Effectiveness of PMTCT programs in Sub-Saharan Africa,

a meta-analysis

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Dedicated with love to my parents Adane Kassa and Huluagerish Adamu.

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Abstract

Background According to the 2011 strategic vision for elimination of vertical transmission of HIV, ten high burden countries of Sub Saharan Africa account for two-thirds of all mother to child transmission infections (MTCT). Prevention of mother to child transmission (PMTCT) refers to a comprehensive management approach aimed at the wellbeing of all women of reproductive age, provision of HIV screening for all women, prevention of new infection among infants born to HIV positive mothers and also provision of management for HIV positive women. While there is enough information about the efficacy of PMTCT interventions to reduce perinatal transmission, our current understanding of their effectiveness is lacking. The purpose of this paper is to do a systematic review on the effectiveness of PMTCT services in countries of Sub Saharan Africa. Country reports on progress of PMTCT services were presented.

Objective The general objective of this paper is to systematically review studies on the effectiveness of PMTCT programs by assessing the rate of vertical transmission of HIV in high HIV prevalence countries of Sub Saharan Africa on studies done from 2005 onwards.

Methods PubMed and Scopus search engines were searched with specific selection criteria. All observational studies done on PMTCT in Sub-Saharan African countries which revealed the test result of HIV exposed infants as outcome indicator from 2005 onwards with specification of test time and standard regimens used were included. Fixed and random effects analyses were done to weigh evidence and analyze results of finally selected eight studies. Overall rate of mother to child transmission was calculated for each of these PMTCT regimens. Test of homogeneity was performed. The presence of publication bias was assessed.

Results Eight studies were selected based on the selection criteria and analysis was done. Weighing of evidence was done based on the prophylaxis taken. Fixed effect analysis was used for the first two prophylaxis options. Rate of mother to child transmission for single dose Neverapine group was 9.7% (7.8%-12%) and for Zidovudine plus Neverapine group it was 7.1% (6%-8.4%). Rate for triple antiretroviral drugs was 4.04% (2.7%-6%) using random effects analysis. The studies for the first two prophylaxis options were homogenous and the studies were heterogeneous for the third prophylactic option. There was no publication bias.

Conclusions Countries should be encouraged to report the dried blood spot test result of HIV sero-status outcomes with all the other indices of PMTCT report. The use of triple ARVs should be considered strongly if rate of mother to child transmission is going to be below 5% and virtual elimination is to become a reality.
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## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANC</td>
<td>Antenatal care</td>
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<tr>
<td>ART</td>
<td>Anti-retroviral treatment</td>
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<tr>
<td>AZT</td>
<td>Zidovudine</td>
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<tr>
<td>DBS test</td>
<td>Dried blood spot test</td>
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<tr>
<td>DHS</td>
<td>Demographic health survey</td>
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<tr>
<td>DNA / PCR</td>
<td>Dried blood spot / polymerase chain reaction test</td>
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<tr>
<td>EFV</td>
<td>Efavirinez</td>
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<tr>
<td>eMTCT</td>
<td>Elimination of mother to child transmission of HIV</td>
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<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<tr>
<td>HEI</td>
<td>HIV exposed infant</td>
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<tr>
<td>3TC</td>
<td>Lamivudine</td>
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<tr>
<td>Lpr/Rvr</td>
<td>Lopinavir boosted ritonavir</td>
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<tr>
<td>NVP</td>
<td>Nevarpine</td>
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<tr>
<td>PMTCT</td>
<td>Prevention of mother to child transmission of HIV</td>
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<tr>
<td>PPTCT</td>
<td>Prevention of parent to child transmission of HIV</td>
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<tr>
<td>Sd-NVP</td>
<td>Single dose nevarpine</td>
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<td>TDF</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Table of contents

ABSTRACT ...................................................................................................................... II

ACKNOWLEDGEMENT .................................................................................................. III

LIST OF ABBREVIATIONS ............................................................................................ IV

TABLE OF CONTENTS .................................................................................................. V

LIST OF TABLES AND LIST OF FIGURES ................................................................ VI

1/ INTRODUCTION ......................................................................................................... 1
   1.1/ UNITED NATIONS COMPREHENSIVE APPROACH TO PMTCT ........................................ 2
   1.2/ TIMING OF MOTHER TO CHILD TRANSMISSION OF HIV ............................................... 3
   1.3/ REGIMENS USED FOR PMTCT ...................................................................................... 3
       A/ Single dose nevirapine ............................................................................................... 3
       B/ Zidovudine plus single dose neverapine (AZT +Sd-NVP) ......................................... 4
       C/ Triple antiretroviral prophylaxis/ HAART ............................................................... 5
   1.4/ HIV DIAGNOSIS IN INFANTS AND CHILDREN .......................................................... 5
   1.5/ EFFECTIVENESS OF PMTCT .................................................................................... 6
   1.6/ COUNTRY REPORTS ON PMTCT SERVICE ................................................................ 8

2/ OBJECTIVES ............................................................................................................. 9

3/ METHODOLOGY ....................................................................................................... 9
   3.1/ SEARCH STRATEGY .................................................................................................. 9
   3.2/ SELECTION CRITERIA ............................................................................................ 10
   3.3/ SEARCH QUERY AND RESULTS FROM THE SEARCH .............................................. 11
   3.4/ STATISTICAL ANALYSIS ....................................................................................... 13

4/ RESULTS AND DISCUSSION .................................................................................. 15
   4.1/ EFFECTIVENESS OF PMTCT AT SIX/EIGHT WEEKS .................................................. 17
       A/ Sd-NVP prophylaxis group ...................................................................................... 17
       B/ AZT +NVP prophylaxis group ................................................................................ 18
       C/ Triple ART prophylaxis group ................................................................................ 20
   4.2/ SUMMARY OF FIXED EFFECT ANALYSIS USING FOREST PLOT ................................ 23
   4.3/ TEST OF HOMOGENEITY ........................................................................................ 24
   4.4/ FIXED AND RANDOM EFFECTS MODELS WITH STUDY SUBGROUP AS UNIT OF ANALYSIS ..................................................................................................................... 25
   4.5/ SUMMARY OF FINDINGS USING BOTH FIXED AND RANDOM EFFECTS ANALYSIS ... 26
   4.6/ PUBLICATION BIAS ................................................................................................ 27
   4.7/ FACTORS ANALYZED IN THE STUDIES .................................................................. 28

5/ LIMITATIONS AND STRENGTHS .......................................................................... 30

6/ CONCLUSIONS AND RECOMMENDATIONS ........................................................... 31
List of Tables and list of figures

Tables

TABLE 1/ Weight of evidence for Sd-NVP at six to eight weeks..................................................18
TABLE 2/ Weight of evidence for AZT + NVP prophylaxis studies .............................................. 20
TABLE 3/ Weight of evidence calculation for triple ART prophylaxis studies...............................21
TABLE 4/ Test of homogeneity between prophylaxis option groups.............................................24
TABLE 5/ Fixed and random effects analysis with study groups as unit of analysis ...... 25
TABLE 6/ Associated factors analyzed in the studies......................................................................29
TABLE 7/ PMTCT services provided in Sub Saharan Africa ..........................................................38
TABLE 8/ Studies excluded in this study and reasons for exclusion ............................................39

Figures

FIGURE 1/ Estimation of timing of perinatal HIV transmission rates............................. 3
FIGURE 2/ Summary of PMTCT services in Sub-Saharan Africa ............................................8
FIGURE 3/ Flow chart on selection of studies ...... Fel! Bokmärket är inte definierat.
FIGURE 4/ Number of publications on PMTCT by country......................................................15
FIGURE 5/ Forest plot of vertical transmission of HIV in Sub Saharan Africa at six to
eight weeks .............................................................................................................................23
FIGURE 6/ Forest plot of MTCT in Sub Saharan Africa at six to eight weeks using both
fixed and random effects analysis ......................................................................................26
FIGURE 7/ Scatter plot of standard error with logarithm of event rate ...............................27


1/ Introduction

Globally, HIV/AIDS is now the leading cause of mortality among women of reproductive age and contributes a great deal to the death of infants and children. Even in countries that were showing substantial progress in providing PMTCT interventions, the major challenges that still remain include making sure the interventions are going on smoothly and that they are bringing about the desired outcomes. The effect of the interventions should be demonstrated by a decrease in pediatric infections, HIV-free survival for infants, and improved maternal and child health. (1)

In Sub Saharan Africa, an estimated 2.3 million children were living with HIV /AIDS in 2010, and an estimated 14.8 million children were orphaned due to AIDS. In the same year, an estimated 350,000 children were newly infected with HIV. Over 90% of these infections occur through mother-to-child transmission (MTCT). Without effective intervention, half of the infected children won’t make it to their second birthday. With effective prevention, the risk of MTCT can be reduced to less than 2%-5%. But without intervention, the risk of transmission ranges from 20% to 45%. (1, 2)

