one city, one town, and two large villages].

Duration	Participants were enrolled between 27 March 2001 and 29 October 2003 for Mashi 2006a and b. Subanalysis of Mashi 2006a is from June 2002 till October 2003.
Type of study Randomisation	This trial compared two approaches for reducing postnatal HIV infection and infant mortality. The Mashi study was a randomized 2 x 2 factorial clinical trial for HIV-infected pregnant women and their infants, designed to compare interventions for both preventing perinatal HIV transmission (Mashi 2006a) and reducing postnatal HIV infection and mortality (Mashi 2006b). Mashi 2006a was a partially double-blind trial assessing the efficacy of adding a single-dose nevirapine to maternal and infant zidovudine to reduce perinatal mother-to-child transmission, compared to placebo. Mashi 2006b evaluated infant feeding strategies comparing breast feeding plus infant zidovudine prophylaxis for six months versus formula feeding plus one month of infant zidovudine.
Sample size	A total of 709 women were analysed in Mashi 2006a and 1200 in Mashi 2006b.
Type of participant	Inclusion criteria: • Between 33 and 35 weeks' gestation; • A positive HIV-1 ELISA on two separate samples; • Were $\geq$ 18 years; • Haemoglobin $\geq$ 8 g/dl; • Absolute neutrophil count $\geq$ 1000 cells/ml; • Alanine amino transferase (ALT) and aspartate amino transferase (AST) $\leq$ 10 times upper limit of normal; • Creatinine $\leq$ 1.5 mg/dl; • No known intolerance to zidovudine or nevirapine.
Type of intervention	All of the mothers received zidovudine 300 mg orally twice daily from 34 weeks' gestation and during labour. Mothers and infants

were randomised to receive single-dose nevirapine or placebo. Infants were randomised to six months of breastfeeding plus prophylactic infant zidovudine (breastfed plus zidovudine), or formula feeding plus one month of infant zidovudine (formula fed).

All women in both Mashi 2006a and Mashi 2006b received zidovudine 300 mg orally twice daily from 34 weeks' gestation until labour onset, and every three hours during labour until delivery.
Those qualified for HAART received HAART.
Randomisation occurred at 34 weeks' gestation.

Mashi 2006a
Group1

- Maternal randomisation to a single dose of 200 mg nevirapine.
- sdNVP 6mg within 72 hours of delivery and ZDV 4mg/kg orally twice daily for one month (premature < 35 weeks and birthweight < 2kg received sdNVP 3mg).

Group 2

- Placebo was given to women after randomisation.
- Infants received placebo until August 2002 after that all infants sdNVP 6mg within 72 hours of delivery and ZDV 4mg/kg orally twice daily for one month (premature < 35 weeks and birthweight < 2kg received sdNVP 3mg).

Mashi 2006b
Group 3

- Women were randomised to breastfed for six months and to wean infant's between five and six months. Free infant

formula was provided from five through 12 months of age to facilitate safe weaning.

- Infants received ARV/placebo as per group 1 and 2 and those who were then randomised to received breatmilk also received zidovudine from birth to the age of six months while breastfeeding (4mg/kg BD from birth until one month and then 6mg/kg eight hourly).

Group4

- Women were randomised to formula feed.
- Infants received ARV/placebo as per group 1 and 2 and those who were then randomised to receive formula discontinued Zidovudine after one month.

Mothers randomised to the formula-fed group were supplied with formula for 12 months.

	Total	Breast & ZDV	Formula
Placebo/placebo	245/1200	122/598	123/602
NVP/NVP	246/1200	120/598	126/602
Placebo/NVP revised	355/1200	179/598	176/602
NVP/NVP revised	354/1200	177/598	177/602

Type of outcome

The primary endpoint for Mashi 2006a was infant HIV infection by the one-month visit, defined as more than one positive DNA PCR test on different blood samples with at least one performed on a sample collected by 45 days of age.

For Mashi 2006b the HIV infection by age seven months and HIV-free survival by age 18 months and infant adverse events by seven months of age.

Secondary outcomes were:

Death of infant and grade 3 or greater adverse events.

Follow up visits	For Mashi 2006a follow up was only done at one month and for Mashi 2006b follow up was done at birth, monthly until age seven months, at age nine months, then every third month through age 18 months.
Infant feeding mode	Infants were randomised to be breastfed for six months plus six months zidovudine or to formula feed.
Random sequence generation (selection bias)	Low risk as centralized randomisation to both Mashi 2006a and Mashi 2006b occurred at study enrolment at about 34 weeks' gestation, using permuted blocks of size eight stratified by site.
Allocation concealment	Low risk a central randomisation was applied.
Performance bias and detection bias	Low risk for Mashi 2006a as both participants and healthcare providers were blinded but high risk for Mashi 2006b as participants could not be blinded for breast feeding or formula feeding.
Incomplete outcome data (attrition bias)	Low risk as attrition at the primary outcome point of one month was low overall at 7.5% and equally distributed across arms. By the seventh and 18-month evaluations, 16 (2.7%) and 53 (9.0%) of the 591 formula-fed and 25 (4.3%) and 53 (9.0%) of the 588 breastfed plus zidovudine infants were lost to follow-up, respectively. There were also very few (<1%) missed DNA PCR tests for reasons other than loss to follow-up.
Notes	In August 2002, as a result of efficacy data from Thailand the peripartum intervention was revised to eliminate infant placebo and provide all infants with open-label nevirapine immediately after being born. The maternal intervention remained unchanged. In October 2002, combination antiretroviral treatment consisting of zidovudine, lamivudine, and nevirapine (HAART) became accessible through a national program in Botswana and so all participating women with CD_4 < 200 cells/μL or with an AIDS-

defining illness were offered HAART and did not receive sdNVP or placebo at onset of labour.

5.5.14 Characteristics of Study 14: Mma Bana 2010

Study Identifier	Mma Bana 2010
Country and location	One city Gaborone, one town Lobatse and two large villages, Molepolole and Mochudi in Botswana.
Duration	5 July 2006 and 12 May 2008
Type of study	Randomised controlled trial.
Randomisation	
Sample size	A total of 730 pregnant women were enrolled. Of the women who were enrolled in the study, 560 were randomly assigned to a treatment group (285 to the NRTI group and 275 to the protease-inhibitor group), and 170 were followed observationally.
Type of participant	Inclusion criteria: • At 26 to 34 weeks gestation; • HIV-1 infected; • Age of 18 years and above; • CD_4 count $\geq$ 200 cells/µl; • Intending to breast-feed the infants; • Antiretroviral naïve at randomisation; • Haemoglobin level of 8.0 g per deciliter or higher; • An absolute neutrophil count of 1000 cells per cubic millimeter or more, and alanine aminotransferase and aspartate aminotransferase levels that were no more than 2.5 times the upper limit of the normal range. Exclusion criteria: • CD_4 < 200 cells/µL or AIDS-defining illness
Type of intervention	Randomised group 1: NRTI group (N=285)

	Women assigned to the nucleoside reverse-transcriptase inhibitor (NRTI) group received either 300 mg of abacavir, 300 mg of zidovudine, and 150 mg of lamivudine coformulated as Trizivir (GlaxoSmith-Kline) twice daily. Randomised Group 2: Protease inhibitor Group (N=275) Women received 400 mg of lopinavir and 100 mg of ritonavir coformulated as Kaletra (Abbott) with 300 mg of zidovudine and 150 mg of lamivudine coformulated as Combivir (GlaxoSmithKline) twice daily. Women in the two randomized groups began to receive HAART between 26 and 34 weeks' gestation and continued it through weaning or six months post partum, whichever occurred first. Routine care group (Observational group) (N=170) (CD_4+ count, <200 cells/mm3 or AIDS) Women received 200 mg of nevirapine, 300 mg of zidovudine, and 150 mg of lamivudine twice daily (after a 2-week lead-in period of once daily nevirapine at a dose of 200 mg). Women in the observational group began to receive HAART between 18 and 34 weeks' gestation and continued treatment indefinitely. All infants received single-dose nevirapine (6 mg) at birth and received zidovudine (4 mg per kilogram of body weight twice daily) from birth through four weeks.
Type of outcome	Infant HIV status at one, three and six months post partum.
Follow up visits	HIV-1 RNA was measured within four days after birth and one, three and six months post partum.
Infant feeding mode	Women were counseled to exclusively breast-feed and to complete weaning three days before the six month study visit.

	Infants were provided free formula and foods from the time of weaning, whenever it occurred, through to 12 months of age.
Random sequence generation (selection bias)	Unclear, only stated as randomly assigned in permuted blocks stratified according to clinical site.
Allocation concealment	Unclear as it is not mentioned.
Performance bias and detection bias	Unclear as participants received different number of tablets, so it is no where mentioned that placebo tablets were added.
Incomplete outcome data (attrition bias)	High risk as greater than 10% loss to follow up. For infants breastfed up to six months, attrition was 88/274 (32.1%) for the Trizivir group and 84/269 (31.2%) for the Combivit group.

5.5.15 Characteristics of Study 15: PEPI 2011a, b

Study Identifier	PEPI 2011a and PEPI 2011b
Country and location	Queen Elizabeth Central Hospital or at one of five other health centers in Blantyre, Malawi.
Duration	20 April 2004 – 7 August 2007 for PEPI 2011a and 20 April 2004 – September 2009 for PEPI 2011b.
Type of study Randomisation	Randomised, controlled, open-label, phase 3 clinical trial.
Sample size	3276 infants were enrolled.
Type of participant	Infants were randomised and women who met the inclusion criteria were enrolled: • HIV-1 infection; • At least 18 years of age (although women <18 years of age could be enrolled if they consented and a guardian gave permission); • Whether pregnant or had given birth within the previous 24 hours at one of the study clinics;

- Was a resident of the study area;
- Was willing to return for postnatal follow-up visits for up to two years;
- Intended to breast-feed;

Exclusion criteria:

- Infants with life-threatening conditions requiring immediate care were excluded.

Type of intervention

Infants of HIV-infected and of breastfeeding mothers were randomised at birth to receive one of three regimens as follows:

Beginning immediately after birth, all infants received a single oral dose of nevirapine (2 mg per kilogram of body weight) plus oral zidovudine (4 mg per kilogram), given twice daily for one week.

Group 1 (N=1090)

- Infants received a single-dose nevirapine plus one week of zidovudine.

Group 2 (N=1160)

- Infants received a single-dose nevirapine plus daily extended prophylaxis nevirapine. The oral dose of nevirapine was 2 mg per kilogram once daily, during week two, then 4 mg per kilogram once daily during weeks three through week 14.

