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Economic Evaluation of Prevention of Mother – To – Child – Transmission of HIV/AIDS interventions in developing countries: A Systematic Review.

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Economic Evaluation of Prevention of Mother – To – Child – Transmission of HIV/AIDS interventions in developing countries: A Systematic Review.

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SUMMARY

Though local governments worldwide and international organizations have placed a high priority in the Prevention of Mother – To – Child – Transmission (pMTCT) of HIV, the situation in developing countries is still deplorable. In developing countries, there is a significant gap between the global and local policy commitments to reduce Mother – To – Child – Transmission (MTCT) of HIV and the access to pMTCT interventions. This can be attributed to the dire economic situation within developing countries. Healthcare interventions therefore need to be strategically prioritized in order to make maximum efficient use of these scarce resources. An effective tool to assist decision makers in identifying which strategies represent value for money is economic evaluation of these interventions. The objective of this study is systematically pool all the existing economic evaluation studies that have been carried out in developing countries on the pMTCT of HIV/AIDS, in order to present the best fit, affordable, yet effective intervention (s). Our review retained 16 articles that met the inclusion criteria. We designed an extraction form which we used to collect relevant data, after which we subjected the articles to a rigorous quality checklist. Our results exposed a number of flaws in methodological quality of the selected studies. We also recorded widespread heterogeneity in the assumptions used to estimate base case cost and effectiveness parameters, in the methodology applied, as well as in the range of valued used in sensitivity analyses. Some interventions involving short course zidovudine or nevirapine therapy were found to be cost effective. Results varied based on the following factors: HIV prevalence, country income classification, available infrastructure, staff costs, and ultimately costs of the interventions, especially drug prices.

Key Words: systematic review, cost-effectiveness, cost-utility, developing countries, HIV /AIDS

RÉSUMÉ

Les gouvernements mondiaux et les organismes internationaux ont placé une haute priorité dans la prévention de la transmission mère-enfant du VIH. Cependant la situation dans les pays en voie de développement est encore déplorable; on y constate un grand écart entre l'engagement international pour réduire cette voie de transmission et l'accès aux interventions. Ceci peut être attribué à la situation économique déplorable dans plusieurs pays en voie de développement. Des interventions prioritaires en santé doivent donc être soigneusement sélectionnées afin de maximiser l'utilisation efficace des ressources limitées. L'évaluation économique est un outil efficace qui peut aider des décideurs à identifier quelles stratégies choisir. L'objectif de cette revue systématique est de recenser toutes les études d'évaluation économique existantes qui ont été effectuées dans les pays en voie de développement sur la prévention de la transmission mère-enfant du VIH. Notre revue a retenu 16 articles qui ont répondu aux critères d'inclusion. Nous avons conçu un formulaire pour l'extraction de données, puis nous avons soumis les articles à un contrôle rigoureux de qualité. Nos résultats ont exposé un certain nombre de défauts dans la qualité des études choisies. Nous avons également noté une forte hétérogénéité dans les estimations des paramètres de coût et d'efficacité de base, dans la méthodologie appliquée, ainsi que dans les écarts utilisés dans les analyses de sensibilité. Quelques interventions comportant la thérapie à la zidovudine ou à la nevirapine à court terme se sont avérées rentables, et ont enregistré des valeurs acceptables de coût-utilité. Les résultats varié sur la base des facteurs suivants : la prévalence du VIH, la classification du pays selon le revenu, les infrastructures disponible, les coûts du personnel, et finalement les coûts des interventions, particulièrement les prix des médicaments.

Mots clés : revue systématique, cout-efficacité, cout-utilité, tiers monde, VIH/SIDA.

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List of Abbreviations

3TC - Lamivudine

AC - April Colosimo

AD - Ako Denis

AIDS - Acquired Immune-Deficiency Syndrome

ANC – Ante Natal Care

ART - Anti-Retroviral Therapy

ARV - Anti=Retrovirals

BMJ – British Medical Journal

CADTH - Canadian Agency for Drugs and Technologies in Health

CBA - Cost Benefit Analysis

CDC - Centre for Disease Control

CEA - Cost Effectiveness Analysis

CHOICE - CHOosing Interventions that are Cost-Effective

CUA - Cost Utility Analysis

DALY - Disability Adjusted Life Years

DG - Dominique Grimard

DMR - Duration of Membrane Rupture

GDP - Gross Domestic Product

GNI - Gross National Income

GNI – Gross National Income

HAART - Highly Active Anti-Retroviral Therapy

HIV - Human Immunodeficiency Virus

HIVNET - HIV Network

JAIDS - Journal for Acquired Immune-Deficiency Syndrome

JAMA - Journal of the American Medical Association

LILACS - Latin American and Caribbean Health Sciences Literature

LMIC – Low and Middle Income Countries

MeSH - Medical Subject Heading

MJ - Mira Johri

MTCT - Mother To Child Transmission

NHS CRD - National Health Services Centre for Reviews and Dissemination

NHS EED - National Health Service Economic Evaluation Database

NVP - Nevirapine

PACTG - Pediatric AIDS Clinical Trials Group

PCR - Polymerase Chain Reaction

PEPFAR - President's Emergency Plan for AIDS Relief

PETRA - Promoting Education Teaching and Research on AIDS

PICO - Patient Intervention Comparison Outcome

pMTCT - Prevention of Mother To Child Transmission

QALY - Quality Adjusted Life Years

RCT - Randomized Controlled Trials

RETRO-CI - Retro Cote D'Ivoire

UNAIDS - Joint United Nations Programme on HIV / AIDS

UNESCAP - United Nations Economic and Social Commission for Asia and the Pacific

UNGASS - United Nations General Assembly Special Session

UNICEF -United nations International Children Emergency Fund

USAIDS – United States Agency for International Development

VCT - Voluntary Counselling and Testing

WHA - World Health Assembly

WHO - World Health Organization

ZDV - Zidovudine

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CHAPTER 1. INTRODUCTION

1.1. Background

After nearly 30 years since the first cases of Acquired Immune Deficiency Syndrome (AIDS) were reported, alarmingly high incidence, prevalence and mortality rates still loom. Eventhough HIV/AIDS is a completely preventable disease, worldwide, over 7,000 people are becoming infected with HIV every day (16% of whom are children), over 33 million people are living with HIV/AIDS (almost 10% of whom are children), and over 7500 people are dying from AIDS daily (UNAIDS 2008). The largest burden of this global epidemic falls in developing countries where UNAIDS reports show that over 90% of infected people live; sub-Saharan Africa being by far the most affected region with over 2/3 of these numbers.

In 2008, globally, around 430,000 new infections of HIV were reported among children less than 15 years of age. Almost all of these infections occur in developing countries with over 90% attributed to Mother-To-Child-Transmission (MTCT) during pregnancy, labor and delivery or during breastfeeding (UNAIDS 2009). It is estimated that without intervention, there is about a 15-45% chance that a baby born to an HIV positive mother will become infected (De Cock et al 2000).

In the United Nations (UN) Millennium Development Goals (MDGs) for 2015, Prevention of Mother-To-Child-Transmission (pMTCT) of HIV directly affects the achievement of three other MDGs (WHO 2007);

- The 4th MDG: Reduce by two thirds the mortality rate among children under five.
- The 5th MDG: Reduce by three quarters the maternal mortality ratio.
- The 6th MDG: Halt and begin to reverse the spread of HIV/AIDS.

Developed nations with MTCT rate of transmission of <2% (WHO 2007) are on track to achieving these goals due to widespread availability and accessibility of pMTCT interventions like effective voluntary counseling and testing, access to anti-retroviral therapy, safe obstetric practices and availability of safe substitutes to breast-milk. However, the reality of the situation in developing countries is extremely deplorable as a significant gap remains between the global policy commitments to reduce MTCT of HIV and the access to pMTCT interventions (Kim et al 2008). In these settings, availability of pMTCT strategies is very limited and very few pregnant women have access to these interventions.

This can be attributed mainly to the fact that in developing countries, resources are very limited, and pMTCT interventions are not widely affordable within these contexts. Another major reason why implementation of effective strategies in developing countries is not occurring at a sufficient scale is because of lack of convincing evidence from economic evaluation of these programs.

Economic evaluations provide a sensible way to identify which of these intervention provides the most efficient and effective use of limited available resources. By comparing the costs and consequences of various pMTCT for HIV/AIDS interventions and identifying efficient strategies and methods of implementation, these types of evaluations assist policy

makers in deciding which interventions represent the best value for money by virtue of their cost and associated effectiveness, thereby helping then properly allocate scarce resources and define healthcare priorities.

1.2. Rationale

Decision makers in developing countries are relying more and more on economic evaluation results, but due to limited local capacity and the high costs of carrying out economic evaluations especially in these resources limited settings, more interest has been generated in pooling data and results of previously published studies into a systematic review (Walker and Fox-Rushby 2000). However, we could identify only two reviews on economic evaluation of pMTCT of HIV/AIDS in developing countries, one in 1998 (Newell et al) and the last one in 2003 (Scotland et al).

The rationale to perform this systematic review of economic evaluations of pMTCT interventions in developing countries arose from the following reason: given that since 2003, more studies of economic evaluation of pMTCT interventions in developing countries have emerged, there is the need to conduct a new review which provides up-to-date existing information. Decision makers can be overwhelmed in keeping abreast with volumes of new literature. Therefore updated systematic reviews can serve as a high quality synthesis of this available information and data, thereby facilitating accessibility to policy and decision makers.

1.3. Objectives

Our aim was to conduct a systematic review of the economic evaluations of interventions to prevent Mother-To-Child Transmission (pMTCT) of HIV in low- and middle-income countries (LMICs). We conducted a comprehensive systematic review to give policy makers in the developing world an indication of which intervention(s) represent value for money

CHAPTER 2. LITERATURE REVIEW

2.1. Presentation of Developing countries.

We defined developing countries according to the 2008 World Bank classification for low and middle income nations. The main criterion used by the World Bank to classify economies is their Gross National Income (GNI) per capita. Based on the 2008 GNI per capita classification, the World Bank categorizes every economy as either low income ($975 or less), lower middle income ($976 - $3,855), upper middle income ($3,856 - $11,905) or high income ($11,906 or more). The low- and middle-income countries are collectively known as "LMICs". Calculation of the GNI per capita is based on a methodology developed by the World Bank whose purpose is to reduce the impact of exchange rate fluctuations in the cross-country comparison of national incomes (World Bank, 2008).

2.2. HIV/AIDS in developing countries.

Since the first cases of Acquired Immune-Deficiency Syndrome (AIDS) were reported in 1981, infection with Human Immunodeficiency Virus (HIV) the virus that causes AIDS, has grown to pandemic proportions, resulting in an estimated 65 million infections and 25 million deaths (UNAIDS 2008). According to the UNAIDS global AIDS epidemic report (2008), during 2007 alone, an estimated 2.7 million people were newly infected with HIV, 33.4 million people were living with HIV/AIDS (2.1 million of whom were children), and 2.8 million persons died from AIDS.

HIV infections are concentrated in the LMICs and particularly in sub-Saharan Africa where 22.4 million (67%) infected people live, the vast majority of whom are unaware of their serostatus (UNAIDS, 2008). In 2007, the Asia-Pacific region as a whole had nearly 6 million (18%) HIV/AIDS infected people, with the South and South-West Asian and South-East Asian sub regions accounting for 4 million of them (UNESCAP, 2007). In Latin America, by the end of 2007, about 2 million (6%) people were living with HIV/AIDS, there were 1.4 million new infections and 63,000 people died of AIDS (UNAIDS/WHO, 2008).

2.3. Background on HIV transmission and AIDS.

AIDS occurs when the HIV infection has severely damaged the immune system, a process that may take years. The Centre for Disease Control and Prevention (CDC, 1999) use a public health reporting definition for AIDS that has changed several times since 1984 as more has become known about the infection. The most recent definition includes "a positive HIV blood test along with a major opportunistic condition or a $CD4^+$ T cell count below 200 per μL of blood or 14% of all lymphocytes" (A normal CD4 count is 800 to 1,200 cells per cubic millimeter of blood). Opportunistic infections that contribute substantially to the overall burden of HIV/AIDS include Tuberculosis, bacterial diseases and Malaria (Lucas, Hounnou et al. 1993; Grant, Sidibe et al. 1998; Rana, Hawken et al. 2000; Eni, Ogbechie et al. 2005).

The ways in which HIV can be transmitted have been clearly identified. Fact sheets from the CDC (2003) and Health Canada (2006) explain that HIV is spread by e.g. transmission of the virus through bodily fluids such as blood or semen. Routes of

transmission include; sexual contact with an infected person; the sharing of needles and/or syringes (primarily for drug injection) with someone who is infected; or less commonly, and now very rarely in countries where blood is screened for HIV antibodies, through transfusions of infected blood or blood-clotting factors. Babies born to HIV-infected females may become infected before or during birth or through breast-feeding after birth.