PMTCT refers to a comprehensive management approach aimed at the wellbeing of all women of reproductive age, provision of HIV screening for all women, prevention of new infection among infants born to HIV positive mothers and also provision of management for HIV positive women. Prevention of parent to child transmission of HIV (PPTCT) is also being used to mean prevention of the vertical transmission of HIV from father and mother. Change from prevention to elimination of mother to child transmission of HIV (eMTCT) is being introduced with the new target of HIV free generation by 2015. (1, 3)

PMTCT was given due emphasis in the international HIV/AIDS response as evidenced in many international forums. Among these were the Declaration of Commitment on HIV/AIDS adopted at the United Nations General Assembly Special Session on HIV/AIDS in 2001, the Abuja Call to Action Towards an HIV-free and AIDS-free Generation in 2005, the Political Declaration of the United Nations General Assembly High-Level Meeting on AIDS to work towards universal access to HIV prevention, treatment, care and support in 2006, U.S. Global AIDS Coordinator PMTCT expert panel in 2009 and numerous other high-level statements by multilateral organizations.(4)

Achievements in PMTCT progress were significant in many countries. The 2009 Universal Access Report states that in 2005 there were 34 countries that have established a national PMTCT expansion plan that includes population based targets, and the number of countries has increased then to 70 of 123 reporting low- and middle- income countries (4). There also has been strong progress in reducing the HIV incidence among children younger than 15 years in sub- Saharan Africa. The estimated 350, 000 children who were newly infected with HIV in 2010 in sub-Saharan Africa were 30% fewer than the 500, 000 who acquired HIV infection in 2001. Fewer children are dying from AIDS-related causes, from an estimated 320, 000 in 2005 to 230,000 in 2010. (5)
According to the 2011 strategic vision for elimination of vertical transmission of HIV, ten high burden countries of Sub Saharan Africa account for two-thirds of all MTCT infections: Democratic Republic of Congo, Ethiopia, Kenya, Tanzania, Mozambique, Nigeria, India South Africa, Uganda and Zimbabwe. Special focus is given to these countries and efforts are more focus is exerted. Study from these countries will provide the data analyzed in this study.

In 2009, UNAIDS called for the virtual elimination of mother-to-child transmission of HIV by 2015. That is aimed at making the rate of vertical transmission of HIV below 5% by 2015. This can only be achieved with high inter-sectorial collaboration, and enormously focused plan, action and follow up especially in the most severely affected countries. (2)

1.1/ United Nations Comprehensive Approach to PMTCT

The UN strategy for PMTCT covers a wide area of HIV-related intervention needs of pregnant women, their children and families. This intervention approach includes four elements:

1. The primary prevention of HIV infection among women of reproductive age group

Avoiding new HIV infection among women that aspire to have children will halt the transmission of HIV to infants. The prevention of HIV should be targeted at “women at risk” and their partners. As vertical transmission is also a route in which new infections can occur, HIV prevention efforts should also address the needs of pregnant and lactating women of high prevalence areas. (6)


Lack of adequate reproductive services poses a problem in halting MTCT of HIV. “Prevention in positives” involves the use of dual contraceptives and other services of reproductive health service package with health education, health promotion and various family planning methods. Most HIV infected women of reproductive age that reside in developing countries don't know their HIV status. Availing counseling and testing services would give them a chance to have screening, which will aid in making informed decision about their reproductive lives. (6)

3. Provision of specific interventions to reduce vertical transmission of HIV.

There are a package of interventions that WHO has organized for HIV positive women that become pregnant. These are aimed at lowering the risk of transmission and includes provision of appropriate prophylactic drugs, provision of safe obstetric procedures, and provision of support on infant feeding options.(6)

4. Provision of treatment, care and support for HIV-infected mothers, their infants and family.

Continuum of care should be established and HIV positive women, their children and families should be given due emphasis on care and support. Their reproductive health needs should be met and other care of new born should continue. (6)
While the goals mentioned are clearly appropriate in their scope, there is clear disparity between the targets of the outcomes. The measures which we use to assess each prong are different and monitoring of effectiveness of PMTCT programs hence becomes very difficult. There is lack of consensus method to date. (7)

1.2/ Timing of mother to child transmission of HIV

Mother to child transmission can occur during pregnancy, at birth or during infancy and childhood. The main time of transmission is presumed to be at and around birth when there will be separation of placenta from uterine wall rendering contact between maternal and fetal blood possible, and during birth when the fetus passes through the vaginal canal. Kourtis and group in 2001 suggested that half of the transmission occurs at labor. Their estimates are based on a hypothetical cohort of 100 children born from HIV positive mother that did not receive any prophylaxis. (8)

![Figure 1/ Estimation of timing of perinatal HIV transmission rates (Adopted from Kourtis and group, 2001, Ref 8)](image)

Figure one presents estimation of probability of vertical transmission of HIV for different times of gestation and delivery in non-breastfeeding populations. The graph shows the risk of mother to child transmission only until birth, implying that the effect of breast feeding on risk of transmission is not shown.

In addition to the aforementioned route of transmission, the exposed infant is at risk of transmission through breastfeeding. De Cock concluded breastfeeding until the age of 6 months leads to 10% excess transmission, while breastfeeding until 18-24 months leads to 17.5% excess transmission, compared to no breastfeeding. (8)

1.3/ Regimens used for PMTCT

A/ Single dose nevirapine

Single dose neverapine is the simplest to administer of all PMTCT drug regimens, and was tested through the HIVNET 012 trial, which took place in Uganda between 1997 and 1999. The study found that Sd-NVP halved the rate of HIV transmission. (9)
The drug is no longer considered effective enough at preventing vertical transmission and it is currently recommended that countries phase it out. However, it is still in use around the world and in 2010, eleven percent of women who needed ARVs to prevent MTCT received single dose nevirapine. (10)

For infants aged six months, when the regimen is combined with breastfeeding, the rate of transmission is expected to be 16%. If the regimen is combined with replacement feeding, the rate of transmission is expected to go as low as 11%. (6)

The consensus now is that Neverapine should only be used when there is no other alternative available for fear of drug resistance. Hence, the usage of a combination of antiretroviral drugs is expected to decrease transmission and avoid drug resistance. (10)

**Summary of drug administration option**

**Mother** Intra-partum Sd-NVP

**Infant** Sd-NVP (11)

**B/ Zidovudine plus single dose neverapine (AZT +Sd-NVP)**

According to WHO 2006 guidelines, this treatment option should be the regimen of choice in resource poor countries of Sub-Saharan Africa. The administration of zidovudine should start as early as twenty eighth week of gestation and should be continued throughout the duration of pregnancy. Single dose neverapine and higher dose of zidovudine should be administered at the onset of labor. (10)

Zidovudine is the most studied drug of all antiretrovirals and its use for the purposes of PMTCT was first established in 1994. The addition of zidovudine to neverapine makes the treatment more effective and is less likely to lead to drug resistance. (9)

Administration of AZT from twenty eight weeks of gestation, uptake of single dose neverapine at birth and combined short breastfeeding is expected to lower the risk as low as 10%. And if replacement feeding is used with the same drugs; rate of transmission is expected to go as low as 2%. (6)

The treatment currently referred to as “Option A” by the World Health Organization is a modification of this treatment option. “Option A” is the administration of zidovudine from fourteenth week of gestation, the addition of neverapine or zidovudine and lamivudine (3TC) at the onset of labor, and continuation of the drugs added at labor for one week post-partum. (6)

**Summary of drug administration option**

**Mother** AZT starting at 28 weeks of pregnancy or as early as possible.

   Intra-partum: Sd-NVP +AZT( +3TC)

**Infant** Sd-NVP + AZT (7 days) (11)
C/ Triple antiretroviral prophylaxis/ HAART

In 2010, the new treatment option of administering triple antiretrovirals was introduced by World Health Organization. This treatment involved various drug combinations which were aimed at halting the vertical transmission of the virus. It also entailed the continuation of this treatment for six months post-partum, during which the exposed infant will be susceptible for transmission through breast feeding. (11)

Administration of triple antiretrovirals has been the most effective in averting MTCT and has the least resistance reported. This treatment option is preferred by WHO in setups that allow and is the best treatment option. (11)

The treatment currently referred to as “Option B” by the World Health Organization is this prophylaxis option. Current recommendations are that the mother continues the prophylaxis even after cessation of breastfeeding.