Group 3 (N=1147)

- Infants received a single-dose nevirapine plus daily extended prophylaxis with nevirapine plus zidovudine until the age of 14 weeks. The oral dose of zidovudine was 4 mg per kilogram twice daily during weeks two through five, 4 mg per kilogram three times daily during weeks six through eight, and 6 mg per kilogram three times daily during weeks nine through to week 14.

Type of outcome	Infant HIV-1 status at one, six, nine and fourteen weeks and nine, 12, 15, 18 and 24 months of age. Secondary outcomes were survival free of HIV-1 infection during follow-up and the safety of the experimental regimens.
Follow up visits	Study visits were conducted at one, three, six, nine and 14 weeks and at six, nine, 12, 15, 18, and 24 months of infant age.
Infant feeding mode	Breastfeeding was promoted but mothers were counselled to stop breastfeeding by six months.
Random sequence generation (selection bias)	Low risk as it was randomized, controlled, open-label, phase 3 clinical trial
Allocation concealment	Low risk as permuted block algorithms with a 1:1:1 allocation ratio was employed with block sizes of 9 and 12 blocked within study site.
Performance bias and detection bias	Unclear, there is no information on blinding of infants and mothers.
Incomplete outcome data (attrition bias)	High risk as the loss to follow up was greater than 10% although fairly similar in the three groups 430/1090 (39.4%), 506/1160 (43.6%) and 474/1147 (41.3%) respectively.

5.5.16 Characteristics of Study 16: PETRA 2002a, b

Study Identifier	PETRA 2002a and PETRA 2002b
Country and location	The trial was done in five sites in three countries: two large public hospitals in South Africa (Chris Hani Baragwanath Hospital in Johannesburg and King Edward VII Hospital in Durban); one large public hospital in Tanzania (Muhimbili General Hospital in Dar es Salaam); one large public hospital in Uganda (Mulago Hospital in Kampala); and one semi-private missionary hospital in Uganda (St Francis Hospital in Nsambya, Kampala).
Duration	June 1996 until January 2000.

Type of study Randomisation	Multicentre, randomised, double-blind controlled trial.
Sample size	A total of 1797 women were enrolled.
Type of participant	Inclusion criteria: • Older than 18 years of age; • Evidence of HIV-1 infection; • Ability to give informed consent; • Estimated gestational period of less than 36 weeks at enrolment; absence of severe fetal anomalies within the limits of local diagnostic possibilities; • Absence of life-threatening disease; • Haemoglobin over 8 g/dl at enrolment; • 18 months' follow-up possible.
Type of intervention	HIV-1-infected mothers were randomised to one of four regimens: Group A (N=475) • Zidovudine 300 mg plus lamivudine 50 mg twice daily starting at 36 weeks' gestation until the onset of labour; • Followed by oral intrapartum dosing consisting of zidovudine 300 mg every three hours and lamivudine 150 mg every 12 hours until delivery; • Followed zidovudine 300 mg plus lamivudine 50 mg twice daily for seven days postpartum; • Infants received zidovudine 4 mg/kg plus lamivudine 2 mg/kg twice daily. Group B (N= 474) • Started treatment at the onset of labour with zidovudine 600 mg and lamivudine 150 mg followed by zidovudine 300 mg every three hours and lamivudine 150 mg every 12 hours until delivery.

	• In addition women received zidovudine 300 mg plus lamivudine 150 mg twice daily for seven days postpartum. • Infants received zidovudine 4 mg/kg plus lamivudine 2 mg/kg twice daily for seven days after delivery Group C (N=471) • Women received zidovudine 600 mg and lamivudine 150 mg at the onset of labour, then zidovudine 300 mg every three hours and lamivudine 150 mg every 12 hours until delivery. • Infants received zidovudine 4 mg/kg plus lamivudine 2 mg/kg twice daily for seven days after delivery Group D (N=377) • Placebo during labour and postpartum for the women and placebo syrup for the infants.
Type of outcome	Primary outcomes were HIV-1 infection and child mortality at week six and 18 months after birth. Grade 3 and 4 events on the Adverse Event Toxicity Scale in mothers and infants. Congenital abnormalities. Neurological events up to 18 months after birth.
Follow up visits	Six weeks and 18 months
Infant feeding mode	Breastfeeding was promoted.
Random sequence generation (selection bias)	Unclear as block randomisation list by site was prepared before the trial.
Allocation concealment	Low risk, as the study medication was packaged by GlaxoWellcome, the manufacturer of zidovudine and lamivudine, according to the randomisation list. Each site received the pre-randomised packs labelled by patients' numbers. There was one

	pack of study medication for each patient's number. The pack included prepartum, intrapartum, and postpartum bottles.
Performance bias and detection bias	Low risk as all the steps following the preparation of the study medication batches was masked. Participants and providers were blinded but no details given about blinding of assessors.
Incomplete outcome data (attrition bias)	High risk as attrition was > 10%. Overall attrition was 29.5% (430/1457) with attrition in Arm A 26.7% (98/366); in Arm B attrition was 32.3% (120/371); in Arm C attrition was 30.7% (113/368); and in the placebo arm attrition was 28.1% (99/352)
Notes	For the sake of masking, all women received one tablet of zidovudine or a matched placebo and one tablet of lamivudine or a matched placebo twice daily from enrolment until the onset of labour. At enrolment, women were also given an intrapartum pack to keep with them and they were instructed to take the medication at the onset of labour and come immediately to the labour ward. This intrapartum pack comprised two tablets of zidovudine or a matched placebo and one tablet of lamivudine or a matched placebo. From 18 February 1998, onwards, women were only randomised to one of the active treatment groups and the placebo group was stopped.

5.5.17 Characteristics of Study 17: PHPT 2000a, b

Study Identifier	PHPT 2000a and PHPT 2000b
Country and location	Women presenting at any of 27 Thai study sites in Thailand, before 26 weeks' gestation.
Duration	24 June 1997 to 3 December 1999.
Type of study	Randomised, double-blind equivalence trial of four regimens.
Randomisation	
Sample size	1114 women

Type of participant	Inclusion criteria: • At least 28 weeks' gestation; • Agreed not to breast-feed; • Haemoglobin level, higher than 8.0 g per decilitre; • Absolute neutrophil count more than 750 per cubic millimeter; serum alanine aminotransferase level, less than five times the upper limit of normal; • Creatinine level, less than 1.5 mg per deciliter (132.6 μmol per liter). Exclusion criteria: • Maternal or foetal abnormality; • Concomitant treatment contraindicating treatment with zidovudine; • Oligohydramnios; • Unexplained hydramnios; • In utero anemia.
Type of intervention	Women were randomly assigned to one of four groups. Group 1(N=419) The long–long group received zidovudine from 28 weeks' gestation through delivery The infant received zidovudine from birth through week six. Group 2 (N=236 before 4 December 1998 then 87 after but not included in the analysis) The short–short group received placebo starting at 28 weeks' gestation and then received zidovudine from 35 weeks' gestation through delivery. The infant received zidovudine for the first three days of life, followed by placebo through week six. Group 3 (N=350)

	The long–short group received zidovudine from 28 weeks' gestation through delivery, with the infant receiving zidovudine for the first three days of life, followed by placebo through week six. Group 4 (N=345) The short–long group received placebo starting at 28 weeks' gestation, followed by zidovudine from 35 weeks' gestation through delivery, with the infant receiving zidovudine from birth through week six. In all groups, the women received oral zidovudine every three hours during labour.
Type of outcome	Infants were considered to be infected with HIV if the results of the PCR test were positive for blood samples obtained on two separate occasions, and infants were considered to be uninfected if the test results were negative on two occasions after one month of age. Infants were considered to have been infected in utero if the first positive test result was obtained within seven days after birth.
Follow up visits	Follow up for women was 32, 35, 38 and 40 weeks gestation then weekly until delivery and six and 18 months postpartum. Follow up for infants was two, four and six weeks of life then four and six months thereafter at three months until 18 months of life.
Infant feeding mode	Formula feeding was promoted.
Random sequence generation (selection bias)	Unclear as the study drugs, packaged by Glaxo Wellcome, were identified by random numbers with the use of permuted blocks of six in a ratio of 2:1:1:2 for the long–long, short–long, long–short, and short–short groups, respectively. After the first interim analysis, new supplies were provided in blocks of five, with a new randomization scheme in a ratio of 1:2:2 for the long–long, long–short, and short–long groups, respectively.
Allocation concealment	Low risk as treatment packs was centrally prepared.

Performance bias and detection bias	Low risk as participants and providers did not know the random allocation. It is not mentioned whether the assessors were aware of the random allocation.
Incomplete outcome data (attrition bias)	Low risk as Attrition was < 10%. First interim analysis (4 December 1998): Overall attrition was 3.6% (17/466); with attrition in the Long-Long group 4.3% (10/230) and in the Short-short group 3.0% (7/236). Final analysis: Overall attrition was 3.1% (35/1114) with attrition in the Long-long 4.3% (18/419); in the Long-short 2.9% (10/350) and in the Short-long 2.0% (7/345).
Notes	After the first interim analysis, the short–short regimen was discontinued, and the study was redesigned to test for equivalence between the efficacy of the long–long regimen and the efficacy of the other two regimens.

5.5.18 Characteristics of Study 18: PHPT-2 2004

Study Identifier	PHPT-2 2004
Country and location	In 37 Voluntary and Counseling and Testing (VCT) programme sites in Thailand.
Duration	15 January 2001 until 28 February 2003.
Type of study	Randomised, double-blind controlled trial.
Randomisation	
Sample size	A total of 1805 Thai women were enrolled.
Type of participant	Inclusion criteria: • HIV-infected; • 28 weeks gestation; • Agreed not to breastfeed; • Had already received 2 weeks of ZDV prophylaxis; • Hb > 8.0g/dL; • ALT < 5 times the ULN;

	• Creatinine < 1.5mg/dL; • Absolute neutrophil count > 750 cells/mm3. Exclusion criteria: • Contraindications to ZDV or NVP (maternal or foetal condition); • Concomitant treatment; • Oligohydramnios; • Unexplained polyhydramnios; • In utero anaemia; • Medical condition that required HAART.
Type of intervention	All women received ZDV 300mg twice daily from 28 weeks or later and 300mg three hourly from onset of labour to delivery. All infants received ZDV 2mg/kg body weight six hourly for one week after birth or for 4-6 weeks if mother received ZDV for <4 weeks. Group1 (N=724) • Women received NVP as a single 200mg dose orally at onset of labour. • Infants received NVP oral suspension as a single fixed dose (6mg in 0.6 ml) 48 to 72 hours after birth. Group 2 (N=721) • Women received NVP as a single 200mg dose orally at onset of labour. • Infants received placebo. Group 3 (N=360) • Women received placebo at onset of labour. • Infants received placebo.
Type of outcome	Infant HIV+ by PCR on two separate occasions - done at birth, six weeks, and four and six months. Secondary outcomes were adverse events.