2.4. Vertical transmission of HIV/AIDS (MTCT).

Vertical transmission of HIV from an HIV positive mother to her child during pregnancy (also termed "In-utero"), during labour or delivery ("intra-partum") or through breastfeeding ("postpartum") is termed Mother – To - Child – Transmission (MTCT) of HIV. In-utero transmission is reported when there is a detection of HIV virus in infant blood within the first 48 hours of birth, while intra-partum is reported when patterns of an HIV negative result are observed during the first week of life, followed by HIV positive tests between days 7 and 90 (Bertolli, St Louis et al. 1996). In most developing country settings, these screening tests are usually not carried out due to difficulties associated with logistics and cost of testing. And this leads to a delay in the detection of paediatric HIV cases.

It is estimated that without intervention, about 15-30% of babies born to HIV positive mothers will be infected during pregnancy or labour, and a further 10-15% through breastfeeding (Kuhn, Abrams et al. 1997; Dabis, Msellati et al. 1999; Ilboudo, Simpore et al. 2009). Eventhough MTCT of HIV is almost entirely preventable where services are available the coverage levels are remarkably low in most resource-limited countries. A UNICEF report (2008) states that at the end of 2007, women accounted for 50% of all

adults living with HIV worldwide (59% in sub-Saharan Africa); an estimated 420,000 children were newly infected with HIV, the vast majority of them through vertical transmission; two million children were living with HIV/AIDS, and almost 300,000 child deaths were attributed to AIDS.

2.4.1. Transmission mechanisms for MTCT.

Few studies have reported that there is a small rate of in-utero transmission early on in pregnancy especially after the first trimester of gestation (Pascual, Bruna et al. 2000), but most perinatal transmission has been shown to occur late in pregnancy or during labour and delivery (Rouzioux, Costagliola et al. 1995; Chouquet, Burgard et al. 1997; Kuhn, Abrams et al. 1997). This can be attributed to events around the time of delivery that tend to increase the infant's exposure to the birth canal and/or the maternal blood (Kuhn, Stein et al. 1994). Obstetrics events that can increase maternal bleeding like episiotomy, perineal laceration, and intrapartum hemorrhage have been shown to increase the rate of vertical transmission in a West African population (Jamieson, Sibailly et al. 2003).

There are several factors associated with maternal-foetal transmission (Bryson 1996; Garcia, Kalish et al. 1999) and knowledge of the relative contribution of each of these factors is critical in the design of prevention strategies. Factors like increase in maternal plasma HIV-1 Ribo-Nucleic Acid (RNA) levels, low maternal CD4 cell count, presence of maternal serum p24 antigen, advanced maternal disease status, infant exposure to maternal blood, prolonged duration of ruptured membranes and breastfeeding have been linked to vertical transmission (Boyer, Dillon et al. 1994; Dickover, Garratty et al. 1996; Mellors, Munoz et al. 1997).

Maternal plasma viral load is known to be inversely related to CD4 count (Ariyoshi, Weber et al. 1992), but a high viral load has been shown to represent a higher risk of maternal-foetal transmission than CD4 cell number and is therefore a more powerful prognostic marker (O'Shea, Newell et al. 1998; Mofenson, Lambert et al. 1999; Shaffer, Chuachoowong et al. 1999). However, a combined measurement of both markers can provide a more accurate prognosis of HIV infection (Mellors, Munoz et al. 1997).

For in-utero transmission, maternal factors like high viral load, low CD4+ T-lymphocyte count and impaired cell- mediated immunity have been found to be potential risk factors (Mock, Shaffer et al. 1999). Low birth weight and prematurity have also been associated with in-utero transmission. For intra-partum transmission, maternal viral load, direct contact with blood or secretions, and immunological factors have been listed as well as several obstetric factors like mode of delivery, duration of labour, duration of membrane rupture (DMR) prior to delivery, invasive obstetric procedures, and other delivery complications (Kuhn, Abrams et al. 1997).

Some earlier studies had revealed that for women who gave birth to twins, the first born was more likely to be infected than the second born, and they attributed this phenomenon to the fact that the second born twin experiences a briefer exposure to the virus in the lower genital tract during delivery (Goedert, Duliege et al. 1991; Kuhn, Stein et al. 1994; Duliege, Amos et al. 1995). In 1996, Biggar et al also reported birth canal exposure as an important route for transmission and recommended a vaginal cleansing intervention (with the use of an antiseptic solution to remove some of the infectious blood

and mucus) as a procedure to reduce risk of infant infection during delivery. However after a much larger and more rigorous prospective study of twin births carried out in Malawi, the same authors (Biggar, Cassol et al. 2003) reported that there was no difference between the risk of transmission in first born twins and that of the second born. This study also had 2 major conclusions; (a) That disinfecting the birth canal with virucidal agents would not prevent most HIV infections and (b) that maternal-foetal micro transfusion (related to placental disruption as a result of more vigorous and more frequent contractions during labour and delivery) rather than birth canal exposure was a more important route for in-utero and intra-partum HIV transmission.

Breast milk of HIV infected mother has been shown to be contaminated with HIV. Nduati et al (1995) reported that in Kenya, low CD4 count especially when it is associated to maternal vitamin A deficiency, might increase the risk of vertical transmission through breast milk. Another study carried out in Malawi showed that an infant born HIV negative but breastfed by a HIV positive mother had a risk of acquiring the virus (Miotti, Taha et al. 1999), with the highest risk associated to the first 6 months of life. The transmission of HIV during breastfeeding has been well documented in several other studies (Newell 1998; De Cock, Fowler et al. 2000; Nduati, John et al. 2000; Newell 2001; Coovadia, Rollins et al. 2007).

These multiple routes of mother-to-child transmission present a challenge to identifying a single effective, yet affordable, public health intervention for use in developing countries (Biggar, Miotti et al. 1996).

2.4.2. Policy context of MTCT in developing countries

In developing countries especially in sub-Saharan Africa and Asia, nearly all children are initially breastfed for at least six months (Nicoll, Newell et al. 2000). In its recommendation in 2001, the World Health Assembly (WHA) endorsed exclusive breast feeding of all infants until 6 months to achieve optimal growth, development and health, after which they should receive safe complementary food while breastfeeding continues up until 24 months.

Breast milk protects infants against several infections and breastfed children are at lower risk of mortality than non-breast fed children (WHO, 2000). The breast milk produced during the first few days of birth contains its highest levels of colustrum inside which we find an ingredient called pancreatic secretory trypsin inhibitor known to have this protective effect. Coovadia et al (2007) recommended exclusive breastfeeding over mixed feeding methods especially during the first few months of life because it ordinarily protects the infants' intestinal mucosa and thereby presents a more effective barrier to HIV.

This protective effect is a topic of much debate when the scenario applies to breastfeeding of HIV-infected infants by HIV-infected mothers. Also, breastfeeding mothers who acquire HIV at the post natal stage have an extremely high risk of transmitting the infection to their infants (Ekpini, Wiktor et al. 1997; Embree, Njenga et al. 2000; Leroy, Karon et al. 2003). Considering the risk of transmission through breastfeeding, and considering that in developing countries exclusive breastfeeding is common, healthcare policy makers, researchers and professionals are faced with the crucial public health concern of reducing this transmission route.

In a study carried out in Kenya, Nagelkerke et al (1995) stated that the risk of HIV transmission outweighs the benefits of breastfeeding in developing countries and they recommended that mothers limit the duration of breastfeeding. In this same line, another study in Ivory Coast (Ekpini, Wiktor et al. 1997) stated that the risk of transmission through breastfeeding does not disappear after the first few weeks of life, but continues throughout the entire breastfeeding period and they recommended weaning infants at about 6 months to solid food. Kuhn et al (1997) also recommended early cessation of breastfeeding in order to lower frequency of transmission.

In a randomized clinical trial carried out in Botswana, Thior et al (2006) reported that alternative feeding methods are expensive and that there is a widespread stigma associated with this practice in developing countries. They also reported that formula feeding had a higher risk of infant morbidity and mortality whereas breastfeeding had a higher risk of neonatal HIV transmission. These rates of infant deaths were associated to lack of accessibility to clean water for formula feed preparation leading to various infant illnesses like diarrhoea and pneumonia.

Therefore in reviewing policies regarding infant feeding by HIV positive mothers in high prevalence areas like developing countries, decision makers need to establish the risk-benefit analysis of breastfeeding, the cost of alternative feeding practice as well as the socio- cultural implications for mothers avoiding to breastfeed. HIV infected women need

to be counselled for the decision whether to breastfeed or not to breastfeed as well about the duration of breastfeeding.

2.5. Prevention of Mother - To - Child – Transmission (PMTCT).

National and international commitment to scale up services and strategies to combat vertical transmission has intensified in low and middle income countries in the past few years. Estimates from the UNAIDS / WHO report (2008) show that in these regions, up to 33% of HIV infected pregnant women received Anti-Retroviral Therapy (ART) in 2007 as compared to only 10% in 2004. However, only 18% of pregnant women consented to and/or received an HIV test in 2007 meaning that very few mothers are aware of their HIV status.

In 2001, the United Nations General Assembly Special Session on HIV/AIDS (UNGASS, 2001) committed to reduce the proportion of infants infected with HIV by 20% in 2005 and by 50% in 2010. The United Nations strategic approach to the prevention of transmission of HIV to infants and young children has four areas;

1. Prevention of HIV infection in general, especially in young women and pregnant women.
2. Prevention of unintended pregnancies among HIV infected women.
3. Prevention of HIV transmission from HIV-infected women to their infants.
4. Provision of care, treatment and support to HIV infected women, and their infants and families.

Much emphasis has been placed on number 3 above with recent approaches targeting the late intrauterine and intra-partum period, which is a relatively short interval of relatively high risk (WHO, 2004).

2.5.1. Approaches to pMTCT.

Several programs aimed at preventing Mother –To-Child-Transmission of HIV have been designed and implemented all over low and middle income nations. They include Voluntary Counseling and Testing (VCT), administration of antiretroviral drugs (ART), modification of obstetric practices and modification of infant feeding options.

2.5.1.1. Voluntary Counseling and Testing.

Antenatal clinics are a key entry point into HIV treatment and care and for several years now, voluntary and confidential counseling and HIV testing have been routinely provided in antenatal clinics in third world cities and rural areas. Programs include group counseling before HIV testing conducted by trained social workers and medical staff, followed by private sessions during which individual women accept or refuse HIV testing; counseling after the test by trained social workers or program doctors; and for women whose test results were positive for HIV, monthly follow up visits with a program midwife (Msellati, Hingst et al. 2001; Painter, Diaby et al. 2004; Kouam, Nsangou et al. 2006).

The benefits of VCT have been well established. Knowledge of HIV- positive status can help assure access to appropriate care, the options for which are expanding in the developing world. And in settings where it is more common to learn one's HIV status, the fear, stigma, and shame that surround AIDS is reduced. The advantages of known HIV

status are especially apparent in pregnancy, where low-cost antiretroviral interventions are increasingly available. Some changes in obstetric practice and especially, a decision not to breastfeed and to use replacement feeds must be based on a mother's knowledge of her positive-HIV status. However in developing countries, there are inevitable dropouts at each step of the voluntary counseling and testing process. Not all women agree to be tested, not all those who are tested return for results, and not all those who learn of an HIV-positive status will take antiretroviral drugs or give birth in health facilities (Kuhn and Stein 1997; Downing, Otten et al. 1998).

2.5.1.2. Anti-Retroviral Therapy (ART).

The first report of the use of anti-retroviral therapy for pMTCT came from a clinical trial in 1994 (PACTG 076), when USA and French researchers demonstrated that a long course oral administration of 100mg of zidovudine (ZDV) five times a day to HIV-infected pregnant women starting at 14-34 weeks gestation, intravenously during labour (2 mg per kilogram of body weight over one hour, then 1 mg/kg/hr during labour until delivery), and orally to their newborns for 6 weeks (2 mg/kg orally every six hours) reduced the risk for perinatal HIV transmission by two thirds after 18 months of life (Connor, Sperling et al. 1994). That same year, this regimen was recommended as standard of care in the United States and most of Western Europe. But because of the regimen's elevated cost, its complexity and practical considerations such as the frequency and length of dosing and intravenous administration intra-partum, it could not be implemented in developing countries (Jamieson, Sibailly et al. 2003), where no other intervention had been efficacious in reducing mother to child transmission.

The first reports of an efficacious intervention in developing countries came in 1996, when the Thailand Ministry of Public Health in collaboration with the CDC, initiated a randomized, placebo-controlled trial of a simpler and less expensive regimen of short course of ZDV to prevent peri-natal HIV transmission in a non breastfeeding HIV+ population (Vuthipongse P 1998). In this study consenting pregnant women were randomly provided with either ZDV (300mg orally twice a day from 36 weeks' gestation until onset of labor and 300mg every 3 hours from onset of labor until delivery) or a placebo. They were all counseled not to breastfeed and provided with infant formula. The HIV status of the infant was monitored at birth, at 2 months and at 6 months of life through Polymerase Chain Reaction (PCR) testing. The results showed a 51% decrease in transmission risk after 6 months of life in the ZDV group. The CDC concluded based on these results that eventhough this regimen was not as successful as the long course regimens (66% reduction in transmission), it was more feasible for implementation in developing countries. Apart from being a shorter regimen, the Thai study was simpler than the PACTG 076 study in that the doses were less frequent, were taken orally rather than intravenously and there were no doses for infants (Shaffer, Chuachoowong et al. 1999).