**Summary of drug administration option**

**Mother** AZT + 3TC + NVP (or EFV) / TDF+3TC (or FTC) + NVP (or EFV)

**Infant** AZT for 7 days

If the mother receives less than 4 weeks of ART during pregnancy, 4 weeks of infant AZT is required. (11)

1.4/ HIV diagnosis in infants and children

The diagnosis of HIV infection in infants remains a difficulty because the mother passes antibodies to the child which will remain in the fetal circulation for a period of up to eighteen months. The signs and symptoms infected children exhibit are different from adults and at times they may show no manifestations at all. (12)

An important method for diagnosing HIV in children is a polymerase chain reaction (PCR) test, for virus in an HIV exposed infant's blood cells. This test involves the detection of viral antigen from a blood sample collected from HIV exposed infants. (13)

Blood sample is collected from the heel or toe of exposed infants using a pin prick. That sample is collected on a litmus paper and wrapped for transportation to a regional hospital. These regional hospitals do amplification and analysis for the presence of viral antigen in the serum of sample collected. The advantages of DBS test are that the sample can be easily transported in an envelope, it is relatively inexpensive, does not need high expertise, it does not require refrigeration and small amount of blood taken from the infant is enough. (13)

A centralized laboratory analyses the specimens collected from various health facilities in high burden countries and results are established. All fifteen high burden countries now have PCR capability. Even though there is limited data available owing to the young age of usage of PCR testing, the test remains the gold standard for diagnosis of HIV in virus exposed infants and this paper uses the test as a core indicator of vertical transmission. (13)
1.5/ Effectiveness of PMTCT

The UNAIDS has defined impact evaluation as an assessment of “the long-term, cumulative effect of programs or interventions over time on what they ultimately aim to change, such as a change in HIV infection and AIDS-related morbidity and mortality”. Assessing effectiveness of PMTCT programs encompasses this and was defined as “the prophylactic benefit of a PMTCT intervention when implemented in everyday practice”. (14, 15)

PMTCT is implemented in an ideal way in the developed world which led to very low vertical transmission of the virus. In contrast, the developing world has a big burden on each and every step of the four prongs of PMTCT. The transmission being a result of efficacy of the drugs, program coverage, implementation and all the other proxy indices, it makes it very difficult to have a single parameter on which to relay as a sole indicator. Biological factors related to the mother also contribute and higher rates of transmission were found with high plasma viral load, low CD4 and lymphocyte count, vaginal delivery and breast feeding. (16, 17)

Due to scarcity of resources and lower participation of mothers on PMTCT services in the developing world, cost-effective regimens that are easier to administer were being used. The issue of replacement feeding in the African context has been aborted due to similar reasons. For these reasons, the few studies conducted on PMTCT in the developing world made their focus on areas more focusing on efficacy and clinical outcome of the drugs than focusing on performance on the field. (18, 19, 20)

A pregnant mother should at first go to a health care providing center for routine antenatal care, this mother should be offered HIV counseling and testing, she should accept taking the test and finally accept the test result. These are the initial steps and this is followed by issues that the mother should agree to antiretroviral prophylaxis, should access effective regimen, and should adhere to the prophylactic drugs as well. The third step involves that the mother should preferably deliver at a health care providing facility, the exposed infant should take the drugs and necessary vaccinations. The final step involves decision on the issue of breast feeding and avoiding mixed feeding, coming on scheduled date and having regular follow up until cessation of breast feeding. All these events can be used to assess the process of PMTCT services. Coverage indicators stating how many mothers were screened, how many were positive for HIV, how many accessed PMTCT services, how many infants took the drugs all can be used as proxy indicators as well. But to date, there is no standard method that has been set to measure the impact of the service due to the vast area it covers. The absence of a consensus method to measure impact of PMTCT programs makes it difficult to make a comparison and generalize, which would have aided in the development of better structure and drawing lesson from area to area. (7, 15)

Unlike all the indicators stated, the outcome indicators of HIV-exposed infant’s sero-status and virus free survival can measure the ultimate target PMTCT programs are set for. This method has the advantage of assessing care and service delivery to sero-positive pregnant mothers including those that did not access health care providing sites. (7)
The best PMTCT results of PEPFAR in seven years were recorded in 2010, with a record of 8.4 million pregnant women being provided HIV counseling and testing, of whom 600,000 HIV positive pregnant women received antiretroviral prophylaxis to prevent mother-to-child transmission, which led to more than 114,000 children estimated to have been born HIV-free. The 114,000 exposed infants that received prophylaxis take the total sum of exposed infants who received prophylaxis to 454,000 which approximates half a million. This being the main donor organization, many other organizations were also involved in alleviation of the problem. Among many, the PEARL and HOPE studies are studies that included several Sub Saharan African countries aimed at the provision of effective PMTCT service. (21)

The current trend of measuring effectiveness of programs is through other indirect measures including the amount of ARVs dispensed to HIV infected mothers, the number of infants of these mothers who received prophylaxis and other coverage indicators. Aiming at virtual elimination, measures of effectiveness of PMTCT programs should be through the prevalence of infants diagnosed with HIV through DBS. HIV DNA polymerase chain reaction (PCR), using the dried blood spot method, can accurately determine the HIV status of an infant 6 weeks after being exposed to the virus, be it six weeks after delivery or six weeks after cessation of breast feeding, and is a great aid in assessing effectiveness (22).

Currently available reporting systems do not include the test result of HIV exposed infants at the end of follow up. This paper will look at the available evidence from the three PMTCT regimens described above and make conclusion on the progress towards elimination of mother to child transmission of HIV. Studies done in the high- burden Sub Saharan African countries will be taken into consideration.
1.6/ Country reports on PMTCT service

The search for available evidence about the rate of mother to child transmission of HIV started by looking at the PMTCT progress report the high burden Sub Saharan African countries submitted to WHO in 2010. The country reports included every PMTCT service provided in each country. Almost all reports included the number of mothers that were screened for HIV, the number of positive mothers that started follow-up and received prophylaxis, and the number of HIV exposed infants born from these mothers that received prophylaxis. Only four countries reported the number of HIV exposed infants that had DBS test at the age of six weeks.

![Figure 2/ Summary of PMTCT services in Sub-Saharan Africa](image_url)

**Figure 2/ Summary of PMTCT services in Sub-Saharan Africa**

Figure 2 shows the prevalence of antenatal coverage (ANC) coverage based on the last DHS survey carried out in each country (bottom of column), the percentage of pregnant mothers tested for HIV (second column from bottom), the percentage of HIV positive mothers given ARV/NVP (third column from bottom) and the percentage of infants of these moms who were tested for HIV at the age of 2 months (upper column).

The graph is arranged based on antenatal coverage of the last demographic health survey carried out in each country with the lowest rate of ANC coverage on the left, and the highest rate on the right. As can be clearly seen ANC coverage is least in Ethiopia and highest in Zambia. Testing, drug provision and infant testing are by far greater in Botswana and South Africa. The graph is meant as a guide and some of the percentages could not be clearly expressed. For example, for Zambia and Zimbabwe, the upper portion of the graph is not clearly visible which shows the very low rate of testing and provision of prophylaxis. Reference to the appendix is highly recommended to know the exact percentage.

As shown on Figure 2, most of the Sub Saharan countries are not reporting those children who had DNA PCR test and of those reporting them only Zambia reported an estimated positivity rate at that specific time. The current WHO measure of effectiveness focusing upon the outcome of DNA PCR test, this paper will try to systematically review studies done in the region and the outcome of interventions as revealed by HIV status of infants.
2/ Objectives

The general objective of this paper is to systematically review studies on the effectiveness of PMTCT programs by assessing the rate of vertical transmission of HIV in high HIV prevalence countries of Sub Saharan Africa on studies done from 2005 until 2011. The specific objectives are

A/ To determine the overall rate of transmission of HIV at six to eight weeks,

B/ To evaluate the effectiveness of different regimens in reducing the rate of mother to child transmission and

C/ To compare the different factors associated with transmission of HIV.

3/ Methodology

“A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria.” The methods employed in a systematic review can be merely descriptive and discuss the findings of the collection of research studies. Quantitative methods of pooling data may also be used, which is termed as a meta-analysis. (23)

A meta-analysis combines the results of similar studies that use the same outcome and indicator variables. This is normally done calculating a weighted average for a selected common measure of effect size. The weighing may be done based on sample size of individual studies, based on the errors that the authors were willing to commit or using other correction factors. It is obvious that studies cannot be exactly similar and there are differences studies should be allowed for, but the ultimate goal of a meta-analysis is to more powerfully estimate the true effect size as opposed to a less precise effect size calculated in a single study under specific assumptions and conditions. (24)

As this study employs usage of quantitative methods for combination of several studies with similar outcome, it is a meta-analysis. Studies done on mother to child transmission of HIV in Sub Saharan African countries with high burden of HIV as indicated by UNAIDS were included in the meta-analysis.

3.1/ Search strategy

PubMed and Scopus search engines were used. As the number of studies was vast on PubMed, with the assistant of a librarian, Mesh terms and scientific specifications were included to create the outputs included in this study. The Scopus engine was easier to deal with because it needed only a search term and specification of the countries. The search queries from the search engines
and the number of studies found is presented on section 3.3. A review was done on relevant studies done from these countries based on the selection criteria presented on 3.2. References were followed up.

### 3.2/ Selection criteria

After screening all titles and abstracts from the individual search engines, potentially eligible studies were selected; full-text articles were retrieved and all were assessed whether they met the inclusion criteria.

Observational studies are studies in which a researcher simply observes behavior, character or outcome in a systematic manner without influencing or interfering with the behavior, characters or outcomes of the study. All observational studies done on PMTCT in Sub-Saharan African countries which revealed the test result of HIV exposed infants as outcome indicator from 2005 up to 2011 with specification of test time and regimens used were included. Non observational studies, studies that were incomplete, studies that used other methods of measure of effectiveness were excluded. Researches not published (gray literature); researches done in languages other than English were also excluded.