Follow up visits	Follow-up was every two weeks for the women until delivery and after delivery at 10 days, six weeks and four months. Infants were seen and examined at birth, at 10 days post birth and at six weeks and then four, six, nine and 12 months. HIV infection was determined in the infant by PCR DNA assay for HIV (Amplicor HIV-1 DNA, Roche version 1.5).
Infant feeding mode	Formula feeding was promoted.
Random sequence generation (selection bias)	Unclear but stated as a randomised, placebo-controlled trial. Randomised in permuted blocks of six in the ratio 1:1:1 but method of generation not specified.
Allocation concealment	Low risk as centrally prepared treatment packs identified by random numbers.
Performance bias and detection bias	Low risk as participants, providers, and assessors were blinded.
Incomplete outcome data (attrition bias)	Unclear. The total number randomised as reported in the text (N = 1844) conflicts with those reported in Figure 1 (N = 1445 for final analysis). At first interim analysis (2 May 2002) including the placebo - placebo group had an overall attrition of 4.9%. At final analysis the attrition, excluding those in the placebo-placebo was 5.5%.

5.5.19 Characteristics of Study 19: Promise PEP 2015

Study Identifier	Promise PEP 2015
Country and location	Ouagadougou University Teaching Hospital (urban site in Burkina Faso), East London Hospital Complex (urban site in South Africa); Mbale Regional Referral Hospital (semi-rural site in Uganda), and Lusaka University Teaching Hospital (urban site in Zambia).
Duration	16 November 2009 and 7 May 2012.

Type of study	A multicentre, randomised, controlled pragmatic trial.
Randomisation	
Sample size	A total of 1273 infants were randomised.
Type of participant	Inclusion criteria for infants at day seven: • Singleton; • Breastfed at day seven by their mothers; • Had a negative HIV-1 DNA PCR at day seven; • Mother and infant had received PMTCT; • Mother was aged 18 years or older; • Mother intended to continue breastfeeding; • Infant was born to a HIV-1 positive mother; • Mother resided within the study area; • Mother was not intending to move out of the area in the next year, mother gave consent to participate for herself and her infant. Exclusion criteria: Infants were not included: • If they had clinical signs or biological abnormalities of grade 2 or higher.
Type of intervention	All women and infants followed the routine national prevention of mother-to-child transmission programmes until trial inclusion at day seven after birth. Group 1 (N=636) Infants received paediatric liquid formulations of lopinavir–ritonavir (Kaletra, Abbott, Chicago, USA); 40 mg of lopinavir and 10 mg of ritonavir, twice a day if weighing 2–4 kg, and 80 mg and 20 mg, twice a day if weighing >4 kg) assigned to lopinavir–ritonavir group. Group 2 (N=637)

	Infants received paediatric liquid formulation of generic lamivudine (7·5 mg twice a day if weighing 2–4 kg, 25 mg twice a day if weighing 4–8 kg, and 50 mg twice a day if weighing >8 kg).
Type of outcome	Infant HIV-1 infection was assessed using HIV-1 DNA real-time PCR on dried blood spots (Generic HIV DNA cell, Biocentric, France) at day seven and at weeks six, 14, 26, 38, and 50. HIV-1 infection was confirmed by the same technique on a second sample. Venous blood was also collected from infants at weeks six, 26, and 38 to check for biological abnormalities.
Follow up visits	Two weeks after enrolment then every four weeks until week 50.
Infant feeding mode	Women were encouraged to exclusively breastfeed their children for six months, to introduce complementary feeds gradually thereafter, and to stop breastfeeding completely at no later than 49 weeks. The study drug was stopped either one week after complete cessation of breastfeeding or at the final visit at week 50.
Random sequence generation (selection bias)	Low risk as HIV-1-uninfected infants were randomly assigned on day seven (plus or minus 2 days) to either lopinavir–ritonavir or lamivudine in a 1:1 ratio. An independent statistician generated the randomisation lists online using the website randomization.com, with stratification by country and in permuted blocks of four and six.
Allocation concealment	Low risk as the statistician prepared sequentially numbered envelopes corresponding to the order of codes on the randomisation list. Study pharmacists used these sealed opaque envelopes to assign participants. All bottles were masked with a study label that prevented primary caregiver or parent from reading the original label.
Performance bias and detection bias	Study pharmacists did randomisation, drug delivery, and adherence counselling, allowing study physicians and clinical staff to remain masked to drug allocation. Mothers, physicians,

	and statisticians were not aware of treatment allocation, and assessors were fully blinded and had no contact with patients. However, given that masking was only partial, some parents might have known their child's treatment allocation.
Incomplete outcome data (attrition bias)	Low risk as loss to follow up was less than 10% and 21 infants were excluded from the analysis in Group 1 and 16 in Group 2.

5.5.20 Characteristics of Study 20: SAINT 2003

Study Identifier	SAINT 2003
Country and location	Eleven public hospitals in South Africa.
Duration	Between May 1999 to February 2000.
Type of study Randomisation	A multicenter open label randomised controlled trial.
Sample size	1319 women were enrolled.
Type of participant	Inclusion criteria: • HIV-1 positive, antiretroviral-naive women 16 years and older who either >38 week gestation or >35 weeks and in labour. Exclusion criteria: • Elective caesarian section; • Presented with life threatening complications.
Type of intervention	Group 1 (N=662): • Women received NVP as a 200mg dose orally in labour followed by a 200mg dose 48 hours later if still in labour and 200mg 24-48 hours postpartum. • Infants received NVP oral suspension as a single 6mg dose 24 to 48 after delivery. If infant was born within two

	hours of maternal dose given in labour then another 6mg dose was given within six hours of delivery. Group 2 (N=655) • Women received a loading dose of ZDV 600mg plus 3TC 150mg orally on arrival in labour and then ZDV 300mg every three hours and 3TC 150mg every 12 hours until delivery. After delivery ZDV 300mg plus 3TC 150mg twice daily for one week. • Infants received treatment at least 12 hours after delivery and continued for one week. If weight >2kg infants received ZDV syrup 12mg BD plus 3TC BD oral solution 3mg. Weight <2kg infants received ZDV 4mg/kg and 3TC 2mg/kg. Infants born within two hours of first maternal dose started treatment within six hours after delivery.
Type of outcome	HIV-1 in infants assessed by PCR DNA or RNA assay at birth and eight weeks. Adverse events in mother and baby
Follow up visits	Birth and eight weeks.
Infant feeding mode	Formula feeding was encouraged and women were given formula feed.
Random sequence generation (selection bias)	Low risk as computer randomised scratch card sheets in permuted blocks of 4 in 2:2 ratio.
Allocation concealment	Unclear risk as reported only as “unknown to investigator until mother prepared to begin treatment” but actual method not described.
Performance bias and detection bias	High risk as no blinding of participants or providers is mentioned but assessors were blinded.
Incomplete outcome data (attrition bias)	High risk as overall attrition > 10% although it was similar between the two groups. Overall attrition was 28.4%

(375/1319) with attrition in the NVP group 28.9% (190/657) and 27.9% (185/662) in the ZDV-3TC group

5.5.21 Characteristics of Study 21: SWEN 2008

Study Identifier	SWEN 2008
Country and location	Addis Ababa in Ethiopia, Pune in India, and Kampala in Uganda.
Duration	Ethiopia: February 2001 - October 2006. India: August 2002 - March 2007. Uganda: July 2004 - January 2007.
Type of study Randomisation	A three-country merged analysis of primary study endpoints for efficacy and safety. Ethiopia and India was a two-arm randomised controlled trial and Uganda a three-arm randomised controlled trial.
Sample size	Ethiopia: 780 delivered mothers in randomised cohort. India: 770 delivered mothers in randomised cohort. Uganda: 517 delivered mothers in randomised cohort.
Type of participant	Inclusion criteria: • HIV-1 infected pregnant women intending to breastfeed their infants; • ≥18 years of age or consent of guardian, ≥32 weeks' gestation (Uganda 32–36 weeks' gestation and India ≥32 weeks' gestation and within 24 hours of delivery, for post-partum enrolment); • Haemoglobin >75 g/L; • Creatinine <1·5 mg/dl, alanine aminotransferase concentrations <5× the upper limit of normal. Exclusion criteria: Ethiopia

	• Any antiretroviral therapy in addition to single-dose nevirapine for prevention of mother-to-child transmission; • Foetal or obstetrical complications; • Hypersensitivity to benzodiazepine. India • Mothers on HAART or receiving antiretroviral therapy, in addition to single-dose nevirapine were not excluded.
Type of intervention	Ethiopia and India: Group 1 (Ethiopia N=383, India N=370), Uganda N=294). • Single dose nevirapine at birth (2 mg/kg) plus multivitamins daily (1 mL/d) days 8–42. Group 2 (Ethiopia N=381, India = 367, Uganda N=229). • Extended dose, single dose nevirapine at birth (2 mg/kg) plus multivitamins daily (1 mL/d) days 8–42, plus nevirapine daily (5 mg/d) days 8–42. Uganda group 1 and 2 as above Group 3 • Single dose oral nevirapine at birth (2 mg/kg) plus one intravenous dose (1·2 mg/24 mL) of HIV immunoglobulin within 18 hours of birth.
Type of outcome	The primary endpoint was HIV infection at six months of age in infants who were HIV PCR negative at birth.
Follow up visits	Infant HIV testing was done at six weeks, 14 weeks, and six months in all three countries. Ethiopia - Birth, at two, six and 14 weeks and six months. India - Birth, at one, two, six, 10 and 14 weeks and six months. Uganda - Birth, at two, six and 14 weeks and six months.
Infant feeding mode	Women who intented to breastfeed their infants.

Random sequence generation (selection bias)	Low risk as all three countries used block randomisation with treatment assignments generated by computer at a central data coordinating centre at Johns Hopkins University.
Allocation concealment	Low risk as the randomisation list was provided to study pharmacists only in each country.
Performance bias and detection bias	High risk as mothers knew what group their infants were in. During the first six weeks post partum, enrolled mothers and their infants met privately with study pharmacists to receive their assigned study drugs and were provided training by the pharmacists about how to properly administer study drugs to their infants. Other study investigators and clinical staff were not provided access to information about treatment assignments.
Incomplete outcome data (attrition bias)	High risk as overall >10% loss to follow up.
Notes	In India, all study infants were randomised post partum, while in Uganda, randomisation was pre-partum only. Initially in Ethiopia randomisation occurred pre-partum; however, because randomised women were deciding not to breastfeed after delivery, randomisation was subsequently changed to post partum.