Concurrently with the Thai study, the CDC was sponsoring a complementary study (RETRO-CI) with an identical regimen, in Cote d'Ivoire but this time in a breastfeeding population. In this study, women were counselled on the risk of vertical transmission of HIV through breastfeeding, and they were informed of alternative feeding methods, but no infant formula was provided. The results showed a 44% decrease in risk of transmission in the ZDV group after 3 months of life, and the authors concluded that a short course of oral ZDV given in late pregnancy (300mg orally twice a day) to breastfeeding HIV-1-infected

women is well tolerated, safe, and lowers risk of HIV-1 transmission to babies in the first few months of life (Wiktor, Ekpini et al. 1999). This study however experienced some difficulties in implementation leading to only 17.5% enrolment of the HIV positive women initially identified. Difficulties associated with low percentage of pregnant women consenting to testing, as well as a low rate of adherence to counselling and treatments were also reported.

Another Randomised placebo-controlled trial carried out by the Ditrame study group in Cote d'Ivoire and Burkina Faso (Dabis, Msellati et al. 1999) recorded results of 38% reduction in early transmission at 6 months despite breastfeeding and stated that short course ZDV was effective, safe and appropriate for developing countries. In this study consenting pregnant women were randomly provided with either ZDV (300mg orally twice a day from 36 weeks' gestation until onset of labor and 300mg every 3 hours from onset of labor until delivery and one week maternal postpartum dose) or a placebo.

In 2003, Leroy et al carried out a clinical trial pooling data from the RETRO-CI and the DITRAME studies to evaluate the long term efficacy of short-course ZDV in a breastfeeding population, and recorded a similar cumulative risk of infant postnatal transmission (about 9%) between the ZDV and the placebo group at age 24 months with an overall ZDV long-term efficacy of 26%.

A randomised, double-blind, placebo-controlled trial named PETRA, carried out under the auspices of the UNAIDS in breastfeeding populations in South Africa, Uganda, and Tanzania between 1996 and 2000 showed ZDV to halve the rate of MTCT-HIV after 6

weeks of life in Africa when used in association with lamivudine (3TC), but further studies as to the tolerability and toxicity in mother-child pairs need to be carried out (Gray 2000; PETRA 2002). This trial was unique among other studies, because of its large sample size, multinational character, diversity of HIV subtypes, and the use of combination therapy. However, the benefits were shown to diminish considerably after 18 months of follow-up. The PETRA study team attributed this to continued breastfeeding with resultant HIV transmission and to the high infant mortality rates in East Africa.

In 1997, another randomised, placebo-controlled, double-blinded study in Uganda (HIVNET 012) assessed the safety and efficacy of another antiretroviral drug, Nevirapine (NVP) which has the advantage of being rapidly absorbed when taken orally, passes quickly through the placenta, and has a longer half-life in pregnant women and babies (Guay, Musoke et al. 1999). In this study, a single dose of 200 mg tablet NVP was given orally to mothers at the onset of labour, and a single oral dose of 2 mg/kg NVP suspension was given to the newborns during the first week of life. The results showed that this regimen significantly lowered the risk of vertical transmission with a reported relative efficacy of 47% at infant age 14-16 weeks.

This NVP regimen has been confirmed as a simple, inexpensive, well-tolerated regimen that has the potential to significantly decrease HIV-1 perinatal transmission in resource limited settings, and has been recommended to be made universally accessible (Jackson, Musoke et al. 2003; Harvey, Figueroa et al. 2004; Kouam, Nsangou et al. 2006). However, the emergence of resistant viruses following NVP use is a concern, occurring in up to 60% of mothers and 50% of infants following a single dose. More work is needed on

the impact of NVP resistance, its effectiveness as well as its safety (Ayouba, Tene et al. 2003; Church, Omer et al. 2008; Flys, McConnell et al. 2008).

See the table 1 below for a summary of the trials on the efficacy of Anti-Retroviral Therapy in developing countries that were analysed in our selected studies. As we read each of the 16 selected articles, we noted the clinical trial from which its input efficacy and/or cost data had been estimated. From the list of all the clinical trials that had been considered in our list of selected studies, we made this table to summarize key information from their procedure and findings. The table 1 below is therefore a summary of the clinical trials that were reported by the 16 selected article.

Study, Location, & Year	Drugs	Antenatal and Intrapartum	Postpartum	Mode of Infant feeding	Efficacy
PACTG 076 trial; USA & France; 1994	ZDV vs. Placebo	Long course (from 14 weeks gestation) + intravenous intrapartum	Long course (6 weeks) infant only	Replacement feeding	66% efficacy at 18 months
CDC-Thai trial; Thailand; 1996	ZDV vs. Placebo	Short course (from 36 weeks intrapartum)	None	Replacement feeding	51% efficacy at 6 months
RETRO-CI trial; Cote d'Ivoire 1996	ZDV vs. Placebo	Short course (from 36 weeks intrapartum)	None	Breastfeeding	44% after 3 months
DITRAME trial; Cote d'Ivoire & Burkina Faso; 1996	ZDV vs. Placebo	Short course (from 36 weeks intrapartum)	Short (one week) maternal only	Breastfeeding	38% after 6 months
Petra trial; South Africa, Uganda & Tanzania; 1996	ZDV + 3TC vs. Placebo	Short course (from 36 weeks and intrapartum)	Short course (one week), maternal and infant	Breastfeeding	63% at 6 weeks and 15% at 18 months.
HIVNET 012 trial; Uganda; 1997	NVP vs. ZDV	No antenatal ARV. Intrapartum (single-dose NVP vs. ZDV)	Single dose (1 week) infant only	Breastfeeding	47% efficacy at 14-16 weeks

Table 1: *Clinical trials used to inform intervention strategies for the economic evaluations included in the review.*

In high income countries where MTCT rates are <2%, the standard of care for PMTCT has been built around the use of triple combination anti-retroviral (ARV) regimens given to HIV-infected women as early as at 12 weeks of pregnancy and during labor (Dorenbaum, Cunningham et al. 2002; Mofenson 2002; van der Merwe, Chersich et al. 2006; WHO 2007). This triple combination therapy together with other evidence-based packages of essential actions such as identifying HIV-infected pregnant women through the

routine offer of early testing, the avoidance of breastfeeding and elective caesarean section has virtually eliminated new HIV infections among children in high income settings.

Meanwhile in low income countries where MTCT rates are 15-30%, the standard of care has been simplified, is generally shorter, less expensive and comparatively less effective; comprising primarily of single dose nevirapine or other short course regimens of one or two drugs administered at the later stages of pregnancy (Mofenson 2003; Wendler, Emanuel et al. 2004; Noel, Mehta et al. 2008). In low income countries, poor implementation of more robust and effective strategies like those that have been successful in high income countries can be attributed to the following factors; lack of resources to sustain a long course regimen beginning early on in pregnancy; missed opportunities to identify pregnant women due to inadequate accessibility to testing; late attendance to antenatal care; poor adherence to treatments available; and widespread breastfeeding (UNICEF/WHO 2003). Also, the majority of interventions in low and middle income countries do not focus on primary prevention of HIV in women of childbearing age, or preventing unintended pregnancies among women living with HIV.

2.5.1.3. Caesarean Section.

Considering that the vast majority of vertical transmission occurs during labour and delivery, caesarean section has been reported as a strategy to reduce the risk of infant infection in a non breastfeeding population (Boyer, Dillon et al. 1994). Read et al (2005) recommended elective caesarean section before labor and before ruptured membranes for the prevention of MTCT of HIV especially among HIV-infected women not taking ARV, or taking only ZDV. Other studies have reported that even when Highly Active Anti-

Retroviral Therapy (HAART) was available, cesarean section delivery is an appropriate clinical management technique especially for persons with detectable viral loads (Mrus et al, 2000, European collaborative study, 2005).

However, it is worth noting that cesarean section deliveries have been reported to be associated with an increased rate of postpartum infant morbidity and maternal complications among HIV infected women compared with vaginal delivery (Read 2000; Fiore, Newell et al. 2004). Studies on the socio-economic inequalities in the access of life saving obstetric care in developing countries have also revealed that in low income countries, large segments of pregnant women have almost no access to cesarean section whereas in middle income countries more than half the population has rates in excess of medical need (Ronsmans, Holtz et al. 2006).

The majority of women in developing countries have very little knowledge of the modes of HIV transmission, poor knowledge of the specific aspects of pMTCT, and a large number are unaware of the association between breast milk and HIV transmission. Even amongst those that have knowledge of the association of breast milk and HIV transmission, affordability of alternative feeding methods is a major constraint due to widespread poverty.

Therefore as developing countries are expressing increased interest and commitment in embarking on rigorous strategies for preventing vertical transmission, there is need to increase the level of knowledge, acceptability and adoption of VCT and other PMTCT strategies among potential beneficiaries. Innovative information and education

techniques need to be developed to provide HIV positive mothers with knowledge and skills that can enable them to make informed choices about infant feeding options and other forms of care.

2.6. Economic Evaluation of PMTCT interventions.

UNAIDS estimated that by the end of 2007 a total of almost 10 billion US$ in global and local AIDS funding was available, with the major international donors being the Global Fund for AIDS, Tuberculosis and Malaria, the World Bank's Global AIDS Programme and the US President's Emergency Plan for AIDS Relief (PEPFAR). One third of all the global AIDS funding has been directed to low and middle income countries and UNAIDS places emphasis on making the money work in order to co-ordinate the most effective and efficient use of resources and financing, and ensuring that these are reaching the people who need it most. This philosophy is reflected in the set of principles for the coordination of national AIDS responses called “the three ones”, adopted in 2004 by UNAIDS in collaboration with the World Bank and the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria, under the slogan “making the money work” (UNAIDS, 2008).

Under the “three ones” are three principles;

1. One agreed HIV/AIDS Action Framework that provides the basis for coordinating the work of all partners.
2. One National AIDS Coordinating Authority, with a broad based multi-sector mandate.
3. One agreed country level Monitoring and Evaluation System.

Under the 3rd principle of a comprehensive monitoring and evaluation systems, cost-effectiveness and /or utility analysis can be categorized.

In resource limited countries were the major burden of HIV is found, there is a paramount need for a low cost, yet effective set of interventions to reduce the impact of the disease. An important tool that can assist decision makers and planners as they struggle to allocate scarce resources among programmes is cost-effectiveness / utility analysis as they provide information on which type or combination of interventions provides the best value from the budget available (UNAIDS technical update, 1998; Scotland, van Teijlingen et al, 2003). Comparing the costs and consequences of various pMTCT for HIV/AIDS interventions can be used to identify efficient strategies and methods of implementation. Due to the magnitude of the pandemic, coupled with the scarcity of resources, highly cost-effective interventions are imperative in developing countries.

CHAPTER 3. METHODOLOGY

3.1. P.I.C.O question.

In order to generate a focussed research question which is relevant to the problem at hand, and which will facilitate or increase precision during searching, we used the P.I.C.O strategy which describes the four elements of a well-formed question. PICO stands for; P (the Patient or Problem being addressed), I (the Intervention being considered), C (the Comparison intervention(s) and O (the Outcomes of interest).

In pregnant women who are diagnosed HIV positive as well as those deemed at risk of being infected, which interventions to prevent vertical transmission of HIV from mother to child is/are the most cost effective?

P- Pregnant women who are diagnosed HIV+ as well as those deemed at risk of being infected.

I- Strategies for prevention of HIV – MTCT (e.g., Voluntary Counselling and Testing, various antiretroviral therapies, safer infant feeding and delivery methods)

C- Different economic evaluations on HIV use different comparison groups. For the purpose of this research, we did not restrict the comparison group as this varies from study to study. 'C' will therefore be implicitly given by each study.

O- We considered Cost-Effectiveness Analysis (CEA), Cost Utility Analysis (CUA) and Cost-Benefits Analysis (CBA) studies. Outcomes were defined by each

study. Typical outcomes evaluated included cost per neonatal HIV infection prevented for CEA and cost per QALY or DALY for CUA.

3.2. Research Domain.

The research design that was applied to this study was a systematic review of the available evidence on the economic evaluations of PMTCT of HIV in developing countries. A systematic review includes a comprehensive, exhaustive search for primary studies on a focused question, selection of studies using clear and reproducible eligibility criteria, critical appraisal of studies for quality, and synthesis of results according to a pre-determined and explicit method(Pai, McCulloch et al. 2004). According to Egger et al (2001), the goal of a systematic review is to primarily summarize available evidence on a specific research question, assessing the quality of the primary studies, as well as assisting in the formulation of new research questions. Glasziou et al (Glasziou P 2001) identify two major advantages of systematic reviews; firstly, combining data of all studies that have attempted to answer the same question considerably improves the ability to study the consistency of available results. Secondly, studying similar outcomes across a wide variety of settings and designs makes it possible to assess the rigor of available evidence, and the transferability of the results.