Due to ethical issues, the scarcity of alternative treatment options and the availability of data, most of the studies conducted had a nature of being a review and cross sectional nature than being a cohort study with real control group. The only cohort study included in this paper is the Mitra plus study, which included an arm of treatment group with similar characters as all the other studies included. Hence, this paper was focused on selecting studies fulfilling the aforementioned criteria and did not focus on the presence of true control group or other characters of cohort study.

Assessing quality of studies using standard formats of Cochrane or other quality assessment tools was not possible for the aforementioned reason. Quality of studies was assessed based on the study characters and outputs. All studies included had an appropriate study design and recruitment strategy. Mother infant pairs were reported for five of the eight included studies and the other three had report of infant status in adequate number making generalization possible. Sample size is adequate. All studies had power calculation and justification was included. Appropriate statistical analysis was employed in all. What this study does as random effects analysis considers the quality aspect of each study and redistributes effect size considering the quality each study had. This is by itself is a way of controlling for quality.
3.3/ Search Query and results from the search

The search query and results included from the engines with the results are presented. The shown query produced 1202 results from PubMed and the one search term prevention of mother to child transmission produced the shown query and 1194 from Scopus.

**PUBMED**

Search query


Results 1202

**Scopus**

Search term Prevention of mother to child transmission of HIV

Search query

TITLE-ABS-KEY(mother to child transmission of hiv) AND (LIMIT-TO(AFFILCOUNTRY, "South Africa") OR LIMIT-TO(AFFILCOUNTRY, "Uganda") OR LIMIT-TO(AFFILCOUNTRY, "Kenya") OR LIMIT-TO(AFFILCOUNTRY, "South Africa") OR LIMIT-TO(AFFILCOUNTRY, "Uganda") OR LIMIT-TO(AFFILCOUNTRY, "Kenya") OR LIMIT-TO(AFFILCOUNTRY, "Zambia") OR LIMIT-TO(AFFILCOUNTRY, "Tanzania") OR LIMIT-TO(AFFILCOUNTRY, "Malawi") OR LIMIT-TO(AFFILCOUNTRY, "Zimbabwe") OR LIMIT-TO(AFFILCOUNTRY, "Botswana") OR LIMIT-TO(AFFILCOUNTRY, "Rwanda") OR LIMIT-TO(AFFILCOUNTRY, "Ethiopia")) Results 1194
Figure 3/ Flow chart on selection and inclusion of studies

Abstracts were read from the relevant 1202 abstracts of PubMed and 1194 abstracts of Scopus

Duplicates were removed and a list was made from papers with results on status of HIV exposed infant during follow up

34 studies

Inclusion and exclusion criteria were used to select

21 studies

Results of studies were included based on availability of standard regimen and HEI test result at six/eight weeks

8 studies

The flow chart shows how many studies were recruited first and how it was finally commenced at eight studies. Please refer to Table 9 to look at studies excluded and reasons for exclusion from the 21 studies.
3.4/ Statistical analysis

The analysis involves calculating an average value for the core indicator from the selected studies which is called a weighted average. The weighted average is an average where results of some of the studies make a greater contribution to the total than other studies. As suggested by Cochrane group, all of the methods available for conducting meta-analyses reviews use forms of weighted averages, the differences among the methods being the data presented by studies to be analyzed. Systematic reviews of effectiveness studies mostly use meta-analysis using weighing of evidence as a preferred method. Other meta-analysis soft wares make use of either weighing of evidence or Mantel-Haenszel method based on the evidence presented by the studies to be analyzed. (25)

This study uses weighing of evidence given that the results of the studies were rates of transmission of HIV from mother to child. The analysis first uses fixed effect model analysis which employs weighing based on within study variability. The Der-Simonian and Laird random effects model of analysis was used in assessing random effects analysis which employs within and between study variability. The rates of transmission with their confidence intervals are presented using both methods. (25)

Fixed effects model

The fixed effect model provides a weighted average of the study estimates, the weights being the inverse of the square of standard error of the study estimate. Thus larger studies get larger weights than smaller studies and if the studies within the meta-analysis are dominated by a very large study, it receives essentially all the weight and smaller studies are ignored.

After the rate of transmission in the different studies were tabulated, the values of the rates of transmission and the confidence intervals were converted to natural logarithmic values to make them normally distributed. Then the standard errors were calculated using the confidence intervals. Weighing of the studies was done using precision, which is the inverse of variance (square of standard error). The weighted rates were calculated by multiplying the weight with natural logarithm of rate of transmission. The overall rate of transmission was then calculated from the ratio of sum of weighted rates to the summed weights. Exponentiation of these outputs was reported.

Random effects model

The Der-Simonian and Laird random effects model of analysis was used in assessing random effects analysis which employs within and between study variability. This involves the consideration of precision given by the authors and a correction factor for considering different studies. Hence, using Der-Simonian and Laird random effects model, weighing of studies is done not based on precision alone, but an additional correction factor Tau squared ($T^2$) is introduced. It is an excess variation introduced due to variability of studies. (26)
One common way of assessing $T^2$ is by

$$T^2 = Q - (K - 1) / C$$

where $C = \sum W - \sum W^2/\sum W$ where $W =$ Weight of study, $W^2 =$Square of weight of study, $K =$ number of studies in the treatment option, $Q =$ Chi square result

Hence, the only difference from the fixed effects model we used for the analysis was the addition of $T^2$. (26)

**Fixed effects model analysis**  \hspace{1cm} Weight = $1 / \text{Variance of the effect size}$

**Random effects model analysis**  \hspace{1cm} Weight = $1 / \text{Variance of the effect size} + T^2$

**Test of Homogeneity**

Heterogeneity of finding between studies is assessed using chi-square test statistic of homogeneity. We considered three different types of prophylaxis options and we will assess consistency in the three groupings. We use the commonly used formula of chi –square with slight modification to calculate $Q$. (25)

$$Q = \sum W (E - Ec)^2$$

Where $Q =$ Chi square test, $W =$weight of study, $E =$ effect of study, $Ec =$Cumulative effect

Test of homogeneity was assessed and results presented using each prophylaxis as a category. The overall weight of studies in Sd-NVP group was considered as an output of one category, The overall weight of AZT + Sd-NVP as an output of another category and the output of triple ARVS as output of another category.

**Publication bias**

Validity of a meta-analysis is assessed by using plots of the trials’ effect estimates against sample size, which are also called funnel plots. This is based on the concept that precision increases as sample size increases. This type of graph assumes that studies with small sample size will distribute at the bottom and hence have lower precision, in contrast to large studies which will have higher precision and will be narrowly spread. This gives the graph a pattern of a symmetrically inverted plot. The absence of such a plot with skewedness or asymmetry will show the presence of publication bias. (25)

The presence of selection bias or publication bias can also be assessed by plotting precision of the study on vertical axis (which is the inverse of standard error) and effect size on the horizontal axis. Presence of symmetry around a line drawn on the overall effect estimate or the absence of funnel shaped out put on plotting the results will imply there is publication bias.
4/ Results and discussion

From the total of 1202 publications in PubMed and 1194 publications in Scopus, the number of publications varied from country to country. The number and country of publications from Scopus was as shown on Figure 4.

The number of publications is expected to be higher in the PubMed group as no country specification is introduced because the search engine does not allow that. The Scopus group is found to be of comparative size to the PubMed group because of the broader search term used.

![Figure 3 Number of publications on PMTCT by country](image)

The graph is presented to provide a bird’s eye view of the number of studies conducted by country. The studies included are for twelve years and this goes to show the field is under researched and it is a long way ahead to make conclusion of complete understanding of the problem at grass root level.

Looking at the time when most of the studies were done, the number was highest between 2008 (72 studies) and 2011 (88 studies) peaking around 2010 (98 studies).