5.5.22 Characteristics of Study 22: Taha 2003

Study Identifier	Taha 2003
Country and location	In six clinics in the Blantrye area, Malawi.
Duration	April 2000 until January 2002.
Type of study Randomisation	A randomised, open-label, controlled phase III clinical trial.

Sample size	A total of 1119 infants were randomised.
Type of participant	Inclusion criteria: • HIV+ve women in advanced labour (as defined by cervical dilatation > 6cm, or in 2nd stage of labour with strong, regular contractions; estimated delivery within two hours after arrival); • Women who delivered immediately post arrival prior to vaginal examination; • Women who did not receive NVP; • Singleton term gestation; • Infant had no abnormalities.
Type of intervention	Group 1 (N=557) Infants received Nevirapine 2mg/kg orally immediately after birth. Group 2 (N=562) Infants received Nevirapine 2mg/kg immediately after birth and Zidovudine 4mg/kg twice daily given orally to infant for seven days after birth.
Type of outcome	Primary outcome: • HIV infection at 6-8 weeks after birth in infants who were HIV-ve at birth Secondary outcomes: • HIV infection at 6-8 weeks after birth in all infants including HIV+ve at birth (HIV-1 RNA assay); • HIV infection at 6-8 weeks after birth for all infants tested at 6-8 weeks but excluding those tested at birth if not also tested at 6-8 weeks; • Death up until one year after birth; • Adverse events.

Follow up visits	Enrolled babies were scheduled for follow-up visits at age one week, 6–8 weeks, three months, six months, nine months and 12 months.
Infant feeding mode	Breastfeeding promoted.
Random sequence generation (selection bias)	Low risk as computer generated random allocations using permutated blocks of 10 with a 1:1 allocation and stratified by clinic.
Allocation concealment	Low risk as newly enrolled infants were sequentially assigned the next study identification number that was in opaque, sealed envelopes.
Performance bias and detection bias	High risk as there was no blinding of participants or providers but assessors were blinded.
Incomplete outcome data (attrition bias)	High risk as attrition > 10%. Overall attrition was 22.7% (254/1119) with attrition in the NVP/ZDV group and 9% (118/562) and 24.4% (136/557) in the NVP group.

5.5.23 Characteristics of Study 23: Taha 2004

Study Identifier	Taha 2004
Country and location	At six clinics in Blantrye, Malawi.
Duration	1 April 2000 and 15 March 2003.
Type of study Randomisation	A randomised open label, phase three trial.
Sample size	A total of 894 infants were randomised.
Type of participant	Inclusion criteria included infants' of women who were: • HIV +ve and presented in early labour; • Who received a single oral dose of NVP 200 mg at two hours before delivery; • Who were not exposed to ARV's before labour.

	Inclusion criteria (infants): • Haemoglobin ≥10 g/dL); • Term gestation; • Not requiring admission to intensive care unit.
Type of intervention	All women received a single oral dose of 200mg NVP in labour. All infants received cotrimoxazole prophylaxis up to six months after birth. Group 1 (N=448) • Infants received Nevirapine 2mg/kg single oral dose at birth. Group 2 (N= 446) • Infants received Nevirapine 2mg/kg single oral dose at birth and Zidovudine 4mg/kg twice daily orally for seven days after birth.
Type of outcome	Primary outcome: • Infants HIV status at 6-8 weeks after birth. Secondary outcomes: • Infant HIV infection at birth; • Infant deaths at 6-8 weeks; • Grade 3 and 4 events on the Adverse Event Toxicity Scale.
Follow up visits	Infants were followed up at birth, six and eight weeks and three to 18 months.
Infant feeding mode	Breastfeeding was promoted.
Random sequence generation (selection bias)	Low risk as Computer generated random allocation was done in permuted blocks of 10 in a 1:1 ratio stratified per clinic.
Allocation concealment	Low risk as study nurses opened sequentially numbered, opaque, sealed envelopes after consent was obtained.

Performance bias and detection bias	High risk as there was no blinding of participants or providers but assessors were blinded.
Incomplete outcome data (attrition bias)	High risk as attrition rate was > 10% with 8.5% (38/446) in the NVP/AZT group and 13.2% (59/448) in the NVP group.

5.5.24 Characteristics of Study 24: Thistle 2004

Study Identifier	Thistle 2004
Country and location	Salvation Army Hospital in Zimbabwe.
Duration	August 1999 until December 2000.
Type of study Randomisation	Double blinded randomised placebo controlled trial.
Sample size	A total of 222 women were randomised, but 29 were lost to follow up but only 179 infant data is reported on.
Type of participant	Inclusion criteria: • HIV-positive women presenting in early before 36 weeks gestation.
Type of intervention	Group 1 (N=90) • Women followed the “Thai Regimen” received ZDV 300mg orally twice daily from 36 weeks to labour and then ZDV 300mg orally three hourly until delivery. Infants: • Received placebo. Group 2 (N=89) • Women received placebo from 36 weeks to labour then ZDV 300mg orally three hourly until delivery. Infants: • Infants received ZDV suspension 2mg/kg orally four times daily for first three days after birth.

Type of outcome	Primary outcome: • HIV infection in infants six weeks after birth. Secondary outcomes: • Cumulative death rate in infants at six weeks, three months, six months and one year; • Maternal death and serious adverse effects.
Follow up visits	Six weeks, three months, six months and one year.
Infant feeding mode	Women were counselled to breastfeed and undertake early and rapid weaning at five months.
Random sequence generation (selection bias)	Low risk Computer generated block randomisation.
Allocation concealment	Low risk as allocation schedule was prepared by off-site statistician and provided in “ordered opaque envelopes”.
Performance bias and detection bias	Unclear participants and provider were blinded but blinding of assessor was unclear
Incomplete outcome data (attrition bias)	High risk as attrition was > 10%. Overall attrition was 19.4% (43/222) but distribution between groups is not provided.

5.5.25 Characteristics of Study 25: Thistle 2007

Study Identifier	Thistle 2007
Country and location	Salvation Army Howard Hospital in Chiweshe, Zimbabwe.
Duration	December 2002 to August 2004.
Type of study Randomisation	A randomised, double blind, placebo controlled trial.
Sample size	A total of 1140 HIV positive women were randomised.
Type of participant	Inclusion criteria: • Pregnant women;

	• HIV-positive; • Ability to give consent; • Willing to attend follow up visits. Exclusion criteria: • Clinical evidence of significant hepatic disease; • Receipt of previous antiretroviral therapy.
Type of intervention	Group 1 (N=569) • Women received a loading dose of 600mg of ZDV orally at onset of labour and then ZDV 300mg three hourly during labour and a single dose of 200mg NVP orally in labour. • Infants received a single dose of NVP 2mg per kg of body weight orally within 72 hours of delivery and ZDV at a dosage of 2mg per kg of body weight orally four times per day for 72 hours after delivery. Group 2 (N=571) • Women received placebo in the same routine as ZDV and a single dose of 200mg NVP orally in labour. • Infants received NVP 2mg per kg of body weight orally within 72 hours of delivery. All mothers were offered free cotrimoxazole prophylaxis of opportunistic infections at three months after delivery and all infants with unknown or HIV-positive status were also provided with cotrimoxazole prophylaxis.
Type of outcome	Primary outcome: • Infant HIV infection or infant death at six weeks of age. Secondary outcomes: • HIV infection status at birth and two weeks. • Maternal death; • Birth outcomes, stillbirths, prematurity; • Admission to nursery.

	• Adverse events.
Follow up visits	Neonatal HIV status was determined from heel prick dried blood spots collected at birth, two weeks, and six weeks.
Infant feeding mode	Breastfeeding was encouraged and women were counselled to consider rapid weaning at 5–6 months of age.
Random sequence generation (selection bias)	Low risk as computer-generated random sequence was used for randomisation.
Allocation concealment	Unclear risk participants and providers were assumed to be blinded as it is reported as “double-blind, placebo-controlled”, but it is not stated how placebo was prepared.
Performance bias and detection bias	Unclear whether assessors in the laboratory were blinded.
Incomplete outcome data (attrition bias)	High risk as the attrition was > 10% with a very high attrition of 53.4% overall and an attrition rate of 54.8% usZDV/sdNVP arm and 52% in the sdNVP arm at six weeks.
Notes	The study was terminated early in August 2004 after results from Taha 2004 demonstrated that there was no benefit in ZDV therapy for the neonate alone.

5.6 Meta-analysis of Included Studies

Information related to the primary outcomes namely: Infant HIV infection status at birth, at two weeks, four to eight weeks and three, six and 12 months as well as secondary outcomes: maternal deaths post randomisation, stillbirths after randomisation, infant deaths before six months and up to 18 months, maternal adverse events and infant adverse events up to 18 months were extracted.

Information was extracted on an excel sheet and then transferred to RevMan 5.3 for meta-analysis. The results are presented in forest plots using risk ratio (RR) and confidence intervals (CI). A short narrative description explains the interpretation of each finding.

5.6.1 Infant HIV-positive at Birth or ≤ at Two Weeks

Seven studies reported on the longer versus a shorter regime and HIV-positive outcome of the infant at birth or ≤ than two weeks. The heterogeneity was not important (I^2 = 16%). Significantly less infants tested HIV-positive when exposed to a longer ARV regime CI 0.51 [0.42-0.63]. The proportion of infants who tested positive in the longer regime group was 8.28% (222/2679) compared to 16.41% (423/2577) in the shorter regime group. (Figure 5.2).

Sixteen studies reported on the use of different antiretroviral therapy treatment and HIV-positive outcome of the infant at birth or ≤ than two weeks. The heterogeneity was not important (I^2 = 0%). There was no statistically significant difference between the experimental group and the control group CI 0.94 [0.82-1.09], although there were slightly fewer HIV-positive infected infants in the experimental group. The proportion of infants who tested positive in the experimental group was 5.30% (347/6535) compared to 5.65% (367/6492) in the control group. (Figure 5.2).