When applied to the concept of economic evaluation of healthcare programs, systematic reviews focus on summarizing results of studies reporting on costs, cost effectiveness, cost benefits or cost utility of different interventions. Published peer-reviewed economic evaluation studies use disparate analytical and reporting methods (Jefferson, Demicheli et al. 2002). Carande et al (Carande-Kulis, Maciosek et al. 2000) also

stated that because of the inconsistencies in the methods employed across economic studies, their results are not comparable and a systematic review can address this problem of comparability.

Systematic reviews are widely considered the best source of evidence (Egger M 2001), and can be of tremendous importance to decision makers as they provide reliable estimates about the effects of interventions. They adhere closely to a set of scientific methods that explicitly aim to limit systematic error in order to answer a specific question (Petticrew 2006). Systematic reviews can provide robust and comparatively inexpensive evidence of what is known about interventions effectiveness, which may often be more likely to convince decision-makers than evidence from single studies (Shemilt, Mugford et al. 2006).

According to the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare (NHS-CRD 2001), the reasons for undertaking a systematic review of economic evaluation of healthcare include;

i) To inform development of a decision model.
ii) To identify the most relevant economic evaluation to inform a particular question.
iii) To identify the key economic trade-offs implicit in a particular treatment choice.

With the background intention to better inform local national and international health policy, this study employs the systematic review design in order to assemble pertinent economic evidence to provide a holistic picture of the costs and outcomes of pMTCT of HIV/AIDS in developing countries.

3.3. Search Strategy.

For this review, we searched several electronic databases for articles published from 1994 to 2010. The choice of 1994 as the start year was chosen to coincide with the first major breakthrough for pMTCT of HIV when United States and French researchers proved that Zidovudine (ZDV) in pregnancy could reduce vertical transmission (Connor, Sperling et al. 1994; Musoke 2004).

Considering their experience in locating and acquiring information sources and their skills in record management, a Librarian (AC) was involved in the search process. An initial scoping search was done to identify existing reviews on cost effectiveness of pMTCT of HIV in developing countries. Performing a scoping search makes it possible to initially identify a number of relevant studies available on a given topic, highlighting further relevant search terms, and helping to clarify inclusion and exclusion criteria (Brettle 2003) as well as eliminating the possibility that this review does not duplicate one that is currently being written. Then a full search was performed in order to reveal a thorough list of published and unpublished studies. An objective, reproducible and thorough search of a wide range of databases not only identifies as many relevant studies as possible, but also helps to minimise bias.

We searched the following databases; Pubmed, Medline, Embase, Web of Sciences, Google scholar, Cochrane Library, Econ Lit, National Health Service Economic Evaluation Database (NHS EED) and Latin American and Caribbean Health Sciences Literature (LILACS). The Cochrane library contains high quality systematic reviews on

specific medical topics (Cochrane Collaboration, 2008), while Pubmed, Medline, Embase are considered as the key bibliographic databases for general healthcare, and they report primary research articles, as well as secondary review articles. Falagas et al (Falagas, Pitsouni et al. 2008) stated that these are the most popular and most reliable electronic resources for researchers and have become the de facto mode for medical information retrieval. Science citation indexes like Web of Science were also searched with its advantage being that after it identifies a relevant source article, it also checks and identifies additional relevant articles that have cited the source article. This way, new unknown articles can be found, based on older known ones. We also searched the National Health Service Economic Evaluation Database (NHS EED) which is noted for systematically identifying and cataloguing health-related economic analyses (Pignone, Saha et al. 2005). A combination of Medical Subject Heading (MeSH) and free text terms was used to search through these databases with application of the Boolean operator "OR" for each component of the PICO set to explode the search and make it sensitive, followed by combining the separate searches using the operator "AND" to narrow the results. The MeSH terms used for Pubmed can be found on appendix A.

We searched subject specific electronic databases like EconLit which indexes more than 30 years of economics literature from around the world from over 14,000 journals and other material. We also searched regional databases like LILACS which is a regional index that offers bibliographic control of scientific and technical literature on health that have been produced and published in Latin American and Caribbean countries since 1982. Consideration was also given to finding other relevant regional electronic databases, but none was identified as appropriate for this study. We also searched for

available grey literature which by definition is the information and resources that do not categorically fall into what is available via standard traditional or commercial publishing channels (Hart 2001) and include conference abstracts, research reports, book chapters, unpublished data, dissertations, policy documents and personal correspondence. The inclusion of grey literature in systematic reviews can broaden the evidence base (McAuley, Pham et al. 2000) and has further been defended by Hopewell et al (Hopewell, McDonald et al. 2007) when they state that including these resources may help to overcome the effects of publication bias that can arise due to selective availability of data, meanwhile their exclusion may artificially inflate results and conclusions.

Additional articles were identified by manually searching bibliographies, while more were obtained by hand searching key journals like JAIDS and AIDS. Thorough hand searching of relevant journals is a complementary search strategy because not all reports are included in electronic databases, and even when they are, they may lack the relevant search terms in the titles or abstracts that allow them to be easily identified (Dickersin, Scherer et al. 1994) We also sent emails of request for information to the first authors of selected studies, known experts and colleagues with an interest in this topic, but no additional studies (published, unpublished, or ongoing) were identified.

The most recent comprehensive search for each database was April 26th 2010. Relevant studies were then exported to Endnote bibliographic software as this allowed us to keep track of references, and maintain a record of why specific studies were excluded.

3.4. Inclusion and Exclusion Criteria.

Stating the inclusion criteria puts the review question into a practical format. It helps reduce the risk of bias, documents the nature and limits of the review, while determining if the P.I.C.O measures are consistent with the focus of the review (Briggs 2000). Drummond et al (Drummond M 2005) state that when the evidence for outcome originates from a systematic review, it is crucial that the reasons for inclusion and exclusion of studies be properly addressed, so that readers can gauge whether or not a biased subset of available evidence was used. We therefore established predefined criteria for inclusion according to study design, and studies that were retained for this review were;

1. Original research articles published in peer-reviewed scientific journals focussing on full economic evaluations of strategies for pMTCT of HIV/AIDS.

An original research is a primary source of research which is not entirely based on a summary or a synthesis of previous research.

An economic evaluation is defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences (Drummond M 2005).

Full economic evaluations i.e. studies presenting a comparative analysis of costs and outcomes of at least two alternatives. The following designs were acceptable; Cost-Effectiveness, Cost-Utility and Cost-Benefit designs

a) Cost Effectiveness Analysis (CEA): Where the effects of an intervention and its comparator(s) are measured in identical units of outcome with the alternative interventions compared in terms of cost per unit effect (Drummond M 2005).

b) Cost Benefit Analysis (CBA): Where both resource inputs and effects of alternative interventions are expressed in monetary units (Drummond M 2005).

c) Cost Utility Analysis: Where alternative interventions produce different levels of effect in terms of both quantity and quality of life, with the effects expressed in utility measures like length of life and subjective levels of well-being e.g. QALY, DALY (Drummond M 2005)

2. Studies published in the English language.

3. Time period: 1994 – 2010.

4. Studies from low- and middle-income countries (we excluded studies from all high-income countries as defined according to the 2008 World Bank Country Classification).

We excluded studies with the following characteristics:

1. Cost effectiveness and cost-utility studies for HIV/AIDS in general. These were studies that did not focus on economic evaluation of pMTCT strategies alone, and as such, their results and conclusion were presented in terms of costs and outcomes for overall HIV/AIDS prevention interventions.

2. Studies assessing costs and effects for children already infected with HIV. These studies were focusing on infants for whom pMTCT interventions had either been inexistent, or had failed. They reported mainly productivity loses, QALY, or DALY as well as health care expenditure for HIV infected infants and children.

3. Studies that are not original, peer-reviewed research articles.

3.5. Data Extraction.

The search yielded a total of 91 studies selected for review and ready for data extraction according to the procedure described below;

The finalised version of the research protocol for this systematic review that had been approved was made available to all the data extraction team which comprised of three reviewers. Reviewers had relevant training and expertise in Public Health (DG), in Health Administration (DA) and in Health Economics (MJ); all had experience in HIV/AIDS research.

The first step was to perform an initial screening of the titles and abstracts on the basis of the inclusion and exclusion criteria in order to validate their selection as part of this review. This process lessens the likelihood of missing relevant studies and reduces subjectivity in study selection (Pai, McCulloch et al. 2004). It was performed independently by DG and DA. As recommended by Edwards et al (Edwards, Clarke et al. 2002), prior to screening, the criteria for eligibility of studies were fully discussed in order to achieve consistency between reviewers who performed screening in separate locations and remained blinded to the results of each other until their tasks were complete. There was a perfect initial agreement among the two reviewers for inclusion or exclusion on 84 of the 91 articles. Differences were discussed for the remaining 7 until a universal agreement was reached. On the basis of this initial screening, 29 articles were retained for the second screening (review of full text articles). Studies were excluded from the review in accordance with the inclusion and exclusion criteria described above .When the decision

about whether to include a study was not clear from the title and the abstract, we evaluated the full article.

For the full text screening, again all 29 studies were screened independently by two reviewers (DG and DA). There was a unanimous agreement to include 15 of these articles, and to exclude 11 of them. Consensus could not be reached on the eligibility of 3 of the articles, and the disagreement was referred to a senior reviewer (MJ) who further included 1 more and excluded 2 articles. Therefore, after full-text screening, 16 articles that met all inclusion criteria were retained for data extraction and quality assessment (see fig 1 below for Quorum flowchart).

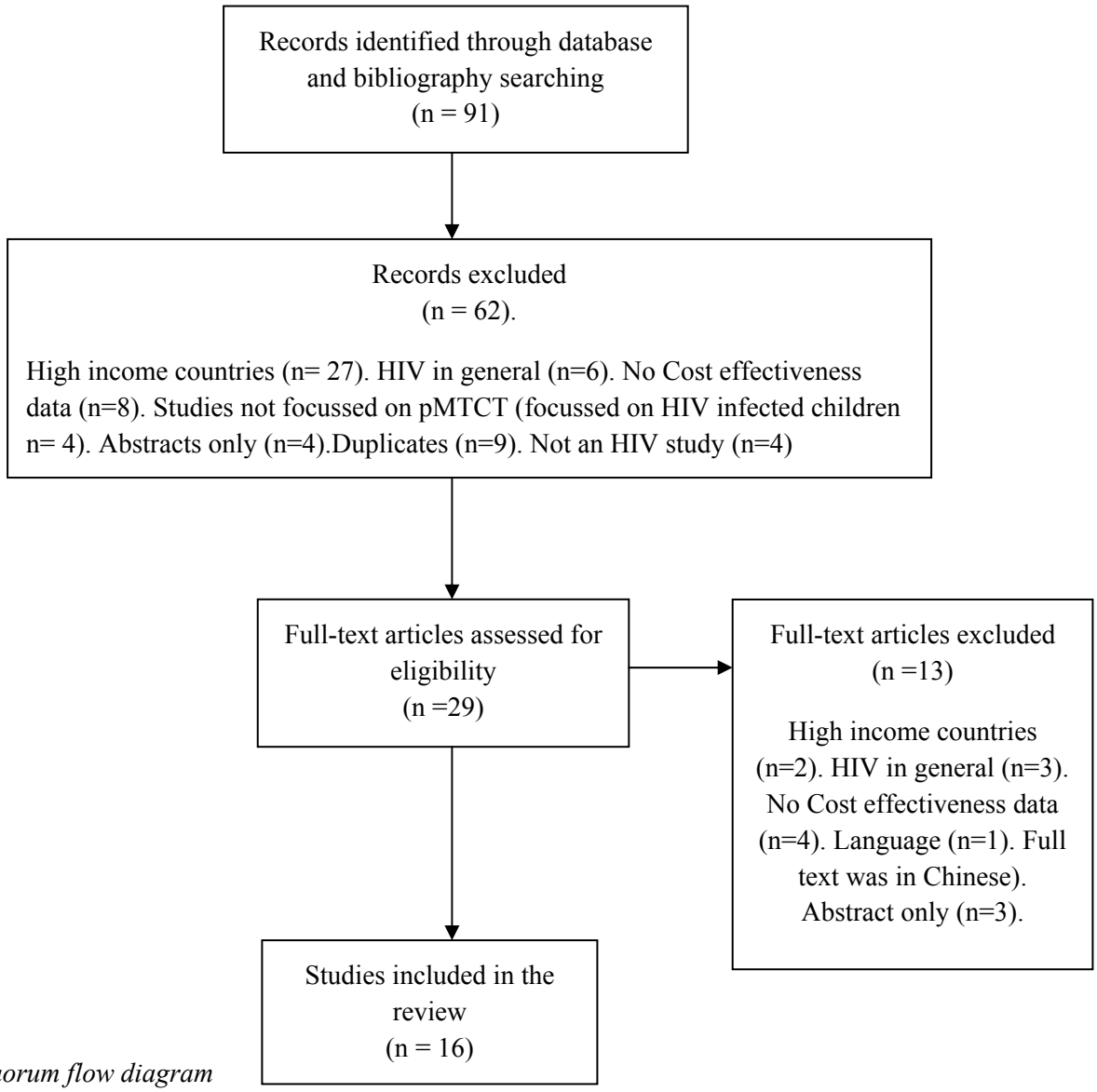

Fig 1: *Quorum flow diagram*

A final standardized version of the data extraction form was designed on excel for retrieving information from each of the 16 studies retained. A data extraction form constitutes the historical record of the decisions and changes that occur during the review process, it is linked to the study question and the inclusion criteria, while constituting relevant elements for data analysis (Meade and Richardson 1997). Pai (Pai 2008) also suggests that the development of a clear, well designed data extraction form, coding

instructions manual and pilot testing is absolutely crucial. A number of data extraction templates were designed and pre-tested before this final version was adopted. To achieve this, we consulted previous published reviews to identify relevant fields. Studies consulted were a review on cost effectiveness of pMTCT strategies of HIV/AIDS in developing countries (Newell, Dabis et al. 1998; Scotland, van Teijlingen et al. 2003) , reviews on cost effectiveness of HIV/AIDS in Africa (Creese, Floyd et al. 2002; Hogan, Baltussen et al. 2005) , and a review on cost-utility of HIV/AIDS (Hornberger, Holodniy et al. 2007) as well as those used in several other cost effectiveness reviews of other healthcare interventions (Whitten, Mair et al. 2002; Elizabeth, Christina et al. 2005; Herman, Craig et al. 2005; Ekwueme, Stroud et al. 2007). Considering the focus of our review, we adapted some of the items retrieved from these previous studies, and formulated new appropriate items with the final data extraction form aimed at reflecting our research question and study objectives.