The purposes of the current paper being to analyze the prevalence of HIV in infants of mothers who have undergone PMTCT services, observational studies that fulfilled the inclusion criteria were selected. Summary of studies that showed HIV test result of virus exposed infants as their study outcome at the age of six to eight weeks are tabulated in Table one with the specific PMTCT regimen.
<table>
<thead>
<tr>
<th>Country</th>
<th>Authors</th>
<th>Reference</th>
<th>Study type</th>
<th>Study period</th>
<th>Mothers received PMTCT service</th>
<th>Numbers of tested infants</th>
<th>Medications used for PMTCT</th>
<th>MTCT six to eight weeks</th>
<th>Overall transmission at six to eight weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>Mirkuze 2011</td>
<td>27</td>
<td>Prospective cohort</td>
<td>2009</td>
<td>191</td>
<td>115</td>
<td>AZT+NVP</td>
<td>8.2</td>
<td>8.20</td>
</tr>
<tr>
<td></td>
<td>Mirkuze 2010</td>
<td>28</td>
<td>Retrospective analysis</td>
<td>2004-2009</td>
<td>896</td>
<td>896</td>
<td>AZT+NVP</td>
<td>8.4</td>
<td>8.40</td>
</tr>
<tr>
<td>Uganda</td>
<td>Namukwaya 2011</td>
<td>29</td>
<td>Retrospective and descriptive review</td>
<td>2007-09</td>
<td>5849</td>
<td>5849</td>
<td>Sd-NVP, AZT+NVP, HAART</td>
<td>11.2</td>
<td>4.6, 1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>Torpeyi 2010</td>
<td>30</td>
<td>Observational</td>
<td>2007-09</td>
<td>8,237</td>
<td>8,237</td>
<td>Sd-NVP, AZT+NVP, HAART</td>
<td>8.5</td>
<td>6.8, 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.80</td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>Mitram plus 2009</td>
<td>31</td>
<td>Prospective cohort</td>
<td>2004-2006</td>
<td>441</td>
<td>441</td>
<td>HAART</td>
<td>4.1</td>
<td>4.10</td>
</tr>
<tr>
<td>South Africa</td>
<td>Geddes 2008</td>
<td>32</td>
<td>Observational cohort</td>
<td>2004-05</td>
<td>302</td>
<td>239</td>
<td>Sd-NVP, HAART</td>
<td>8.2</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Coetze 2005</td>
<td>33</td>
<td>Cross sectional study</td>
<td>2005</td>
<td>410</td>
<td>410</td>
<td>AZT+NVP</td>
<td>5.1</td>
<td>5.10</td>
</tr>
<tr>
<td></td>
<td>Fitzelgerald 2010</td>
<td>34</td>
<td>Retrospective analysis</td>
<td>2002-2008</td>
<td>367</td>
<td>217</td>
<td>HAART</td>
<td>8.8</td>
<td>8.80</td>
</tr>
</tbody>
</table>
As presented in table 1, eight studies had an age of 45 days or six weeks as their testing time for the exposed infant and those studies were analyzed. The results of transmission using each regimen was be dealt with separately and an average transmission rate calculated.

The results of these studies focused on HIV infection rate among newborns and the rate of transmission of HIV from mother to child given the different study designs and the different setting, intervention and follow-up each set up demonstrated. The similarity being their determination of effectiveness through the final HIV test result of the exposed infants and from those the ones that are infected, table one summarizes the nature of studies conducted.

Given that the recommendations are to test the infant at the age of six weeks and eighteen months, most of the studies reported them as the time when the infant was tested. The numbers beside Sd-NVP imply that both mother and infant received single dose Neverapine and the rate of transmission was as depicted. The same holds true for other combination types of treatment. The overall transmission of HIV from mother to infant implies that was the finding forwarded by the author taking into consideration the specific scenario they studied.

### 4.1/ Effectiveness of PMTCT at six/eight weeks

#### A/ Sd-NVP prophylaxis group

There were three studies that determined the transmission of HIV from mother to child using single dose of neverapine at the onset of labor as the means of prophylaxis for PMTCT. These studies were done in Uganda, Zambia and South Africa.

The study done in Uganda was done by Namukwaya and group, and determined the impact of maternal HAART and short-course combination antiretroviral for PMTCT on early infant infection rates at the Mulago National Referral Hospital in Kampala. Pregnant women identified to be HIV positive were provided Sd-NVP if they presented in labor or short course ARV prophylaxis and Sd-NVP at the onset of labor, or HAART. Infants were given AZT +Sd-NVP for one week. HIV infection rates were determined 6 weeks after delivery. Among the group that received only Sd-NVP, infection rate was found to be 11.2% (8.1%-14.8%). This study was given 48.8% of the weight in the analysis of this category. (29)

The study done by Torpeyi and group estimated mother to child transmission rates in a program setting in Zambia. The study analyzed DNA PCR result data and selected client information from DBS samples from HIV exposed children aged less than one year. The observed HIV transmission with Sd-NVP was 8.5% (5.9%-11%) among infants 6weeks of age. This study was given 45.7% of the weight in the analysis of this category. (30)

The study done in South Africa was an observational cohort study done in McCord hospital. The study followed pregnant women with an HIV sero-reactive status and determined the operational effectiveness of PMTCT programs. In the study 6 week PCR test was taken by 80% of those mothers that have delivered. Transmission was found to be highest in the group that took Neverapine only regimen and it was found to be 8.2% (3.1% - 18.8%). This study was given 5.4% of the weight due to its wide confidence interval. See Table 2 for calculations. (32)
Table 1 Weight of evidence for Sd-NVP at six to eight weeks

<table>
<thead>
<tr>
<th>Authors</th>
<th>Rate of MTCT</th>
<th>Natural logarithm of rate</th>
<th>Standard error</th>
<th>Weight</th>
<th>Weight percentage</th>
<th>Natural log of weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namukwaya 2011</td>
<td>11.2 (8.1,14.8)</td>
<td>2.4159 (2.0918,2.6946)</td>
<td>0.02365</td>
<td>42.283</td>
<td>48.8</td>
<td>102.14</td>
</tr>
<tr>
<td>Torpey 2010</td>
<td>8.5 (5.9,11)</td>
<td>2.14 (1.775,11)</td>
<td>0.02525</td>
<td>39.604</td>
<td>45.7</td>
<td>84.75</td>
</tr>
<tr>
<td>Geddes 2008</td>
<td>8.2 (3.1,18.8)</td>
<td>2.1041 (1.1314,2.9339)</td>
<td>0.21144</td>
<td>4.7295</td>
<td>5.4</td>
<td>9.9513</td>
</tr>
<tr>
<td>SUM</td>
<td></td>
<td></td>
<td></td>
<td>86.6165</td>
<td>100%</td>
<td>196.84</td>
</tr>
</tbody>
</table>

Table 2 shows the calculated values of the three studies presented in the first column. As shown on the table, to determine the rate of transmission, the weight that was given to each study was summed and it equaled 86.615. The multiplication of the weight each study had with the rate of transmission of each study gave the result in the last column. The results in the last column were added and their sum equaled 196.84.

The result of the division of the sum on the last column to the sum of the weights, 196.84/86.6165 will give us 2.2726. This will result in exp (2.2726), which will give the result 9.7%. Hence we can conclude that based on these studies, the rate of MTCT of HIV among users of Sd-NVP is 9.7% (7.84%, 11.96%).

In order to provide comparison, results of studies published before 2005 and did not fulfill the selection criteria are presented.

Between 2002 and 2004, rate of transmission between 8.6% and 13.7% was found by the Good Start Study Group, a cohort study on operational effectiveness of single-dose nevirapine in preventing mother-to-child transmission of HIV in South Africa. (35)

The result of HIV NET 102 study conducted between 2001 and 2003 in Abidjan and between 2003 and 2005 in Soweto, found transmission rate of 13.2% (4.4%, 28.1%) and 11.1% (5.5%, 19.5%) respectively. (10)

Compared to the studies of HIV NET 102 and The Good Start Study Groups outcomes, the results found in the present study have similar rates. The previous studies being randomized controlled trials, the results of this study should have been higher. That was not the case probably due to higher PMTCT program effectiveness that matched efficacy in the following years. The narrow confidence interval suggests that the findings of this paper are more precise.

B/AZT + NVP prophylaxis group

Five studies fulfilled the inclusion criteria and were analyzed in the regimen consisting AZT started at twenty eighth week of gestation (or as soon as possible) accompanied by single dose of nevirapine at the onset of labor. The studies were from Uganda, Zambia, Ethiopia and South Africa.
The study from Uganda was the previously mentioned study done by Namukwaya and group. It determined the impact of maternal HAART and short-course combination antiretroviral for PMTCT on early infant infection rates at the Mulago National Referral Hospital in Kampala. In this review, there were 1793 mothers that took the regimen as recommended in this category and there were a total of 32 infants that were infected upon testing at six weeks. This implies the rate of transmission of HIV in the group was 4.6% (3.2%, 6.4%). This study was given 22% of the weight on the analysis of this category. (29)

The study from Zambia was the study from Zambia included in the prophylaxis option Sd-NVP. The study analyzed DBS results and client information in a program setting that provided ARVs for the purpose of PMTCT. The rate of mother to child transmission of HIV in the group that took AZT+ Sd-NVP and HIV exposed infants were tested at six weeks was 6.8% (4.5%, 9.1%). This study was given 21% of the weight on the analysis of this category. (30)

There were two studies from Ethiopia by the same author but done in two consecutive years. The first study was done in 2010 and it analyzed data collected from ten sub-cities of Addis Ababa in 2009. It looked at the proportion of women that were tested, that were positive and those that received prophylaxis. From mothers that were offered zidovudine and single dose of nevirapine, 8.2% (5.5%-11.97%) of the infants were positive upon testing at the age greater or equal to forty five days. This study was given 18% of the weight on the analysis of this category. (28)

The other study from Ethiopia was published in 2011. This study was a prospective cohort study that included 282 mothers that were followed for the outcome of their birth after providing them zidovudine and single dose of nevirapine. For infants that had DBS test at six weeks, the rate of transmission of HIV was 8.4% (4%-17%). This study was given 5% of the weight in the analysis of this category due to its sample size. (27)

The study from South Africa, done by Coetzee and group, assessed the effectiveness of district wide program of MTCT of HIV in South Africa. It involved a consecutive sample 658 mother-infant pairs. After receiving the regimens in this category effectively, the rate of transmission of HIV was found to be 8.8% (6.2%-10.9%). This study was given 33.37% of the weight in the analysis of this category. (33)
As shown on table 3, to determine the rate of transmission in the studies, the weight each study has were added and the sum of the weights was found to be **144.6** as shown above. The product of the weight each study had with the logarithm of the rate of transmission gives the result of the last column. Those values were added and the result was found to be **283.48**.