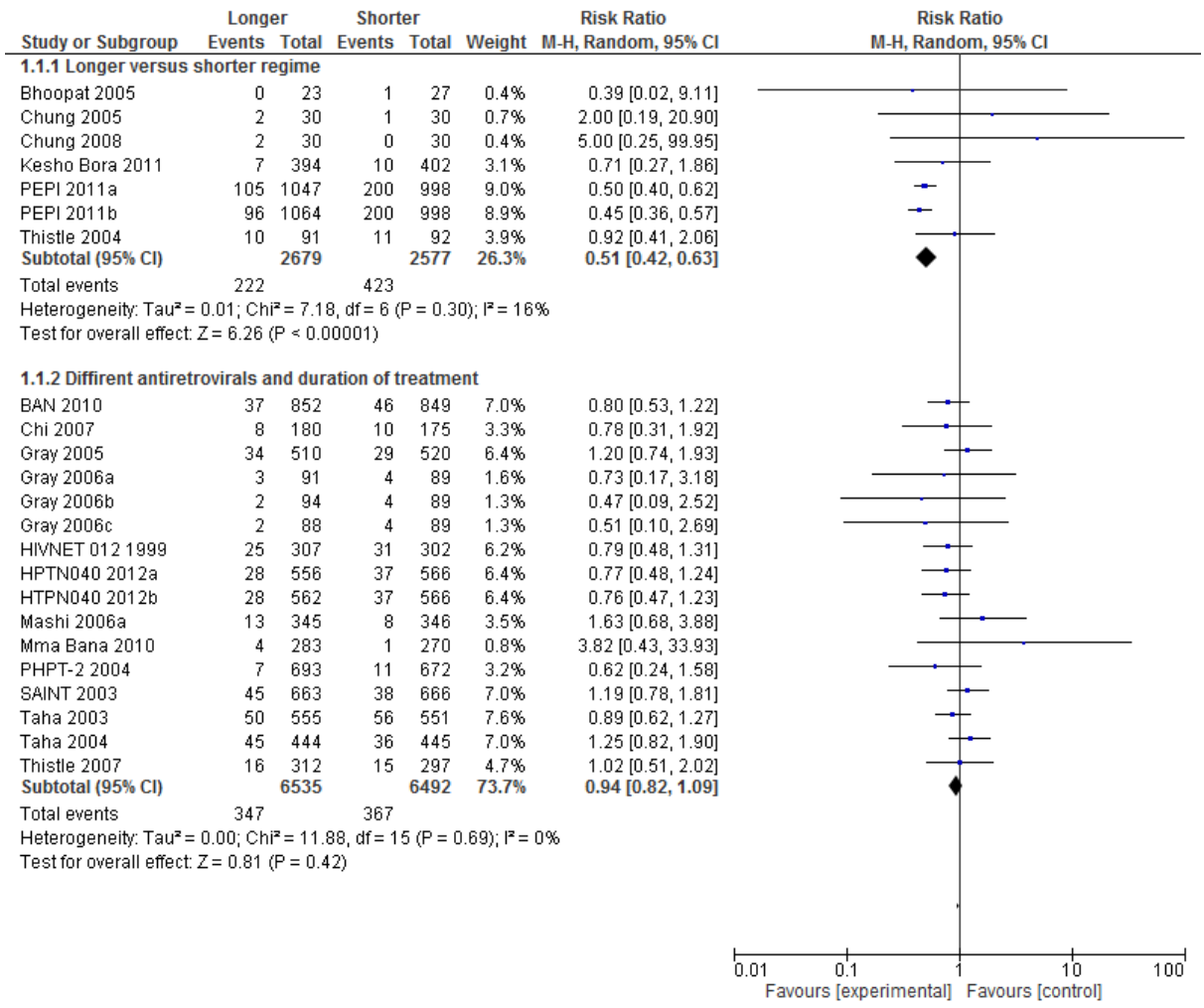

Figure 5.2 Infant HIV-positive at Birth or ≤ than Two Weeks

5.6.2 Infant HIV-positive Between Four to Eight Weeks

Eight studies reported on the longer versus a shorter regime and HIV-positive outcome of the infant between four to eight weeks. Heterogeneity among the studies was substantial (I^2 = 64%). Significantly less infants tested HIV-positive when exposed to a longer ARV regime CI 0.51 [0.32-0.79]. The proportion of infants who tested positive in the longer regime group was 2.65% (94/3546) compared to 5.92% (203/3429) in the shorter regime group. (Figure 5.3).

Fifteen studies reported on the use of different antiretroviral and HIV-positive outcome of the infant between four to eight weeks after birth. Heterogeneity among the studies was moderate (I^2 = 55%). There was a statistically significant difference between the experimental group and the control group CI 0.79 [0.63-1.00], with fewer infants testing HIV-positive in the experimental group. The proportion of infants who tested positive in the experimental group was 5.94% (325/5471) compared to 7.32% (401/5472) in the control group. (Figure 5.3).

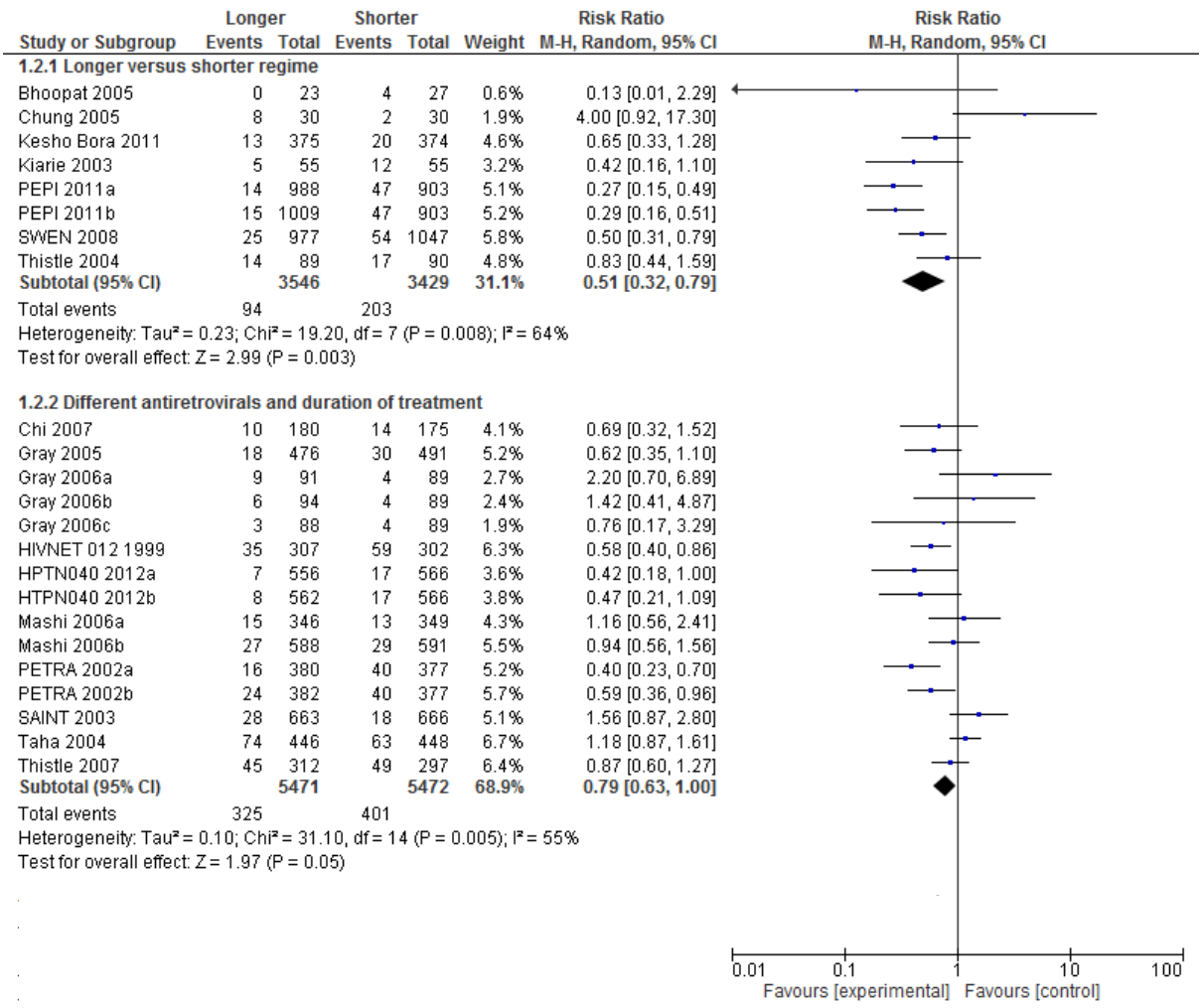

Figure 5.3 Infant HIV-positive Between Four to Eight Weeks

5.6.3 Infant HIV-positive Between 12 to 14 Weeks

Four studies reported on the longer versus a shorter regime and HIV-positive outcome of the infant between 12 to 14 weeks. Heterogeneity among the studies was substantial (I^2 = 72%). Significantly less infants tested HIV-positive when exposed to a longer ARV regime CI 0.40 [0.22-0.73]. The proportion of infants who tested positive in the longer regime group was 3.30% (65/1969) compared to 9.40% (162/1723) in the shorter regime group. (Figure 5.4).

Six studies reported on the use of different antiretrovirals and HIV-positive outcome of the infant at 12–14 weeks. Heterogeneity among the studies was moderate (I^2 = 58%). There was no statistically significant difference between the experimental group and the control group CI 0.79 [0.48-1.29], but slightly fewer infants were HIV-positive in the experimental group. The proportion of infants who tested positive in the experimental group was 4.88% (83/1698) compared to 7.34% (125/1701) in the control group. (Figure 5.4).