For the sake of convenience, environmental considerations and due to the fact that data extraction and data entry can be combined into a single step, an electronic data abstraction form was preferred over a paper form. Data extraction was also performed independently by two reviewers (DA and MJ). Each reviewer independently extracted data from all 16 studies and the pair met to reconcile their separate extraction sheets for each study, and hence created the final version of the consensus data for all the relevant items.

Data was documented keeping in mind some key categories that were considered appropriate to be reported. For each study, after presenting items like the author(s) and the year of publication, we collected and reported the following category of data;

- Data on socio-economic and demographics of the study population and the country or region where the study was conducted. For studies that were carried out in specific countries, we reported their Gross National Income (GNI) and HIV prevalence rates, but for those studies that carried a regional approach, like sub-Sahara African studies, it was not possible to report these item. Most of the data here were not available in the studies, so they were collected through other external sources. Data on GNI and the World Bank country classifications for the nations in which the studies were performed, were obtained from the World Bank's 2008 data; and Data on HIV prevalence was obtained from the Epidemiological factsheets of UNAIDS. We believed that these characteristics could have an impact on cost-effectiveness, so we found it appropriate to include them.

- Then we reported data on the details of the types of interventions compared. Here we reported details of the contents of each pMTCT strategy, the recipients (mother and/or child), the dosage, the timing and the duration.

- Data on the epidemiological, clinical and efficacy parameters used in each study. Here we reported key input parameters that the authors analyzed and the base case values recorded. These were reported in most cases as percentages, but some reported numerical values as well.

- We presented data on costs. Here we extracted the quantities of the resources used and their corresponding unit costs. We extracted both the point estimate and the measure of uncertainty for the costs. We also collected information on the cost breakdown, total cost of each intervention, the price year, the currency used, the discount rate applied, and the viewpoint used to calculate estimates of costs and incremental costs. We reported the approach to costing (whether the source of the cost data was from the actual study itself, from another study, an overview of studies, from micro costing, step down allocation approach or from an ingredient approach). This is important since reviewers need to form a judgement of the accuracy of the cost estimates in the studies (Drummond M 2005). We also mentioned if the national cost estimate originated from the country itself.

- For the effectiveness data, we collected the description of outcome(s) and their corresponding units. Effectiveness data that was extracted was typically; number of infant HIV cases averted, QALY, or DALY. Furthermore, and wherever applicable, we also collected effectiveness data to reflect the impact of the intervention on maternal health via HIV treatment, as well as estimates of reduction in forward transmission due to impact of VCT. For utility measures, we recorded the techniques used for estimating the DALY and QALY where reported by the author(s).
- For the cost effectiveness and/or utility data, we recorded in the appropriate units, the type of economic evaluation design(s) that the author(s) had considered for their study.

- There were also some miscellaneous data that was retrieved from the studies and this ranged from the type of sensitivity analysis done, sub-group analysis, the funding source, and the modelling software used. The data extraction form also had a notes section on which reviewer could make relevant comments about the study.

In the event that any data needed clarifications, contact was initiated with the author(s) of the article to resolve this. All the extracted information formed the basis for the comparison across studies of their methodology, results, conclusions and recommendations. Details of these are illustrated in figure 1.

3.6. Assessment of study quality.

The extent to which a systematic review can guide health care decisions depends on the quality of the studies available (Jadad, Moher et al. 1998). Quality assessment of the studies selected for a review is a crucial step in identifying and reducing bias and an important component in any systematic review (Battaglia M 2002).

The two reviewers (DA and MJ) independently rated each article using the British Medical Journal checklist for assessing the quality of economic evaluations in healthcare, and discrepancies were resolved by consensus. The British Medical Journal checklist is a feasible tool to collect baseline information on the quality of reporting of economic analyses in healthcare (Gerard, Seymour et al. 2000). Jefferson (2002) and the Centre for

Reviews and Dissemination (2009) also recommended the BMJ checklist as a validated and acceptable instrument for quality assessment of economic evaluations. To the original checklist developed by BMJ, an additional criterion was added; which identified whether the article had included information on study sponsorship or conflict of interest, as these will help further evaluate the potential presence of publication bias in the conduct and/or the reporting of the cost effectiveness analyses. Studies which failed to include information of at least one of these categories were scored as unsatisfactory for that criterion.

Reviewers rated the quality of the study by assigning predefined scores to each criterion. We developed a scoring system based on the BMJ template, in which each criterion within the checklist, was assigned either a YES (=0), which meant it was adequately reported in the study, a NO (=1), which meant shortcomings in the study design, analysis and/or report, or N/A which meant non applicable. As specified in the BMJ checklist, a judgment of non-applicable could only be given to certain questions. If a study failed to report an item which the BMJ checklist does not include under the list of items allowed to be reported as non-applicable, the study was assessed as unsatisfactory for that item. Following Pegurri et al (2005), we summed negative responses to obtain a quality score in which higher scores represent poorer quality. Responses of yes or non-applicable did not contribute to the overall score. For all selected studies, our summary score shown on fig 2 (results section) hence represents the number of overall identified quality limitations.

Mindful of the fact that variability in quality can account for variability in results (Wilson and Lipsey 2001) our goal of performing a quality assessment was also to investigate the variations in the study designs, in the collection of data, and in the analysis

and interpretation of results of pMTCT for HIV/AIDS interventions across the selected studies.

CHAPTER 4. RESULTS

4.1. Quality Assessment.

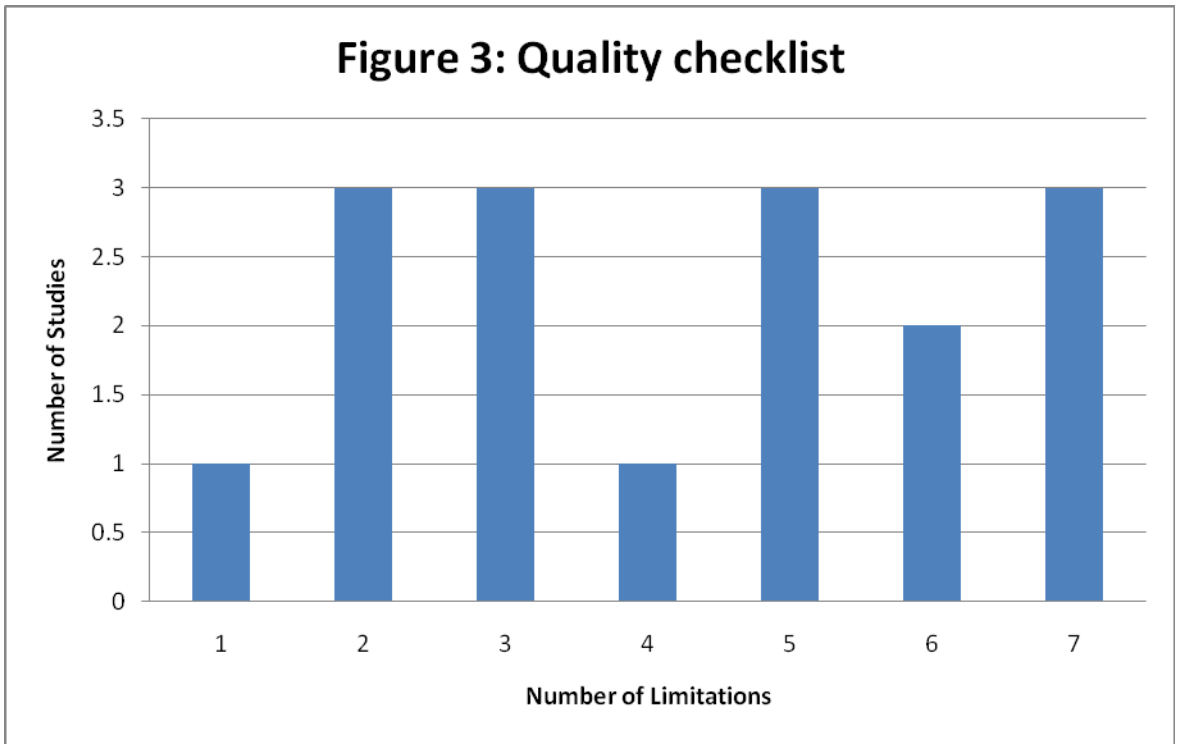

Fig.2: *Number of limitations in the quality of evidence of economic evaluations of pMTCT for HIV/AIDS interventions in developing countries.*

We used a modified version of the BMJ checklist for quality assessment of economic evaluation of healthcare interventions to identify deficiencies in this group of published studies. A summary of study limitations identified is shown on fig 3 above. We found that of the 16 studies, almost 60% had 4 limitations or more. Three of the studies (Sweat et al, 2004, Stringer et al 2000 and Wilkinson et al, 2000) had the highest number of limitations (7 each), while Mansergh et al (1996) had just one quality limitation.

Our assessment exposed flaws in the following key areas; 9 studies failed to provide details on price adjustments for inflation or currency conversion, 5 studies did not state the time horizon used for measuring costs and benefits, 6 studies did not provide explanations if the costs or benefits were not discounted, 6 studies did not declare any potential conflict of interest or sponsorship, and 4 studies did not disclose the model used. Three studies also failed in each of the following areas; Lack of clarity on the alternatives been compared, methods for the estimation of quantities and unit costs not described, choice of model not justified, discount rate not stated, details of statistical tests and confidence intervals not given for stochastic data, and unclear approach to sensitivity analysis.

As we reviewed the articles for quality rigor using the BMJ checklist, there were three points that arose which are worth mentioning; firstly, there were some criteria within the checklist that were not reported in some papers but for which the author(s) either provided an external link, or referenced a previous article for clarification. In these cases, we did not score the paper as unfavourable for those criteria. Secondly, the BMJ checklist allows a select number of criteria which can be reported as non-applicable in economic analysis. In all cases where criteria falling under this category were not reported in the articles, we did not consider this as a limitation. Finally, although the BMJ checklist provides a good approximation to study quality, some elements of quality were not effectively captured by questions on the list. For example, we identified errors in two of the published studies; however, there was no related question on the checklist. In addition, because the checklist asks only about presence or absence of a given element, questions did not permit identification of finer quality gradations. Differences amongst papers in areas in

which there exists a wide variety of techniques and approaches with varying degrees of methodological adequacy, such as sensitivity analyses, were very difficult to capture.

4.2. Overview of the studies.

Our review identified 16 articles, published in 9 journals between the years 1996 and 2008. The journals that most frequently published studies on this topic were the Journal of the International AIDS society (AIDS) and the Journal of Acquired Immune Deficiency Syndromes *(*JAIDS) and The Lancet which each published 3 articles. The journal of Sexually Transmitted Diseases and the journal of Health Policy and Planning each published 2 articles. The following journals published one study each: The Journal of the American Medical Association *(*JAMA), the British Medical Journal (BMJ), and the journal of Cost Effectiveness and Resource Allocation.

About 80% of the studies were carried out in the sub-Saharan region which is made up mainly of low and middle income countries. One study was carried out in Thailand (lower middle income), one in India (Low middle income) and another in Mexico (upper middle income). HIV prevalence varies substantially across these locations. According to epidemiological factsheets from UNAIDS (UNAIDS 2008), the lowest recorded HIV prevalence was in Mexico, followed by India, then Thailand, and the highest was in South Africa followed by Zambia.