The division of **283.48/144.6** will give us 1.96, and **exp (1.96)** will give us the final result, which is the rate of transmission in this treatment group. Hence in studies conducted in high burden countries of Sub Saharan Africa, in group using AZT+ Sd-NVP, the rate of transmission is **7.1% (6.03%, 8.36 %)**.

The Mashi clinical trial conducted in Botswana has shown that the rate of transmission in a group that receives this treatment is 4.6% at four to six weeks of gestational age. The study involved usage of formula feeding. The Mashi study was not included in the present analysis because it was a clinical trial and not an observational study. (36)

The rate of MTCT found in this study is higher because it was an effectiveness study. The precision is higher in this study as it reveals the cumulative effect of five studies done so far.

**C/Triple ART prophylaxis group**

The triple ART regimen was used by studies conducted in South Africa, Tanzania, Uganda and Zambia. The studies included treatment modalities with triple anti-retroviral therapy.

There were two studies conducted in South Africa that are included in this group. One study was mentioned previously and was conducted by Geddes and group. The study was an observational cohort study done in McCord hospital. The study followed pregnant women with an HIV sero-reactive status and determined the operational effectiveness of PMTCT programs. Transmission rate of HIV in women that took triple ARVs was found to be 1.8% (0.3%, 6.8%). This study was given 22.17% of the weight in the analysis of this category. (32)
The other study in South Africa was a retrospective analysis of an observational cohort at a community ART clinic in Cape Town. With most of the women commencing ART at twenty eight weeks of gestational age, the rate of transmission was found to be 5% (2.8%, 9%). This study was given 13.7% of the weight in the analysis of this category. (34)

The Mitra plus study was an open label, nonrandomized, prospective cohort study. It aimed to determine the rate of MTCT of HIV by treating mothers with triple ARVS in Dar es Salaam, Tanzania. AZT+3TC+NVP regimen was used for eligible women and the rate of mother to child transmission at six weeks was found to be 4.1% (2.2%, 6%). This study was given 18.5% of the weight in the analysis of this category. (31)

The study done in Uganda was done by Namukwaya and group, and determined the impact of maternal HAART and short-course combination antiretroviral for PMTCT on early infant infection rates at the Mulago National Referral Hospital in Kampala. The rate of transmission of HIV among mothers that were taking triple ARVS was found to be 1.7% (0.8%, 7.2%). This study was given 19.65% of the weight in the analysis of this category. (29)

The study from Zambia was the previous study from Zambia and the study analyzed DBS results and client information in a program setting that provided ARVs for the purpose of PMTCT. The study observed both the rate of transmission of HIV at six to eight weeks and client information. It found the rate of transmission at six weeks to be 5% (3%, 7%). This study was given 25.96% of the weight in the analysis of this category. (30)

### Table 3/ Weight of evidence calculation for triple ART prophylaxis studies

<table>
<thead>
<tr>
<th>Research</th>
<th>Rate</th>
<th>NL of rate</th>
<th>SE</th>
<th>weight</th>
<th>Weighted percentage</th>
<th>Natural log of weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitra plus 2009</td>
<td>4.1 (2.2,6)</td>
<td>1.410987 (.788457,1.791759)</td>
<td>0.0655</td>
<td>15.27</td>
<td>18.5</td>
<td>21.55</td>
</tr>
<tr>
<td>Torpeyi 2010</td>
<td>5 (3,7)</td>
<td>1.609438 (1.098611,1.94591)</td>
<td>0.04672</td>
<td>21.4</td>
<td>25.96</td>
<td>34.44</td>
</tr>
<tr>
<td>Geddes 2008</td>
<td>1.8 (0.3,6.8)</td>
<td>0.587787 (1.00000,1.91692)</td>
<td>0.234</td>
<td>18.28</td>
<td>22.17</td>
<td>10.75</td>
</tr>
<tr>
<td>Namukwaya 2011</td>
<td>1.7 (0.8,7.2)</td>
<td>0.530628 (1.00000,1.97408)</td>
<td>0.248</td>
<td>16.2</td>
<td>19.65</td>
<td>8.6</td>
</tr>
<tr>
<td>Fitzelgerald 2010</td>
<td>5 (2.8,9)</td>
<td>1.60944 (1.029619,2.19722)</td>
<td>0.298</td>
<td>11.27</td>
<td>13.67</td>
<td>18.13</td>
</tr>
<tr>
<td>SUM</td>
<td></td>
<td></td>
<td>82.45</td>
<td>100%</td>
<td>93.478</td>
<td></td>
</tr>
</tbody>
</table>

As shown on table 4, the sum of the weight each study has gave an overall weight of 82.45. The multiplication of the weight of each individual study with the rate of MTCT gives the value at the last column. The sum of the values at the last column gives a result 93.478.

To find the overall transmission from mother to child we divide 93.478/82.45 which will give us the result 1.134, and exp (1.134) will give us the final result 3.11%, which is the rate of MTCT of HIV at six weeks in the group using triple ARVS. According to the findings of these
papers, MTCT of HIV among those using triple ARVs in high burden countries of Sub Saharan Africa is \(3.11\% (2.51\%, 3.86\%)\).

DREAM study is a cohort study conducted in three sub Saharan African countries involved the provision of HAART for HIV positive women at twenty fifth week of gestation, irrespective of clinical stage, CD4 count or viral load. The study showed a rate of transmission of 1.2\% in breast fed infants at the age of one month. Another DREAM study by Marazzi showed a rate of transmission of 3.8\% (3.1\%, 4.5\%) at six weeks. The study was not included in the present analysis because it included countries not included in the present study (37, 38)

The study done by DREAM study group revealed a similar rate to the findings of this study.

Different triple therapy regimens were used in the five studies. This analysis however assumes that there is no inter study variation and only the error given by the author is included. The departure point being triple ARVs and no specific medication type was employed; it mandated another statistical weighing that considers inter study variability.
4.2/Summary of fixed effect analysis using forest plot

From the eight studies included, three used Sd-NVP as a prophylaxis option, five used AZT+Sd-NVP as a prophylaxis option and five used triple ARVs as a prophylaxis option. The confidence intervals of the studies are better visible using forest plot and are presented in Figure 5.

![Forest plot showing rate of MTCT of HIV in Sub Saharan Africa, fixed effect analysis](image)

**Figure 4/ Forest plot of vertical transmission of HIV in Sub Saharan Africa at six to eight weeks**

The forest plot in Figure 5 shows that the rate of vertical transmission of HIV is similar in most researches done in the region and it approximates efficacy as the time of testing is quite early for breastfeeding to ensue changes. The numbers presented show the rate of transmission as proportions, the way they were presented by the authors.

Grossly looking at the rates, it is evident that the confidence intervals for each regimen type overlap, which means that they are similar. But further analysis is needed using the chi square test to say there is similarity between the confidence intervals depicted.
4.3/ Test of homogeneity

Consistency of findings between studies is assessed using test of homogeneity (also called test of heterogeneity).

First we subtract the log values of event rates and square the result. For example for the Sd-NVP group and the study by Giddes,E was 2.4159 (from table 2). The rate of the overall result (Ec) was 2.2726 (calculation below table 2). We subtract expected from observed and square the result as shown on the formula, and we get a value of 0.020. We multiply it by the weight of the study and we get the result 1.52. We do the same for all the studies in the same prophylaxis option and sum the result. The results of this calculation yield the following results and the interpretations too are tabulated.

The degrees of freedom is calculated by (number of studies minus one).

P values of alpha 0.05 are read from chi-square table.

Table 4/ Test of homogeneity between prophylaxis option groups

<table>
<thead>
<tr>
<th>Prophylaxis option</th>
<th>Chi square value calculated</th>
<th>Degrees of freedom</th>
<th>x²-value using 0.05</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sd NVP</td>
<td>2.35</td>
<td>2</td>
<td>5.991</td>
<td>Q is smaller than p-value, hence we say there is homogeneity</td>
</tr>
<tr>
<td>AZT+Sd-NVP</td>
<td>9.12</td>
<td>4</td>
<td>9.488</td>
<td>Q is smaller than p-value, hence we say there is homogeneity</td>
</tr>
<tr>
<td>Triple ART</td>
<td>19.92</td>
<td>4</td>
<td>9.488</td>
<td>Q is bigger than p-value, hence we say there is heterogeneity</td>
</tr>
</tbody>
</table>

Based on the conclusions from table 5 we say there is homogeneity in the finding of studies included in the first two prophylaxis options but there is heterogeneity in the finding of the triple ART group which makes sense as we took the concept of three ARV drugs and not specific regimen type. It is worth doing the analysis using both methods of fixed and random effects model.
4.4/ Fixed and random effects models with study subgroup as unit of analysis

As described in the methods section, the random effects model of meta-analysis assumes that there is no one number to estimate in the meta-analysis. Rather it assumes there is a distribution of numbers which should be considered when considering effect estimates of a study. The most common random effects model assumes normal distribution of the different true effects and tries to synthesize an overall value that can summarize the values. (25)

Table 5/ Fixed and random effects analysis with study groups as unit of analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of studies</th>
<th>Fixed effect analysis</th>
<th>Random analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sd-NVP</td>
<td>3</td>
<td>9.7 (7.84, 11.96)</td>
<td>9.67(7.64,12.23)</td>
</tr>
<tr>
<td>AZT+ Sd-NVP</td>
<td>5</td>
<td>7.1 (6.03,8.36)</td>
<td>7.37 (5.88,9.22)</td>
</tr>
<tr>
<td>Triple ART</td>
<td>5</td>
<td>3.11 (2.51,3.86)</td>
<td>4.04 (2.69,6.06)</td>
</tr>
</tbody>
</table>

We can see from the results in table 6 that the outputs are very similar and very small differences are observed between the fixed and random effects analysis outputs.