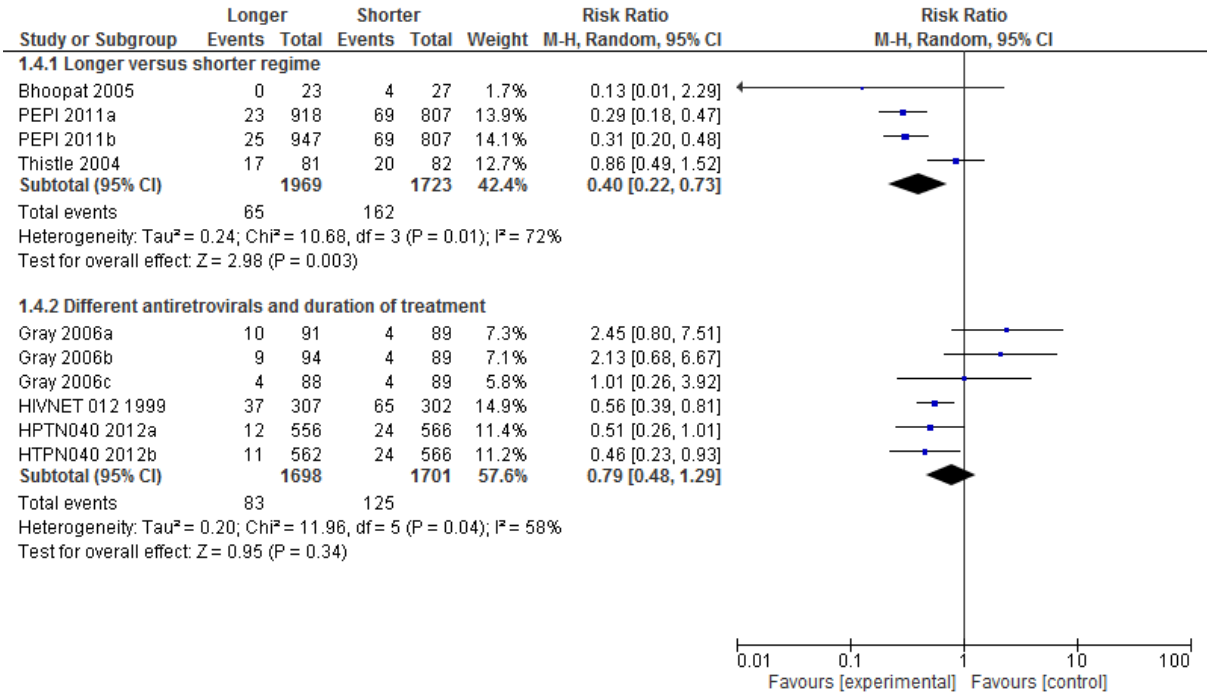

Figure 5.4 Infant HIV-positive Between 12–14 Weeks

5.6.4 Infant HIV-positive at Six Months

Nine studies reported on the longer versus a shorter regime and HIV-positive outcome of the infant at six months. Heterogeneity among the studies was substantial (I^2 = 76%). Fewer infants tested HIV-positive when exposed to a longer ARV regime CI 0.74 [0.51-1.05], but the difference was not statistically significant. The proportion of infants who tested positive in the longer regime group was 5.43% (243/4473) compared to 8.22% (350/4255) in the shorter regime group. (Figure 5.5).

Eleven studies reported on the use of different antiretrovirals and HIV-positive outcome of the infant at six months. Heterogeneity among the studies was moderate (I^2 = 44%). There was no statistically significant difference between the experimental group and the control group CI 0.89 [0.66-1.20]. The proportion of infants who tested positive in the experimental group was slighty less at 4.40% (189/4288) compared to 5.38% (226/4195) in the control group. (Figure 5.5).

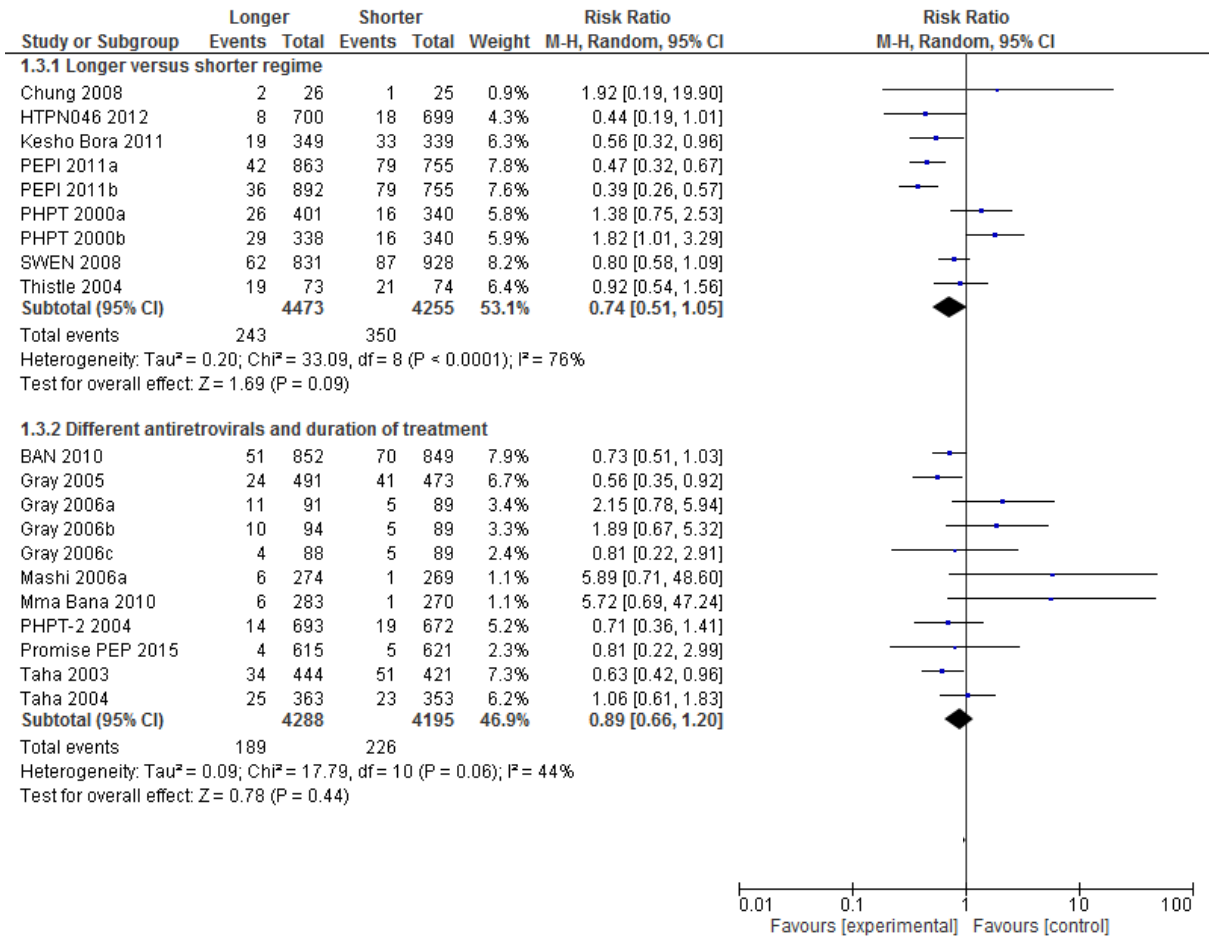

Figure 5.5 Infant HIV-positive at Six Months

5.6.5 Infant HIV-positive at 12 Months

Five studies reported on the longer versus a shorter regime and HIV-positive outcome of the infant at 12 months. Heterogeneity may not be important at (I^2 = 21%). There was a statistically significant difference between the two groups and fewer infants tested HIV-positive when exposed to a longer ARV regime CI 0.63 [0.51-0.78]. The proportion of infants who tested positive in the longer regime group was 6.52% (165/2530) compared to 10.67% (241/2257) in the shorter regime group. (Figure 5.6).

One study reported on the use of different antiretroviral and HIV-positive outcome of the infant at 12 months. There was no statistically significant difference between the experimental group and the control group CI 0.90 [0.35-2.31], similar proportions of

infants tested HIV-positive at 12 months. The proportion of infants who tested positive in the experimental group was 1.30% (8/615) compared to 1.44% (9/621) in the control group. (Figure 5.6).

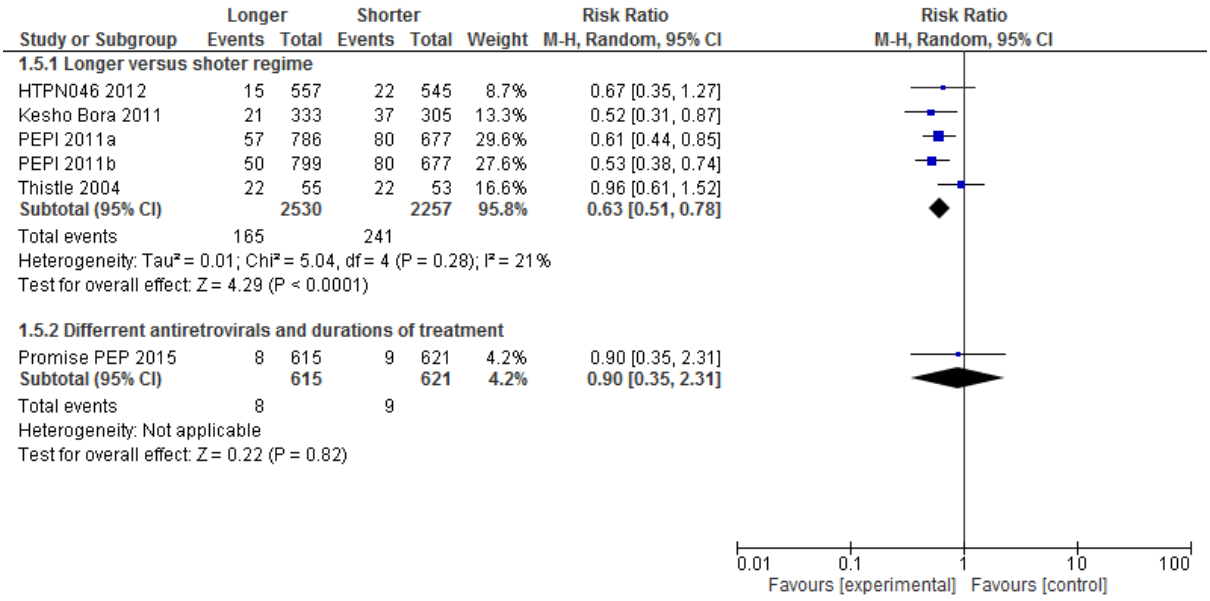

Figure 5.6 Infant HIV-positive at 12 Months

5.6.6 Maternal Deaths Anytime Post Randomisation

Eleven studies reported on maternal deaths anytime post randomisation. Heterogeneity was not important (I^2 = 0%). There was no statistically significant difference in maternal deaths post randomisation between the two groups, CI 0.84 [0.50-1.42]. The proportion of maternal deaths in the experimental group was 0.68% (24/3501) compared to 0.83% (29/3490) in the control group. (Figure 5.7).

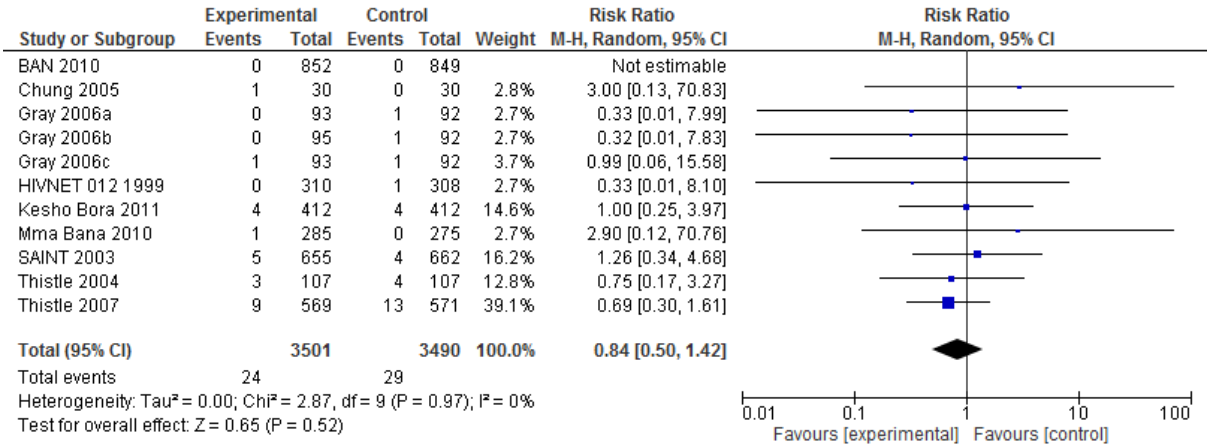

Figure 5.7 Maternal Deaths Anytime Post Randomisation

5.6.7 Infant Deaths at or before Six Months after Birth

Twenty six studies reported on infant deaths before six months. Heterogeneity among the studies was not important (I^2 = 6%). The difference between the experimental and the control group was statistically significant, CI 0.71 [0.62-0.82]. Significantly fewer infants died in the experimental group 3.25% (370/11380) compared to the control group 4.66% (518/11110). (Figure 5.8).