We recorded 9 studies that performed only cost-effectiveness analyses, 5 that evaluated both cost-effectiveness and cost-utility in their analyses and 2 that carried out only cost-utility analyses. No study performed a cost-benefit analysis. Since “cost-effectiveness” is a broad term that can encompass several styles of analysis, we categorised

study design based on an examination of the outcome measures. In keeping with terminology suggested by Drummond et al (Drummond M 2005) studies that used a general outcome measure, such as a QALY or a DALY, are reported as cost-utility analyses.

It was not possible to determine the funding source for 8 of the studies. For those that disclosed the source of funding, we found that it was mostly public funding. Three of the studies were funded by international organisations or programmes; UNAIDS, Family Health International/USAIDS OR International AIDS Research and Training Programme, one was sponsored by a national government, and the rest of the studies which disclosed their funding source were sponsored by charitable foundations mainly the Elizabeth Glazer paediatric AIDS foundation.

The studies were all full economic evaluations (comparing two or more interventions). In one study (Mansergh et al, 1996), a single pMTCT intervention was compared with the current practice (no intervention). But in the remaining 13 studies, different interventions were compared against each other as well as in combinations. The different interventions that were compared ranged from anti-retroviral mono-therapy, HAART, feeding practices, obstetric practices, family planning, antenatal screening and current practice (no intervention). The Anti-retroviral therapies (ART) that were compared either individually or in combinations were mostly zidovudine (ZDV), nevirapine (NVP) and lamivudine (3TC). Voluntary Counselling and Testing (VCT) was included as part of the prevention strategies during antenatal care in 12 of the studies. It is worth noting that VCT was not considered in any of the studies as a standalone intervention, but was rather examined under different regimens in combination with ART.

The interventions in all the studies involved the use of antiretroviral therapy. The dosage and the timing for the ART given varied across the studies, but the timing generally revolved around the intra-partum and postpartum periods. The antiretroviral-based approaches to pMTCT were all based on four main clinical trials which were; PATCG 076, the CDC Thai Regimen, HIVNET 012, and PETRA plus which are commonly used as standard of care in developing countries. Paediatric AIDS Clinical Trial Group Study (PATCG 076) was a long course oral administration of ZDV given five times a day to HIV-infected pregnant women starting at 14-34 weeks' gestation, intravenously during labour, and orally to their newborns for 6 weeks. In the CDC Thai Regimen, pregnant women were randomly provided with either ZDV (300mg orally twice a day from 36 weeks' gestation until onset of labor and 300mg every 3 hours from onset of labor until delivery) or a placebo. They were all counseled not to breastfeed and provided with infant formula. In HIVNET 012 a single dose of 200 mg tablet NVP was given orally to mothers at the onset of labour, and a single oral dose of 2 mg/kg NVP suspension was given to the newborns during the first week of life. In the PETRA trials ZDV and 3TC were given at week 36 of pregnancy until the onset of labour, given intrapartum and for one week following delivery (mother + child). The population was largely a breastfeeding one. Scenarios explored in model-based analyses in the 14 studies were mainly an adaptation of the protocols from these 4 trials.

Four studies (Soderlund et al, 1999, Wilkinson et al, 2000, Rely et al, 2003 and Maclean et al, 2005) evaluated different approaches to infant feeding in the context of ART-based pMTCT. Different durations of breastfeeding with various combinations of ART were evaluated in 1 of these studies (Maclean et al, 2005), while the other 3 studies

considered exclusive formula feeding. For the remaining 12 studies, in general it was difficult to infer if the populations were breastfeeding or not. However, based on the clinical protocol and the common practice in each region, one could deduce the feeding practice to be predominantly breastfeeding except in the study from Thailand by Teerawattananon Y et al (2005).

Two studies (Sweat et al, 2004 and Reynolds et al, 2006) evaluated the efficacy of family planning strategies like the use of contraceptives to prevent HIV in young women, and to reduce unintended pregnancies among HIV positive women. One study from Mexico (Rely et al, 2003) evaluated the cost-effectiveness of elective caesarean section following ART. In two studies (Teerawattananon et al, 2005 and Soorapanth et al, 2006), the interventions where examined considering 2 VCT sessions; one early on in pregnancy and a repeat screen closer to delivery. John et al (2008) also examined cost effectiveness of 2 types of VCT; individual VCT (mother only) versus couples' VCT (Mother and partner). Table (2) shows the details of the study overview data.

Table 2. Overview of economic evaluations of interventions to reduce mother to child transmission (MTCT) of HIV

Study	Location	Income Level[1]	HIV Prevalence (15-49 years)[2]	Study Population[3]	Interventions Compared	Study design/Type of Economic Evaluation[4]	Funding Source[5]
(Mansergh, Haddix et al. 1996)	SSA[6]	LMIC	1% - 26%	100,000 pregnant women	(a) CDC Thai regimen (b) No intervention	CEA	UND
(Marseille, Kahn et al. 1998)	SSA	LMIC	1% - 26%	100 pregnant women	(1) PETRA - A (2) PETRA - B (3) PETRA - C (4) No intervention	CEA & CUA	PUB
(Wilkinson, Floyd et al. 1998)	South Africa	UM	18.10%	8421 pregnant women representing a South African health district (26% (n=2189) assumed HIV+)	(1) ACTG 076 with breastfeeding, delivered within current infrastructure (2) ACTG 076 without breastfeeding delivered through enhanced infrastructure (3) PETRA - A delivered through enhanced infrastructure (4) No intervention	CEA	UND
(Marseille, Kahn et al. 1999)	SSA	LMIC	1% - 26%	20 000 pregnant women	1) HIVNET 012 (targeted) (2) HIVNET 012 (universal) (3) PETRA- A (4) PETRA - B (5) CDC Thai (targeted)	CEA & CUA	PUB

Study	Location	Income Level[1]	HIV Prevalence (15-49 years)[2]	Study Population[3]	Interventions Compared	Study design/Type of Economic Evaluation[4]	Funding Source[5]
(Soderlund, Zwi et al. 1999)	South Africa	UM	18.10%	20 000 pregnant women	(1) FF recommended from birth (2) FF recommended from 4 months only (3) FF recommended from 7 months only (4) FF recommended from birth (formula and bottles supplied) (5) ACTG076 (6) PETRA - B (7) CDC Thai regimen (8) CDC Thai regimen + FF recommended (9) CDC Thai regimen + FF supplied	CEA	UND
(Stringer, Rouse et al. 2000)	SSA	LMIC	1% - 26%	10 000 pregnant women	(1) Early HIVNET 012 (targeted) (2) Early HIVNET 012 (universal) (3) Labour and delivery maternal NVP (Universal) (4) Universal Infant-only therapy = no maternal dose, but immediate postpartum treatment of all infants (5) No intervention	CEA	PUB
(Wilkinson, Floyd et al. 2000)	South Africa	UM	18.10%	1,340,797 women	(1) CDC Thai regimen (targeted) + FF supplied within an enhanced infrastructure Vs usual care	CEA	UND

Study	Location	Income Level[1]	HIV Prevalence (15-49 years)[2]	Study Population[3]	Interventions Compared	Study design/Type of Economic Evaluation[4]	Funding Source[5]
(Wood, Braitstein et al. 2000)	South Africa	UM	18.10%	920 000 HIV+ pregnancies nationally over a 5-year period	(1) 25% HIV +ve pregnant women and infants would receive ART (2) 75% HIV +ve pregnant women and infants would receive ART (3) 100% ART provided to all pregnant women (HIV+ and HIV-ve) (4) Triple-combination antiretroviral treatment of 25% of non-pregnant HIV-1-positive adults (5) No intervention	CEA	PUB
(Rely, Bertozzi et al. 2003)	Mexico	UM	0.30%	958294 pregnant women	(1) 4% VCT to pregnant women + ACTG 076 or HIVNET 012 (2) 85% VCT to pregnant women + ACTG 076 or HIVNET 012 (3) 30% VCT to pregnant women at highest risk + ACTG 076 or HIVNET 012 (4) VCT to HIV+ pregnant women + ACTG 076 or HIVNET 012 (5) VCT to HIV+ pregnant women and to 15% of late presenters + ACTG 076 or HIVNET 012	CEA	UND
(Sweat, O'Reilly et al. 2004)	SSA	LMIC	1% - 26%	Not Specified	(1) HIVNET 012 (2) No Intervention (Current Practice)	CEA & CUA	UND

Study	Location	Income Level[1]	HIV Prevalence (15-49 years)[2]	Study Population[3]	Interventions Compared	Study design/Type of Economic Evaluation[4]	Funding Source[5]
(Maclean and Stringer 2005)	Zambia	L	15.20%	40,000 pregnant women	(1) UC[8] + BF for 6 months (2) UC + BF for 12 months (3) UC + BF for 6 months + daily infant NVP (4) VCT + Maternal 3-drug ART during pregnancy + 3-drug ART during 6 months of BF (5) Same as (5), but only for women with CD4<=200 (6) UC + FF for 12 months	CUA	PUB
(Teerawattananon, Vos et al. 2005)	Thailand	LM	1.40%	100,000 pregnant women	(1) 1 or 2 VCT + ACTG 076 (2) 1 or 2 VCT + HIVNET 012 (3) 1 or 2 VCT + ACTG 076 (early ANC attenders) or HIVNET 012 (late ANC arrivals) (4) ACTG 076 + HIVNET 012	CEA	PUB
(Manoj, Stephen et al. 2006)	India	LM	0.50%	100 000 sexually active women aged 15-49	(1)Universal screening in all states +HIVNET 012 (2)Universal screening in the six highest prevalence + HIVNET 012	CEA & CUA	UND
(Reynolds, Janowitz et al. 2006)	SSA	LMIC	1% - 26%	100 000 sexually active women aged 15-49	(1) Family planning programs(contraceptive use) (2) VCT + HIVNET 012 (15% coverage) (3) VCT + HIVNET 012 (5% coverage)	CEA	PUB

Study	Location	Income Level[1]	HIV Prevalence (15-49 years)[2]	Study Population[3]	Interventions Compared	Study design/Type of Economic Evaluation[4]	Funding Source[5]
(Soorapanth, Sansom et al. 2006)	South Africa	UM	18.10%	100 000 pregnant women	(1) VCT (at 20 and 28 weeks) + ACTG 076 (from 28 weeks) + plus HIVNET 012 with ART to HIV +ve children (2) VCT (at 20 and 28 weeks) + ACTG 076 (from 28 weeks) + plus HIVNET 012 without ART to HIV +ve children (3) VCT (at 20 and 34 weeks) + ACTG 076 (from 34 weeks0 + HIVNET 012 with ART to HIV +ve children (4) VCT (at 20 and 34 weeks) + ACTG 076 (from 34 weeks) + HIVNET 012 without ART to HIV +ve children (5) VCT (at 20 and 36 weeks) + HIVNET 012 with ART to HIV +ve children (6) VCT (at 20 and 36 weeks) + HIVNET 012 without ART to HIV +ve children	CUA	UND
(John, Farquhar et al. 2008)	Kenya	L	8.3%	10,000 pregnant women	a) Couple VCT b) Individual VCT	CEA	PUB

[1] According to the 2008 World Bank classification. LMIC = Low and Middle income countries. UM = Upper Middle Income. LM = Lower Middle Income. L = Low Income.

[2]Source: UNAIDS countries epidemiological factsheet 2008.

[3]Hypothetical cohorts

[4]CEA = Cost Effectiveness Analysis. CUA = Cost Utility Analysis. CBA = Cost Benefit Analysis.

[5]UND = Undisclosed. PUB = Public. PRI = Private

[6]SSA = Sub-Saharan Africa

FF = Formula feeding

UC = Usual care (VCT and single dose NVP intrapartum and to infant, drawn from the HIVNET 012 study)

4.3. Intervention costs.

All the studies in this review considered costs incurred under the perspective of the public healthcare provider. In addition to considering costs under the public healthcare payer's viewpoint, one study (Mansergh et al, 1996) also considered costs incurred under a societal perspective. The Canadian Agency for Drugs and Technologies in Health (CADTH) in its guidelines for economic evaluation of health technologies (2006) recommended that for the reference case analysis, the perspective that should be adopted should be that of the public healthcare system. The costs related to this viewpoint include direct costs and time costs to patients and their families, as well as direct costs to the health care system. Most of the studies did not adopt a societal approach probably because the only major additional cost that would have been included will be those related to productivity changes; and there is lack of unanimously acceptable tools to calculate these in developing countries.

Two of the studies did not report the cost year (Marseille et al, 98, 99), but for the rest the year into which costs were converted spanned from 1994 up to year 2003**.** The costs were also all converted to US dollars with the exception of Wilkinson et al (2000) which reported its cost items in South African Rand, and Manoj et al (2006) which reported its cost items in Indian Rupees. There was considerable consistency in the choice of discount rate used. An equal number of studies each reported either a 3% or a 5% discount rate. Discounting of future dollar costs and benefits offers a means of standardizing different cost time profiles so that total costs can be compared, and it is usually recommended to use a rate of either 3% or 5% widely applied in existing economic evaluations (Drummond et

al, 2005). One study discounted (at 5%) only the average lifetime paediatric treatment costs (Rely et al, 2003), and another study did not discount any costs at all (Reynolds et al, 2006). This is consistent with the CADTH and Drummond et al (2005) who recommend that only costs incurred beyond a 1 year time horizon should be discounted. One other study discounted life year gained at both 3% and 6% to allow comparability with other related economic analysis in developing countries (Wilkinson et al, 1998).