If the studies included in the analysis have similar findings, the result of fixed and random effect analysis will be nearly equal. For example for the Sd-NVP group, the results 9.7(7.84, 11.96) are nearly the same as 9.67(7.64, 12.23). Hence, this is another way of stating the findings of the studies are homogeneous. The same hold true for the studies in the AZT+ Sd-NVP group.

For the triple ARV group, there is difference in both rate of MTCT and confidence intervals. The random effects analysis model should be taken as an output with which we draw conclusion as the studies included are heterogeneous.

The confidence intervals of AZT +Sd-NVP just overlap with Triple ART prophylaxis group which implies their effects are almost similar. The overall rate of MTCT being below five, we highly recommend the use of triple ARVs for PMTCT if elimination of transmission is to be achieved.
4.5/Summary of findings using both fixed and random effects analysis

After both fixed and random effects analysis for the three prophylaxis options and having done test of homogeneity it is apparent that we should use fixed effects analysis for the first two prophylaxis options and random effects analysis for the triple ARV prophylaxis studies.

A forest plot on Figure 6 presents summary of findings.

![Forest plot](image)

**Figure 5/ Forest plot of MTCT in Sub Saharan Africa at six to eight weeks using both fixed and random effects analysis**

It is apparent form the figure that confidence interval for overall effect of Sd-NVP studies overlap with overall effect of AZT+ Sd-NVP studies. The confidence intervals of overall effect for AZT+ Sd-NVP and triple ARVs overlap as well. The overall effects of AZT + Sd-NVP and triple ARV prophylaxis groups are shown to just touch at their tips, implying slight similarity.
The effect of Sd-NVP as a prophylaxis was shown not to be significantly different from that of triple AZT+ Sd-NVP as the confidence intervals overlap, but the prophylaxis entails drug resistance and should be used when it is the only option available.

4.6/ Publication bias

The presence of publication bias was assessed by plotting event rate against standard error. The presence of publication bias would have been apparent by the absence of a specific funnel shaped pattern or symmetry of the scatter plot on both sides of the vertical line on event rate two (which is the rate for the overall cumulative vertical transmission of HIV calculated from the overall effect estimates).

Figure 6/ Scatter plot of standard error with logarithm of event rate

The presence of funnel pattern and absence of symmetry indicate that there was no publication bias. Log event rate is the logarithm of rate of vertical transmission. That is presented on the tables 2, 3 and 4 of calculation of fixed effects analysis.
4.7/ Factors analyzed in the studies

Some of the studies included in the present analysis were powered to detect factors that may have affected their results. Based on the analysis they performed they had factors which they considered were important and made their conclusion based on that analysis and the results. The factors which they analyzed are presented on Table 7, and the positive finding they had and their conclusions are dealt with.

The study by Coetzee was not powered to detect differences in transmission based on risk factors or the regimens received, but a multivariate analysis of the impact of a number of factors on transmission revealed that mothers with age more than twenty five were more likely to transmit infection towards their infants. It concluded by documenting the feasibility of effective PMTCT program in an urban public-sector setting.

The study by Mirkuzhe in 2011 assessed if there was association between medication ingestion and other socio demographic characteristics. In the study medication ingested by mother-infant pairs at birth was significantly and independently associated with place of delivery. There was no association with other maternal factors shown in the table five. Hence, the study recommended that the rate of institutional delivery should be increased, the quality of obstetric services should be improved and that missed opportunities to exposed infant follow up should be minimized. (28)

Namukwaya and group found that the risk of infection increased with reduction in CD4 cell count. Maternal usage of antiretroviral drugs reduced the risk of infection with the rates of specific drugs documented in the order Sd-NVP, AZT+NVP and triple ARV showing protection in an increasing manner. Mothers with post-secondary level of education and male infants were less likely to be infected compared with female infants. Hence the study concluded there are low rates of infant infection for mothers receiving combination ARVs and demonstrated that provision of combination ARV for PMTCT is feasible and effective. (29)

Geddes and group found that attrition has no statistically significant association with maternal variables shown on the table. It concluded that it was possible to provide services at western standards despite shortcomings. (32)

In the Mitra Plus study, there was a significant association between viral load at enrollment and transmission but no significant association between CD4 cell level at enrollment and transmission. Hence the study concluded that the extended maternal prophylaxis with HAART for prevention of mother-to-child transmission of HIV-1 for breastfeeding mothers who do not need HAART for their own health should be further evaluated for implementation. (31)

In the study by Fitzgerald and group, duration of ART before birth was found to be significantly associated with transmission. Advanced maternal disease stage (stage III or IV compared with I or II), gestation at enrolment and first follow-up viral load >50 copies/ml were also significantly associated. The study concluded that interventions that facilitate earlier ART commencement and improve programmatic retention of pregnant women are required. (34)
Collectively, these studies suggest that an effective PMTCT service to the standard of western countries is some settings in Sub Saharan Africa. Early commencement and continuing provision of antiretroviral is essential in other settings of Sub Saharan Africa. The provision of combination ARVs has shown to be effective and feasible in other settings as well. Institutional deliveries should be increased, quality of obstetric services should be improved and missed opportunities to exposed infant follow up should be minimized yet in other settings.

**Table 6/ Associated factors analyzed in the studies**

<table>
<thead>
<tr>
<th>Research name and year</th>
<th>MTCT rate</th>
<th>Confidence interval</th>
<th>Factors adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coetzee 2005</td>
<td>8.8</td>
<td>6.2-10.9</td>
<td>Maternal age, mode of delivery, regimen type</td>
</tr>
<tr>
<td>Mirkuze 2010</td>
<td>8.2</td>
<td>5.55-11.97</td>
<td>No factors adjusted</td>
</tr>
<tr>
<td>Mirkuze 2011</td>
<td>8.4</td>
<td>4-17</td>
<td>Medication ingestion with age, Education, Number of pregnancies, GA at enrollment, CD4 cell count/cubic mm, Disclosure, partner involvement</td>
</tr>
<tr>
<td>Namukwaya 2011</td>
<td>5</td>
<td>4.1-5.9</td>
<td>Age, marital status, employment, education level, CD4 cell count/cubic mm, median CD4, median gestation at first ANC visit</td>
</tr>
<tr>
<td>Mitra plus 2009</td>
<td>4.1</td>
<td>2.2-6</td>
<td>Age, Hemoglobin, CD4%, and WHO stage of mother at enrollment, type of delivery, sex, and birth weight of child, the cohort factor (Mitra Plus/Petra) and CD4 absolute cell counts</td>
</tr>
<tr>
<td>Geddes 2008</td>
<td>2.9</td>
<td>1.3-6.2</td>
<td>Age, marital status, gestation at first visit, CD4 counts and delivery method) and loss to follow-up at 6 weeks</td>
</tr>
<tr>
<td>Fitzgerald 2010</td>
<td>5.1</td>
<td>2.8-9</td>
<td>Duration of ART, WHO stage, viral load at follow up, Age, TB at enrollment, GA at enrollment, CD4 at baseline, weeks on ART, mode of delivery, breast feeding,</td>
</tr>
<tr>
<td>Torpeyi 2010</td>
<td>6.5</td>
<td>5.1-7.8</td>
<td>province, infant feeding, mode of delivery and where delivery took place</td>
</tr>
</tbody>
</table>
5/ Limitations and strengths

This study did not consider the timing of start of prophylaxis, the specific types of triple ARVs taken, and the specific effect of breastfeeding on transmission due to the primary selection criteria used. Consideration of viral load, W.H.O. stage of mother on start of prophylaxis, and CD4 count were not considered and that may make conclusion difficult. To make conclusion about the effect of MTCT based on clinical characteristics, Meta regression need to be done and that was not possible to do provided the nature of studies included and data that were available for this meta-analysis.

The study used two search engines and that may have contributed to the number of studies included. The selection criteria did not allow the inclusion of gray literature as does most Meta analyses, which may have contributed to the same problem. English language was used as criteria with the assumption that it is the working language in most of the countries included but that may have been a window too.