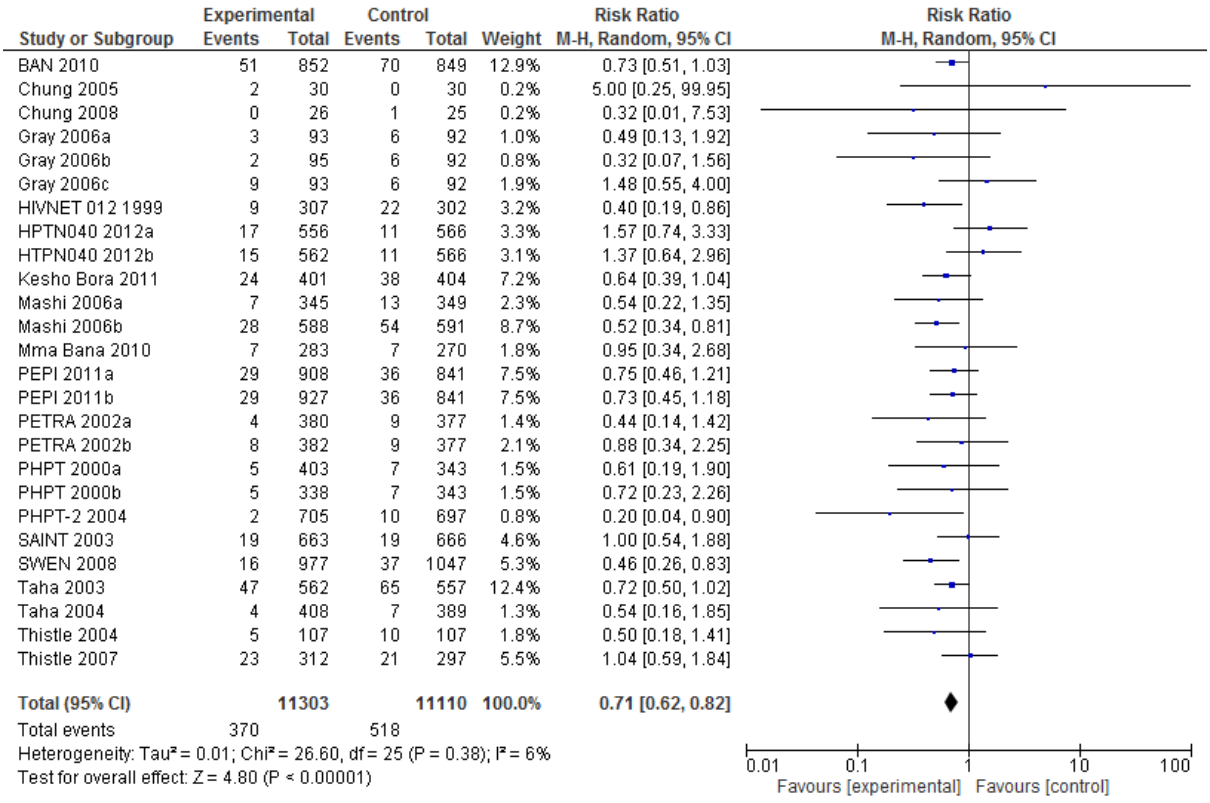

Figure 5.8 Infant Deaths at or before Six Months after Birth

5.6.8 Infant Deaths up to 18 Months After Birth

Eight studies reported on infant deaths up to 18 months after birth. Heterogeneity among the studies was not important (I^2 = 0%). The difference between the experimental and the control group was statistically significant, CI 0.82 [0.71-0.94]. Significantly fewer infants died in the experimental group 8.21% (323/3931) compared to the control group 9.93% (372/3746). (Figure 5.9).

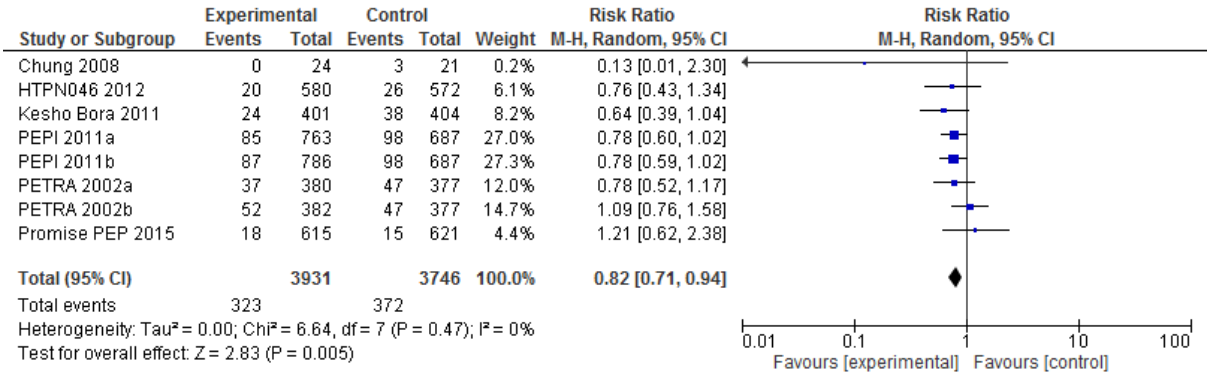

Figure 5:9 Infant Deaths up to 18 Months after Birth

5.6.9 Any Maternal Adverse Events

Ten studies reported on maternal adverse events after randomisation. The most common adverse events were postpartum anaemia, bronchopneumonia and maculopapular rash. Heterogeneity among the studies was not impotant (I^2 = 39%). There was no statistically significant difference between the experimental and the control group, CI 0.89 [0.67-1.18]. Slightly less maternal adverse events were reported in the experimental group 4.99% (175/3506) compared to the control group 5.57% (195/3500). (Figure 5.10).

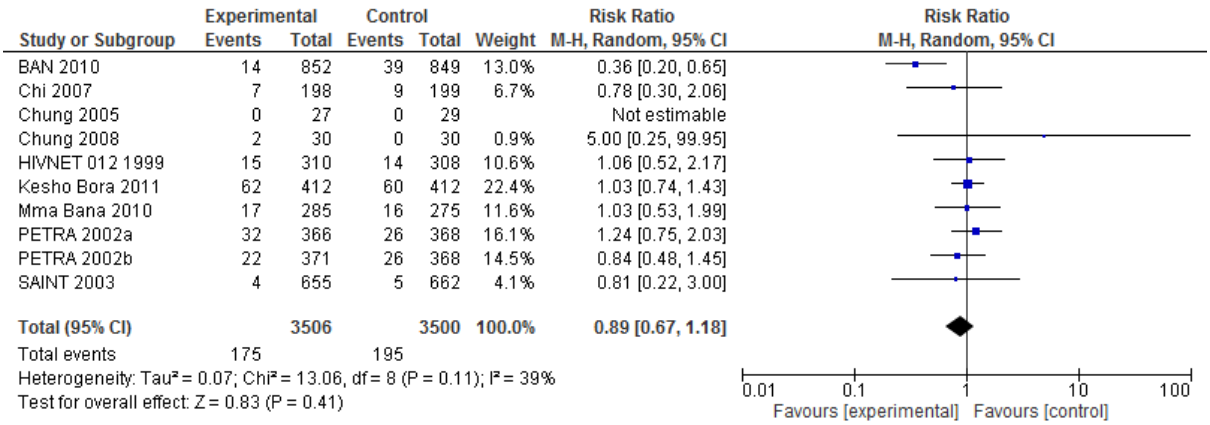

Figure 5.10 Any Maternal Adverse Events

5.6.10 Stillbirths before Labour after Randomisation

Seventeen studies reported on stillbirths before labour after randomisation. Heterogeneity among the studies was not important (I^2 = 0%). The difference between the experimental and the control group was not statistically significant, CI 1.06 [0.71-1.58]. Similar proportion of women had stillbirths before labour but after randomisation with experimental group 0.97% (53/5446) compared to the control group 0.95% (51/5368). (Figure 5.11).

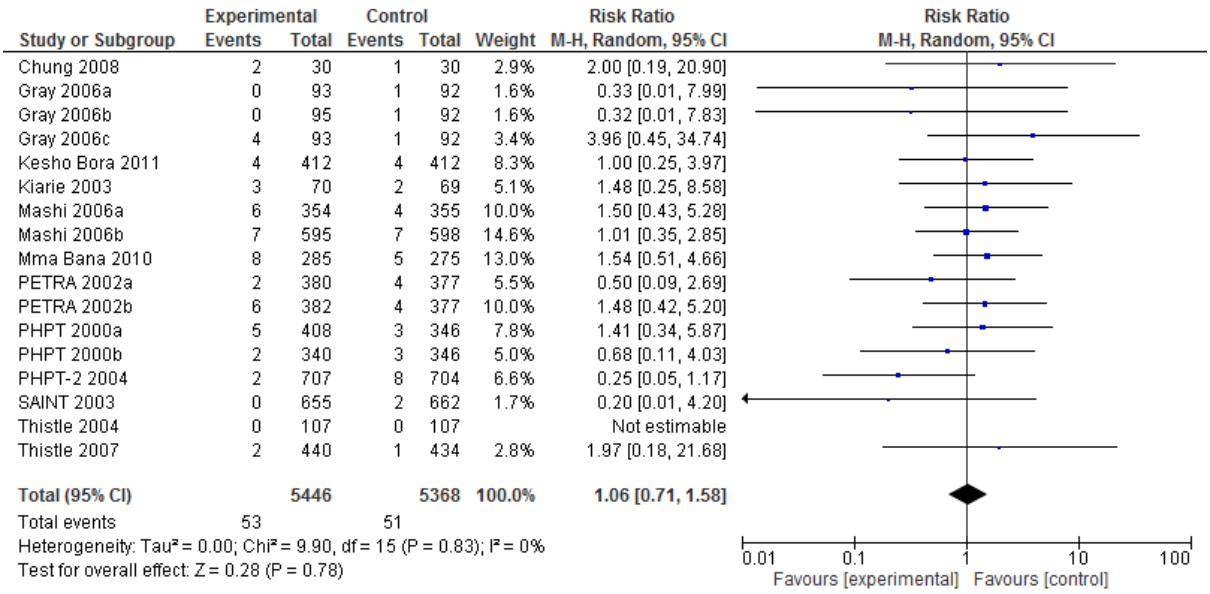

Figure 5.11 Stillbirths before Labour after Randomisation

5.6.11 Infant Adverse Events up to 18 Months after Birth

Twenty three studies reported on infant adverse events up to 18 months after birth. Heterogeneity among the studies was not important (I^2 = 7%). There was no statistically significant difference between the experimental and the control group, CI 1.01 [0.97-1.06]. Some of the adverse events reported were, septicaemia, pneumonia, gastroenteritis, fever and maculopapular rash. The proportion of adverse events reported in infants up to 18 months was similar between the experimental group 25.58% (2967/11596) compared to the control group 25.29% (2909/11500). (Figure 5.12).