Most of the studies applied the ingredient approach for cost estimation. The approach to costing is considered an ingredient approach since the physical quantities of the necessary inputs are multiplied by their unit prices to obtain total costs (Johns, Adam et al. 2006). The authors reported most of the unit costs for each intervention and the cost estimates were based on data from published studies, informal sources and previous trials. Drug cost, test costs and cost of formula feed were generally obtained from recent market prices or based on existing local standards, while staff costs were obtained from salary figures. In more than half of the papers the cost estimates came from the country itself where the study was carried out, and in the rest of the papers, which were all from sub-Saharan Africa, estimates originated from other developing countries.

The type of costs that were included across the studies was quite dissimilar and depended on the pMTCT strategies being evaluated and on the study perspective. Drug costs and VCT costs were typically reported in all studies. One study (Rely et al, 2003) also included costs and frequency of caesarean section. Two studies also considered the costs required to enhance the available infrastructure (Wilkinson et al, 1998 and Sweat et al, 2004), while another single study (Reynolds et al, 2006) included costs for contraceptive

pills, contraceptive devices and condoms. Discounted lifetime costs of treating an HIV positive infant was included in a majority of the papers and was calculated based on estimates that varied slightly from one study to another. Considering the fact that calculating the lifetime costs of treating an HIV positive child will entail a full account of lifetime costs of HIV negative children and due to the scarcity of this data, most studies simply reported estimates from other studies. For studies that actually calculated this cost, they estimated it based on medical costs for adults with AIDS, and applied relevant inflation rates and cost year conversions.

The reported unit costs for each PMTCT intervention varied greatly across all the studies. This is as a result of the different countries in which the costs were recorded, the year the cost was recorded and the price of the intervention at that point in time. Our selected articles were published between 1996 and 2008; during this 12 year period, drug prices had significantly dropped, the duration of the PMTCT interventions have also been shortened, and adherence to treatment has increased. For VCT, costs were expressed in US $ per mother. Few studies split the VCT cost to reflect the actual cost for the two components (counseling costs and testing costs). With the exception of one study which reported a cost of $18.50 per mother in 1996 (Mansergh et al, 1996), the variations in the VCT costs in sub-Saharan Africa ranged typically between $4.0 to around $10 across all the studies. The VCT costs estimated for Mexico was $8.0 and for Thailand it was $7.10. The Thai study was the only one that reported the HIV testing costs for babies born by infected mothers ($5.61).

Drug costs reported reflected acquisition costs only and were mostly expressed per dose while a few expressed the costs per person or as per the duration of the program. Drug prices per dose varied in the case of ZDV from $1 to $3.10 and in the case of NVP they ranged from $0.8 to $5.2. The lowest rate ($0.8) was reported in 2006. Only one study reported the cost of 3TC ($3.73 per dose). Four studies (Stringer et al, 2000, Rely et al, 2003, Maclean et al, 2005, and Teerawattananon et al, 2005) actually reported the cost for infant doses and these ranged from $0.18 to $4 for NVP and about $2 for ZDV.

Three studies (Soderlund et al, 1999, Wilkinson et al, 2000, and Rely et al, 2003)that included the strategy of replacement feeding reported the cost of formula feeding to cost somewhere around $15 per month in sub-Saharan Africa and around $30 per month in Latin America. The only study that compared the efficacy of cesarean section (Rely et al, 2003) reported it to cost approximately $300.

The total costs for each intervention as reported by each author(s) is also recorded and this varies considerably from one study to another. This is as a result of the kind of intervention under scrutiny, as well as the differences in the input cost parameters that each study included in their base case analysis. Different analysts included different costs across different studies, making various assumptions, using various estimates and models for different interventions carried out in different countries with a wide range in population sizes. The recorded total costs ranged from anywhere near a few hundreds, up to several millions of dollars.

One study (Sweat et al, 2004) calculated the total cost of an intervention which contained the cost of NVP, costs to enhance the public health system and VCT costs, then reported the findings from 8 sub-Saharan countries. These countries all had a high HIV prevalence and the acceptance and adherence to treatment was variable. Presenting the results across these 8 countries exposed the impact of cross-country variations as the total cost for this same intervention ranged from about $400K in one country to over $6 million in another. Table (3) shows the variations in the intervention costs.

Table 3. Economic evaluations of interventions to reduce mother to child transmission (MTCT) of HIV: Study perspective and costs

Study	Perspective[1]	Cost Year and Currency	Discount Rates[2]	Cost Breakdown			
				Direct Costs to the public payer			Indirect Costs
				Costs of offering the intervention	Costs offset by the intervention[3]	Health system enhancements[4]	
(Mansergh, Haddix et al. 1996)	SOC	1994 US$	5%	VCT[5] costs Drug costs	Lifetime medical costs for HIV +ve children		Productivity costs: Loss of productivity due to premature mortality of HIV infected infants
	GOV	1994 US$	5%	VCT[5] costs Drug costs	Lifetime medical costs for HIV +ve children		
(Marseille, Kahn et al. 1998)	GOV	US$	5%	VCT costs Drugs costs Staff salaries	Lifetime medical costs for HIV +ve children		
(Wilkinson, Floyd et al. 1998)	GOV	1997 US$	3% and 6%	VCT costs Drug costs Staff salaries Training costs		Increased counseling capacity requirements	
(Marseille, Kahn et al. 1999)	GOV	US$	3%	VCT costs Drug costs	Lifetime medical costs for HIV +ve minus HIV –ve children		
(Soderlund, Zwi et al. 1999)	GOV	1998 US$	5%	VCT costs. Drug costs. Cost of formula feeds and bottles	Lifetime medical costs for HIV +ve minus HIV –ve children		

Study	Perspective[1]	Cost Year and Currency	Discount Rates[2]	Cost Breakdown			
				Direct Costs to the public payer			Indirect Costs
				Costs of offering the intervention	Costs offset by the intervention[3]	Health system enhancements[4]	
(Stringer, Rouse et al. 2000)	GOV	1999 US	3%	VCT costs Drug costs	Lifetime medical costs for HIV +ve children		
(Wilkinson, Floyd et al. 2000)	GOV	1997 Rand	Not stated	VCT costs Drug costs Staff salaries Training costs			
(Wood, Braitstein et al. 2000)	GOV	2000 US$	Not stated	Drugs costs			
(Rely, Bertozzi et al. 2003)	GOV	2001 US$	5%	VCT costs Drug costs Cost of formula feed Elective caesarean costs	Lifetime Medical costs for HIV +ve children and HIV +ve adults[6]		
(Sweat, O'Reilly et al. 2004)	GOV	2000 US$	3%	VCT costs Drug costs	Lifetime medical costs for HIV +ve children	Costs for enhancement of the health system	
(Maclean and Stringer 2005)	GOV	2003 US$	5%	VCT costs Drug costs Cost of Formula Feeding	Lifetime medical costs of HIV +ve children		

Study	Perspective[1]	Cost Year and Currency	Discount Rates[2]	Cost Breakdown			
				Direct Costs to the public payer			Indirect Costs
				Costs of offering the intervention	Costs offset by the intervention[3]	Health system enhancements[4]	
(Teerawattananon, Vos et al. 2005)	GOV	2003 US$	5%	VCT costs. Drugs costs. Formula feed costs NVP resistance cost	Lifetime medical costs of HIV +ve children		
(Manoj, Stephen et al. 2006)	GOV	2006 Rupees (Rs)	5%	VCT cost Drug cost	Lifetime medical costs of HIV +ve children		
(Reynolds, Janowitz et al. 2006)	GOV	2000 US$	n/a[7]	VCT costs Drug costs Staff salaries Supplies costs Family planning costs		Cost of commodities, distribution of commodities & facility overhead.	
(Soorapanth, Sansom et al. 2006)	GOV	2003 US$	3%	VCT costs. Drugs costs. Cost of formula feed.	Lifetime medical costs of HIV +ve children		
(John, Farquhar et al. 2008)	Not stated	US$	Not stated	Staff salaries. Supplies costs.			

[1]SOC = Societal (considers direct and indirect costs); GOV = Government (considers direct costs only)

[2]Rates listed apply to both costs and effects.

[3]Costs of HIV-related care avoided (either the public healthcare expenditure on HIV +ve persons, or the difference in average public healthcare expenditure on HIV +ve versus HIV- persons)

[4]Additional health system infrastructure and personnel needed to offer the program.

[5]VCT = Voluntary counselling and testing

[6]This was included in order to order to measure the impact of VCT on sexual behavior change and horizontal transmission.

[7]n/a = non applicable

4.4. Effectiveness Parameters.

The base case values used for the epidemiological and efficacy parameters were adapted as estimates from a variety of sources. HIV transmission rates (in-utero, intra-partum and postpartum) and adherence to treatment were typically obtained from other major clinical trials (HIVNET 012, PETRA, and ACTG 076) as well as from published reports, studies or systematic reviews. Country specific demographic data like HIV prevalence, life expectancy, rate of breastfeeding, annual number of live births, and proportion of women utilizing antenatal services were typically obtained from epidemiological factsheets of UN agencies, some international databases and previous publications. Sweat et al (2004), in estimating their efficacy parameters, calculated the average from all the figures from the 8 countries in which their study was conducted.

HIV prevalence estimates among pregnant women used in the base case analysis across the studies varied from 0.7% in India, 1.5% in Thailand, through 9% in Mexico to 30% in sub-Saharan Africa. Epidemiological characteristics of HIV and AIDS in children were not estimated by most of the studies. However, Marseille et al (1999) included a rate of progression from pediatric HIV to AIDS of 25%, 80% and 100% by ages 12 months, 60 months and 120 months respectively. Three studies (Marseille et al 1999, Wood et al 2000, Soorapanth et al, 2006) also assumed that after progression to AIDS, children could live for an average of 12 months. The average life expectancy of uninfected children was generally assumed at around 60 years.

Estimates of acceptance of HIV testing ranged from 64% to 85%. The estimates for the number of women accepting treatment ranged from 50% to 90%. The adherence rates to

anti-retroviral therapy were estimated at around 75% for ZDV and a little over 90% for NVP. NVP was estimated to have higher adherence rates because of the ease of oral administration, and its shorter regimen compared with a longer ZDV regimen which is applied intravenously. The percentage of women to whom treatment was offered differed depending on the regimen, and was based on factors like financial constraints, available infrastructure, human resources and differences in logistics.

Estimated rates of MTCT of HIV in the absence of treatment also varied across the studies ranging from 19% to 30%. These estimates did not include the rate of transmission through breastfeeding. Transmission rates as a result of breastfeeding were dependent on the duration of breastfeeding. Considering exclusive breastfeeding assumed in almost all studies, and duration of up to at least 12 months of the child age, rate of transmission through breastfeeding was estimated between 10% to about 16%. The risks associated with bottle feeding, the need to maximize benefits of breastfeeding as well as cultural beliefs and societal norms explains this 100% breastfeeding rates estimated in the base case analyses of almost all studies. Among women who were aware of their HIV status and aware of the fact that breastfeeding transmits HIV to infants, this feeding practice was rated around 50-80%.

The following outcome measures were reported; Neonatal HIV infections averted, life year gained, DALY and QALY. The units used were not standardized from one study to another and reflected the size of the population. Neonatal HIV infection averted was calculated in over 65% of the studies. Two studies (Mansergh et al, 1996 and Sweat et al, 2004) calculated the infant infections averted, and reported an annual value while Sweat et al (2004) went ahead to report the outcome values in all the 8 countries under their analysis.

DALY loss averted was reported in 35% of the studies, QALY gained was reported in 14% and life years gained was reported in 21%. One study (Manoj et al, 2006) reported the potential years of life lost (PYLL). The methods used to estimate DALY or QALY were not reported in several papers, and for the few that did, the method was unclear. Marseille et al (1998), Wilkinson et al (2000), and Sweat et al (2004) seemed to have projected time to AIDS and death, then plugged in disability weights for HIV and AIDS from Murray and Lopez and also applied an age-weighting function (Murray and Lopez 1996). One study however (John et al, 2008) clearly reported how the DALY was estimated providing formulae and explanatory details.

There was also variation in how the benefits of pMTCT were evaluated. All studies calculated effectiveness via an impact on the health of children of HIV+ women. In addition three studies (Marseille et al, 1998, 1999 and Rely et al, 2003) considered a reduction in forward transmission due to the impact of VCT. They estimated a 30% reduction in adult to adult transmission due to VCT. No study considered the possible impact on maternal health via HIV treatment or of possible benefits related to deferring or avoiding orphan children due to increased maternal longevity.

Table (4) shows the variation in effectiveness parameters. They varied considerably from one study to another based on several factor like differences in regimens and scenarios of PMTCT interventions, differences in assumptions and estimates of base case parameters, differences in the study population etc.