The present study analyzed the different prophylaxis options and determined rates for each in collective terms. This has not been done before for observational studies which make it better and different. The confidence intervals presented were narrow enough to show the difference between usage of triple ARVs and AZT +Sd-NVP with the implication it brings. This too is another strength that was not apparent in other study conducted on the region.
6/ Conclusions and recommendations

Only four countries reported the number of infants tested using DBS and of these only two reported the number of HIV positives from those tested in 2010. DBS test being an ideal way to determine the rate of vertical transmission, it assists not only in monitoring effectiveness but also in enrolling those that need treatment. In 2009, PMTCT evaluative meeting by W.H.O. and other concerned bodies advocated for the inclusion of DNA PCR test of infants on DHS survey for countries with high burden of the disease. Countries should be encouraged to report DBS result as most high burden countries already provide the service.

Studies have shown that effective PMTCT service is feasible in an African setting. They have outlined the importance of site specific recommendations based on the findings of their studies. The selected observational studies showed vertical transmission of HIV varies depending on the type of prophylaxis used and was

i/ 9.7 % (7.84%,11.96%) using fixed effect analysis for Sd-NVP studies

ii/ 7.1%(6.03%,8.36%) using fixed effect analysis for AZT + Sd-NVP studies and

iii/ 4.04% (2.69%,6.06%) using the random effects analysis for triple ARV studies.

A meta-analysis of randomized controlled trials that assessed the efficacy of anti-retroviral drugs in Africa found that the combined effect estimate of using ARVs is 10.6% (95% CI: 8.6–13.1) vertical transmission at 4–6 weeks. The regimens in this study included Sd-NVP, AZT only prophylaxis, 3TC only prophylaxis and many other prophylaxis provisions. The overall rate of transmission in this study was similar to the Sd-NVP prophylaxis group of the present study. The analysis was not disaggregated by regimen while the present study did subgroup analysis. It is difficult to make comparison with the other prophylaxis options because sub group analysis was not done. (39)

The current WHO guideline states that the use of AZT+ Sd-NVP has the same effectiveness compared to using triple ARVS. This was based on the Kesho Bora study group found that the cumulative rate of HIV transmission at 6 weeks was 3.3% (95% CI 1.9-5.6%) in the triple antiretroviral group compared with 5.0% (3.3-7.7%) in the zidovudine and single-dose nevirapine group in a randomized controlled trial done between 2005 and 2008 and included 805 HIV exposed infants. The findings in this study were similar to the findings of our analysis in that the rate of transmission was below five for the triple ARV group and five for the two drug group. The difference though is the rate using AZT +Sd-NVP was above five with its confidence intervals in our analysis. This implies the use of AZT+ Sd-NVP will not make elimination of MTCT a reality. Hence we recommend use of triple ARVs for elimination of MTCT. (40)
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http://blogs.state.gov/index.php/site/entry/world_aids_day_2010


http://www.effectivehealthcare.ahrq.gov/index.cfm/glossary-of-terms/?pageaction=showterm&termid=70


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Appendix

Table 7/ PMTCT services provided in Sub Saharan Africa (refer to figure 2)

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference number</th>
<th>ANC coverage</th>
<th>Tested</th>
<th>Positive Range</th>
<th>ARV/NVP mom</th>
<th>ARV/NVP baby</th>
<th>HIV test by 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRC</td>
<td>41, 42</td>
<td>74.7% (2005)</td>
<td>253297</td>
<td>9%</td>
<td>20000-54000</td>
<td>2232</td>
<td>6%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>41, 43</td>
<td>12.2% (2005)</td>
<td>488554</td>
<td>16%</td>
<td>17000-51000</td>
<td>6721</td>
<td>13-40%</td>
</tr>
<tr>
<td>Uganda</td>
<td>41, 44</td>
<td>47.2% (2006)</td>
<td>968157</td>
<td>64%</td>
<td>48000-130000</td>
<td>46948</td>
<td>53%</td>
</tr>
<tr>
<td>Cot d Ivor</td>
<td>41, 45</td>
<td>45.3% EIS</td>
<td>342698</td>
<td>47%</td>
<td>10000-31000</td>
<td>11064</td>
<td>---</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>41, 46</td>
<td>71% (05/06)</td>
<td>175223</td>
<td>46%</td>
<td>28000-69000</td>
<td>28208</td>
<td>56%</td>
</tr>
<tr>
<td>Malawi</td>
<td>41, 47</td>
<td>57.1% (2004)</td>
<td>316000</td>
<td>52%</td>
<td>31000-83000</td>
<td>33156</td>
<td>58%</td>
</tr>
<tr>
<td>Zambia</td>
<td>41, 48</td>
<td>N/A</td>
<td>532484</td>
<td>&gt;95</td>
<td>37000-94000</td>
<td>47175</td>
<td>69%</td>
</tr>
<tr>
<td>Mozambique</td>
<td>41, 49</td>
<td>53.1% (2003)</td>
<td>672020</td>
<td>77%</td>
<td>53000-130000</td>
<td>68248</td>
<td>70%</td>
</tr>
<tr>
<td>Tanzania</td>
<td>41, 50</td>
<td>N/A</td>
<td>1194172</td>
<td>66%</td>
<td>45000-120000</td>
<td>58833</td>
<td>70%</td>
</tr>
<tr>
<td>Kenya</td>
<td>41, 51</td>
<td>47.1% (2009)</td>
<td>961990</td>
<td>63%</td>
<td>81000</td>
<td>58591</td>
<td>73%</td>
</tr>
<tr>
<td>South Africa</td>
<td>41, 52</td>
<td>56% (2003)</td>
<td>1099712</td>
<td>&gt;95</td>
<td>120000-290000</td>
<td>188200</td>
<td>88%</td>
</tr>
<tr>
<td>Botswana</td>
<td>41, 53</td>
<td>73.3% BFHS7</td>
<td>44386</td>
<td>93%</td>
<td>6900-17000</td>
<td>12406</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Country</td>
<td>Reference number</td>
<td>Author and year of publication</td>
<td>Title</td>
<td>Reason for exclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>54</td>
<td>L. Ahoua 2009</td>
<td>Evaluation of a 5-year program to prevent mother-to-child transmission of HIV infection in Northern Uganda</td>
<td>Determination of serostatus of exposed infants was done at eighteen months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>55</td>
<td>L. Ciaranello 2011</td>
<td>WHO 2010 Guidelines for Prevention of mother-to-child HIV transmission in Zimbabwe: Modeling clinical outcomes in infants and mothers</td>
<td>Determination of serostatus of exposed infants was done at eighteen months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>S. Dube 2008</td>
<td>Estimating vertically acquired HIV infections and the impact of the prevention of mother-to-child transmission program in Zimbabwe</td>
<td>Specifies both regimen and test result at six to eight weeks, but a decision analysis model and not an observational study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>57</td>
<td>M. Braun 2011</td>
<td>Inadequate coordination of maternal and infant HIV services detrimentally affects early infant diagnosis outcomes in Lilongwe, Malawi</td>
<td>Rate of MTCT not determined with specific regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>Van Lettow 2011</td>
<td>Uptake and outcomes of a prevention-of mother-to-child transmission (PMTCT) program in Zomba district, Malawi</td>
<td>HEI test time was not determined, cumulative rate of survival and transmission determined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>59</td>
<td>C J. Chibwesha 2011</td>
<td>Optimal Time on HAART for prevention of mother-to-child transmission of HIV</td>
<td>HEI test time was between three and twelve weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>60</td>
<td>Nuwagaba-Biribonwoha 2010</td>
<td>Introducing a multi-site program for early diagnosis of HIV infection among HIV-exposed infants in Tanzania</td>
<td>HEI test time was four months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>61</td>
<td>W M Nyandiko 2010</td>
<td>Outcomes of HIV-Exposed Children in Western Kenya: Efficacy of Prevention of Mother to child Transmission in a resource-constrained setting</td>
<td>Determined combined end point of infant HIV status and mortality at three and eighteen months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>S Khamadi 2008</td>
<td>Rapid identification of infants for antiretroviral therapy in a resource poor setting: The Kenya experience</td>
<td>HEI test time and regimen type were not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>63</td>
<td>W.M. Bancheno 2010</td>
<td>Outcomes and challenges of scaling up comprehensive PMTCT services in rural Swaziland, Southern Africa</td>
<td>HEI were tested between six weeks and eighteen months of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Year</td>
<td>Author</td>
<td>Study Details</td>
<td>Result/Note</td>
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<td></td>
<td></td>
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<tr>
<td>---------</td>
<td>------</td>
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<td>-------------------------------------------------------------------------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botswana</td>
<td>2008</td>
<td>Creek</td>
<td>Early diagnosis of human immunodeficiency virus in infants using polymerase chain reaction on dried blood spots in Botswana’s national program for prevention of mother-to-child transmission</td>
<td>Rate of transmission for the specific regimens is not determined, pilot study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>2011</td>
<td>A Joseph Afe</td>
<td>Outcome of PMTCT services and factors affecting vertical transmission of HIV infection in Lagos, Nigeria</td>
<td>Transmission was not determined with specific medication type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>Paul Imade</td>
<td>Effect of prevention of the mother to child transmission program on the prevalence of postnatal HIV infection in Benin City, Nigeria</td>
<td>Drugs taken for PMTCT were not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>