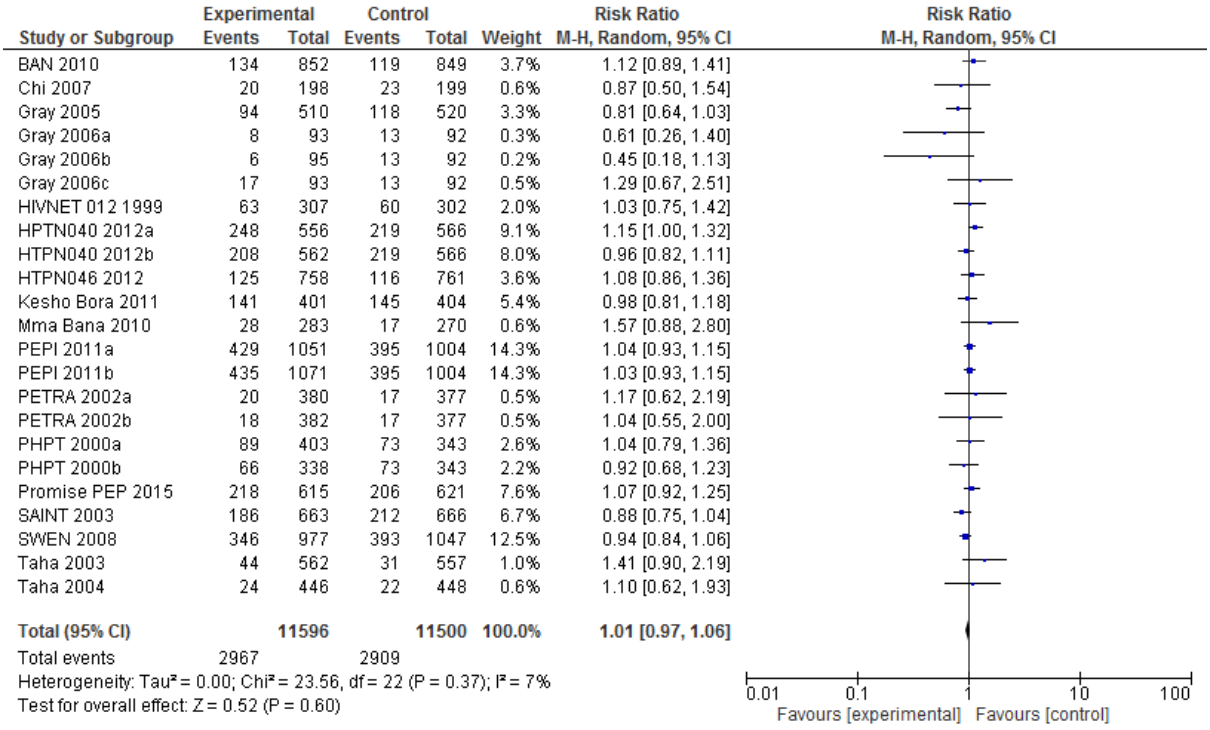

Figure 5.12 Infant Adverse Events up to 18 Months after Birth

5.7 Summary

Chapter five presented the systematic review of 25 randomised controlled trials executed to assess the effects of ART on the prevention of MTCT of HIV. The randomisation for the first trial began in 1997 and the last trial ended in 2012. Twenty-five trials including 18,901 participants with a median trial sample size of 627 ranging from 50 to 1,844

participants were included in this update. Twenty-two trials randomised mothers (18 pre-natally and four in labour) and followed up their infants. Three trials randomised infants. The first trial began in April 1991 and assessed zidovudine (ZDV) versus placebo and since then, the type, dosage and duration of drugs to be compared has been modified in each subsequent trial. The results presented are stratified by regimen and type of feeding. An inclusion criterion was presented and references of included and excluded trails presented. The characteristics of included studies were described followed by the results of the meta-analysis. Chapter six presents the study conclusion and recommendations.

Chapter Six
Conclusion and Recommendations

6.1 Introduction

This research was undertaken to determine whether PMTCT policies were based on evidence. The endeavour was to do a document analysis of the latest South African PMTCT policy and a systematic review of available literature that addresses the effectiveness of ARVs to prevent maternal to child transmission of the HIV.

Chapter six presents the findings from the document analysis and the systematic review. A brief dialogue follows to show that the aim and objectives stated in Chapter one were fulfilled. Furthermore, Chapter six concludes with a few recommendations that maybe used by policy makers.

6.2 Research Findings

6.2.1 Findings from the Literature Review

Chapter two highlighted the history of HIV/AIDS and provided information on the prevalence of HIV/AIDS as well as the development of ARVs. The millennium development goals that were appropriate at the time of the review were mentioned. Intervention strategies implemented to decrease MTCT have also been engaged upon.

The literature review showed that the time of the origin of the HIV cannot be exactly determined and there is no knowledge on accuracy of how many people got infected before the identification of the HIV, but what is known for sure is that the beginning of our understanding of the AIDS epidemic officially began on 5th June 1981 (Katrak, 2006; Glanz, 2013). Over the years millions of people have died due to HIV/AIDS and these include people of note such as Freddy Mercury and Liberace to mentioned a few

(Johnson, 2011; David, 2010). Chapter two emphasised the turbulent past related to acknowledging HIV/AIDS as a communicable disease in South Africa (Pope et al., 2009) and traced the history back to the first known diagnosed case. The literature review demonstrated that huge progress has been made over the years in developing antiretroviral medications to treat infected people. The burden of HIV/AIDS is once again highlighted with the frightening news that nearly 6.19 million people are living with HIV/AIDS in South Africa (Statistics South Africa, 2015a).

6.2.2 Findings from the Primary Research

The overall aim of this study was to conduct a systematic review of the available literature comparing PMTCT antiretroviral regimens published between the years 2000 to 2015 and to do a document analysis of the current implemented PMTCT programme to evaluate if it is based on best evidence.

Research Objective One was to:

Embark on a document policy analysis to evaluate whether the current PMTCT policy guidelines were formulated based on best evidence.

Findings from the document analysis have shown that the PMTCT policy is mainly based on evidence from systematic reviews and randomised control trials. Occasionally some statements are still based on lower categories of evidence such as non-experimental descriptive studies.

Research Objective Two was to:

Systematically review literature that assessed the efficacy of ARV regimens to prevent mother-to-child transmission of the HIV during pregnancy, birth, and the postnatal periods.

Findings from the systematic review showed that significantly less infants tested HIV-positive when exposed to a longer ARV regime although the difference was no longer significant once the infants reached six months of age. Different ARVs have a similar

effect on maternal deaths, but a double or triple combination of ARVs is superior to monotherapy to decrease infant deaths. Common maternal adverse reactions to ARVs include anaemia, bronchopneumonia, and maculopapular rash. Infant adverse events include septicaemia, pneumonia, gastroenteritis, fever and maculopapular rash.

6.3 Conclusions Obtained from the Study

Results showed that the research objectives were addressed. Firstly, *The National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults, April 2015* is based on evidence, but the policy itself does not include any reference to evidence. All the WHO guidelines include references hence the above recommendation (World Health Organization [WHO], 2001; 2006; 2010; 2013).

In the document review it was noted that, the worst challenge in HIV management is adherence. Simoni et al. (2006) stated that issue of non-adherence poses a great threat in managing chronic illness. Chesney (2000) as well as Sax et al. (2012) and Stone et al. (2001) have conducted studies and have found that pill burden is a high indicator to non-adherence. Therefore combining different pills into one can improve adherence and remedy the problem of inconsistency in treatment. In addition, evidence has supported efficacy of tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV) in the following studies; Pozniak et al. (2006), Gallant et al. (2004) and Gallant et al. (2006).

Antiretrovirals have been effective as the MTCT of HIV has significantly decreased. As evidenced by Bertolli et al. (1996) that, before MTCT programmes the risk of infant infection was as high as 5-20%, through pregnancy, 10-40% during birth and 5-20% during the postpartum period. Hence the guideline recommends that pregnant women commence antiretroviral therapy on the day of diagnosis and should stay on treatment for life (NDOH, 2015).

Secondly, the systematic review showed that double and triple ARV therapy is better than monotherapy and the longer the mother and her infant are exposed to the ARV therapy the better the results to prevent MTCT. Siegfried et al. (2011) uphold the stance that triple therapy is more superior among all therapies aimed to prevent the vertical transmission of HIV. In support of triple therapy supremacy in PMTCT, UNAIDS, 2015 reported a 58% worldwide decline since 2000 of new HIV infections amongst children. The more innovative the treatment regimens were the greater the decline in new infections among children was observed.

Results showed that the research objectives were addressed. Adverse events are always posing a challenge and as with any other medication caregivers must be aware of potential adverse reactions. *The National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults, April 2015* is based on evidence, but the policy itself does not include any reference to evidence.

6.4 Recommendations

The document analysis uncovered shortcomings in that the policy statements are not referenced with best evidence available even though the evidence exists. It is therefore recommended that policymakers included scientific evidence to substantiate the statements in the PMTCT policy. The inclusion of reference on best evidence may enhance adherence to implement policies.

6.5 Summary

Chapter Six shows evidence that the two research objectives stated in Chapter one were successfully addressed through the document analysis and systematic review. This project supported the stance of EBP. Recommendations have been computed and the researcher hopes to inform policymakers to include reference to best evidence when new policies are formulated.

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