Table 4. Economic evaluations of interventions to reduce mother to child transmission (MTCT) of HIV: estimates of effectiveness

Study	Effectiveness (Number of infant HIV cases averted)	Effectiveness (Reduction in forward (adult-to-adult) transmission due to impact of VCT[1])	Effectiveness (QALY[2] or DALY[3])	Life years gained
(Mansergh, Haddix et al. 1996)	(1) CDC Thai regimen (Government perspective = 3764; societal perspective = 3764) (2) No intervention (healthcare system perspective = 4250 societal perspective = 4250) per 100,000 births	n/a[4]	n/a	n/a
(Marseille, Kahn et al. 1998)	(1) PETRA A: 0.70 HIV infections for every 100 women (2) PETRA B: 0.62 HIV infections for every 100 women (3) PETRA C: 0.31 HIV infections for every 100 women per 100 women	A 30% external benefit of reduced adult to adult transmission was incorporated in the base case and varied from 10-50% in sensitivity analyses	(1) Regimen A: 13.2 (2) Regimen B: 11.6 (3) Regimen C: 5.8 DALYs per 100 women	n/a
(Wilkinson, Floyd et al. 1998)	(1) ACTG 076 with BF[5], delivered within current infrastructure: 99 (2) ACTG 076 without BF delivered through enhanced infrastructure: 272 (3) PETRA - A delivered through enhanced infrastructure: 307	n/a	n/a	n/a

Study	Effectiveness (Number of infant HIV cases averted)	Effectiveness (Reduction in forward (adult-to-adult) transmission due to impact of VCT[1])	Effectiveness (QALY[2] or DALY[3])	Life years gained
(Marseille, Kahn et al. 1999)	(1) HIVNET 012 (targeted): 476 (2) HIVNET 012 (universal): 603 (3) PETRA-A: 315 (4) PETRA-B: 229 (5) Thai (targeted): 309 per 20 000 women	Assumed to be zero in the base case. A 30% external benefit of reduced adult to adult transmission was considered in sensitivity analyses.	(1) HIVNET 012 (targeted): 12572 (2) HIVNET 012 (universal): 15862 (3) PETRA-A: 8326 (4) PETRA-B: 6041 (5) Thai(targeted): 8163 DALY per 20000 women	n/a
(Soderlund, Zwi et al. 1999)	(Total deaths averted) (1) FF[6] recommended from birth: 26. (2) FF recommended from 4 months only: 25. (3) FF recommended from 7 months only: 5. (4) FF recommended and supplied: 37. (5) ACTG076 regimen: 200. (6) PETRA B regimen: 124. (7) CDCThai regimen: 160. (8) CDCThai regimen + FF recommended: 188. (9) CDCThai regimen + FF supplied: 200.	n/a	n/a	<u>Strategy</u>: (1) 461 (2) 449 (3) 98 (4) 661 (5) 3655 (6) 2260 (7) 2926 (8) 3434 (9) 3654

Study	Effectiveness (Number of infant HIV cases averted)	Effectiveness (Reduction in forward (adult-to-adult) transmission due to impact of VCT[1])	Effectiveness (QALY[2] or DALY[3])	Life years gained
(Stringer, Rouse et al. 2000)	(1a) Early HIVNET 012 (targeted): 137. (1b) Early HIVNET 012 (universal): 160. (2a) Labour and delivery maternal NVP (Universal): 89 (2b) Universal Infant-only therapy:142	n/a	n/a	n/a
(Wilkinson, Floyd et al. 2000)	CDC Thai regimen (targeted) + FF supplied within an enhanced services infrastructure: 23,181	n/a	n/a	
(Wood, Braitstein et al. 2000)	n/a	n/a	n/a	n/a
(Rely, Bertozzi et al. 2003)	(1) 4% VCT to pregnant women + ACTG 076 or HIVNET012: 4 & 3 (2) 85% VCT to pregnant women + ACTG 076 or HIVNET012: 91 & 64 (3) 30% VCT to pregnant women at highest risk + ACTG 076 or HIVNET012: 46 & 32 (4) VCT to HIV+ pregnant women + ACTG 076 or HIVNET012: 91 & 64 (5) VCT to HIV+ pregnant women and to 15% of late presenters + ACTG 076 or HIVNET012: 102 & 72	Assumed to be zero in the base case. A 30% external benefit of reduced adult to adult transmission was considered in sensitivity analyses.	n/a	n/a

Study	Effectiveness (Number of infant HIV cases averted)	Effectiveness (Reduction in forward (adult-to-adult) transmission due to impact of VCT[1])	Effectiveness (QALY[2] or DALY[3])	Life years gained
(Sweat, O'Reilly et al. 2004)	Botswana: 243 Ivory Coast: 435 Kenya: 904 Rwanda: 1380 Tanzania: 2774 Uganda: 1375 Zambia: 629 Zimbabwe: 1013	n/a	Botswana: 7571 Ivory Coast: 12,984 Kenya: 27,784 Rwanda: 39,095 Tanzania: 82,806 Uganda: 39,846 Zambia: 18,873 Zimbabwe: 31,462 DALYs saved	n/a
(Maclean and Stringer 2005)	Not measured	n/a	(1) UC[8] + BF for 6 months: 446,208. (2) UC + BF for 12 months: 445,922. (3) UC + BF for 6 months + daily infant NVP: 447,391 (4) VCT + Maternal ART (pregnancy) + ART (6 months of BF): 451,250. (5) Same as (5), but only for women with CD4<=200: 446,869. (6) UC + FF for 12 months: 446,187 QALY gained	
(Teerawattananon, Vos et al. 2005)	(1) 1 or 2 VCT + ACTG 076: 233 & 245 (2) 1 or 2 VCT + HIVNET 012: 258 & 271 (3) 1 or 2 VCT + ACTG 076 (early ANC attenders) or HIVNET 012 (late ANC arrivals): 273 & 300 (4) 1 or 2 VCT ACTG 076 + HIVNET 012: 337 & 353	n/a	n/a	n/a

Study	Effectiveness (Number of infant HIV cases averted)	Effectiveness (Reduction in forward (adult-to-adult) transmission due to impact of VCT[1])	Effectiveness (QALY[2] or DALY[3])	Life years gained
(Manoj, Stephen et al. 2006)	(1) Universal screening in all states +HIVNET 012: 9880 (2)Universal screening in the six highest prevalence states + HIVNET 012: 4403	n/a	n/a	a)Universal screening (nationwide) : 131,700 b) Targeted screening (high prevalence settings): 58,700 Potential years of life lost (PYLL)
(Reynolds, Janowitz et al. 2006)	(Number of HIV-Positive Births) (1) Family planning programs(contraceptive use): 1940 (2) VCT + HIVNET 012 (15% coverage): 1940.5 (3) VCT + HIVNET 012 (5% coverage): 1973.1 (Additional HIV-positive Births Averted) (1) Family Planning: 33.1 (2) VCT + HIVNET 012: 32.5	n/a	n/a	n/a

Study	Effectiveness (Number of infant HIV cases averted)	Effectiveness (Reduction in forward (adult-to-adult) transmission due to impact of VCT[1])	Effectiveness (QALY[2] or DALY[3])	Life years gained
(Soorapanth, Sansom et al. 2006)	(1) Repeat screen (at 28 weeks) + ZDV from 28 wk plus single-dose NVP with ART to HIV +ve children: 3436 (2) Repeat screen (at 28 weeks) + ZDV from 28 wk plus single-dose NVP without ART to HIV +ve children: 3436 (3) Repeat screen (at 34 weeks) + ZDV from 34 wk + single-dose NVP with ART to HIV +ve children: 3406 (4) Repeat screen (at 34 weeks) + ZDV from 34 wk + single-dose NVP without ART to HIV +ve children: 3406 (5) Repeat screen (at 36 weeks) + single-dose NVP with ART to HIV +ve children: 5031 (6) Repeat screen (at 36 weeks) + single-dose NVP without ART to HIV +ve children:5031	n/a	Strategy: (1) 776.48 (2) 1158.74 (3) 1299.76 (4) 1939.63 (5) 1147.84 (6) 1712.92 QALYs saved	n/a
(John, Farquhar et al. 2008)	(1) Couple VCT: 91 (2) Individual VCT: 88	VCT may avoid HIV acquisition during pregnancy/BF in discordant couples.Or modify sexual behavior in concordant couples.	n/a	n/a

[1]VCT = Voluntary counseling and testing

[2]QALY = Quality adjusted life years

[3]DALY = Disability adjusted life years

[4]n/a = not applicable

[5]BF = Breastfeeding

[6]FF = Formula feeding

4.5. Sensitivity Analysis:

As reported above, there was wide range of heterogeneity and uncertainty in the estimated input parameters that the authors used in their base case analysis. In order to evaluate the impact that these assumptions or estimated values would have on the results of the analysis, all the authors performed a sensitivity analysis. A sensitivity analysis is the process of systematically examining the influence of the variables and assumptions used in an evaluation and to explore their impact on the cost-effectiveness of the intervention. It is an indicator of study quality; it helps evaluate reliability of conclusions, and can facilitate generalizability of findings (Brigg 1995; Walker & Fox-Rushby 2001).

The two types of sensitivity analyses that were reported by the authors in the selected studies were univariate and multivariate sensitivity analysis. In a univariate sensitivity analysis, only one parameter is varied over a range of values at a time, while several parameters can be varied over a range at a time in a multivariate sensitivity analysis. Six authors performed a univariate analysis (Wilkinson et al 1998; Soderlund et al, 1999: Wilkinson et al, 2000; Rely et al 2003; Reynolds et al 2006; John et al, 2008) while the remainder performed both a univariate and a multivariate analysis (Mansergh et al 1996; Marseille et al 1998; Marseille et al 1999; Marseille et al 2000; Stringer et al, 2000; Wood et al 2000; Sweat et al 2004; Maclean et al 2005; Teerawattananon et al 2005; Manoj et al 2006; Soorapanth et al 2006).

The input parameters that were analyzed through a range of assumed values were; drug costs, lifetime medical costs, productivity costs, formula costs, discount rates, HIV

prevalence among pregnant women, percentage of women who breastfeed, rate of prepartum vertical transmission of HIV, rate of transmission through breastfeeding, VCT acceptance and adherence rates, rate of couple counselling uptake, rates of adherence to therapy, drug efficacy rates, costs of caesarean-section birth, life expectancy, QALY, DALY, formula costs, lifetime discounted pediatric and adult AIDS treatment costs .

Estimates of these key parameters were varied over different ranges by the authors in order to access how the resulting cost-effectiveness estimates will in turn vary. The lower and upper bounds in the ranges used for sensitivity analysis varied from one study to another and we report here the lowest and highest values estimated by the authors; costs of VCT was varied between $1-$40; cost of ZDV and 3TC was varied between $0 to $7 per dose; NVP costs were varied from $0.15 to $8 per dose; discount rate between 0% to 12%, lifetime treatment cost for HIV positive child was varied between $0 to $25000; estimates for maternal HIV prevalence rates were varied in sensitivity analyses from 0.03% to 45% across the studies; risk of vertical transmission was varied from 16% to 64%; VCT acceptance was varied from 30% to 100%; rate of couple counselling uptake was varied between 0% to 100%; external benefits of VCT were varied between 10% to 50%; adherence to therapy was varied between 0% to 95%; breastfeeding rates were varied from 75% to 100%, while rate of transmission through breastfeeding ranged across studies from 12% to 18%.

Cost effectiveness of the interventions was most sensitive to differences in rates of HIV prevalence, with an increase in cost effectiveness recorded as rates increase.

Adherence to therapy, drug cost and feeding practice also had a strong effect on cost-effectiveness outcomes.

4.6. Cost-Effectiveness and Cost-Utility: see table (5)

4.6.1. Cost per life years gained /lost: Cost per life years gained estimates were reported by only 2 authors in 1998 (Wilkinson et al) and 1999 (Soderlund et al). One author (Manoj et al, 2006) reported the cost per potential years of life lost (PYLL). The World Development Report (WorldBank 1993) and Jamieson (Jamieson 1993) suggested that interventions costing less than $100 per life year saved are cost effective for middle income countries whereas in developing countries in general, they recommended a willingness to pay of $50 per life-year gained as a reasonable benchmark.

Taking this benchmark into considerations, the following interventions were cost effective; (a) The PETRA regimens consisting of short-course ZDV plus 3TC delivered through enhanced infrastructure discounted at 3% (Wilkinson et al 1998 & Soderlund et al 1999); (b) CDC Thai regimen (Soderlund et al 1999); (c) CDC + formula recommended (Soderlund 1999); (d) CDC + formula supplied (Soderlund et al, 1999). It was projected that even ACTG076 regimen would be reasonably cost effective if drug costs were dropped to about a quarter of their prices at that time (Soderlund et al 1999).

4*.6.2. Cost per QALY / DALY:* The WHO-CHOICEs' (World Health Organisation-CHOosing Interventions that are Cost-Effective) standards to classify cost effectiveness of healthcare interventions uses a country's Gross Domestic Product (GDP) per capita as an indicator and has 3 categories; very cost effective if the DALY averted is less than the

country's GDP per capita; cost-effective if the DALY averted is between 1-3 times the country's GDP per capita; and not cost effective if the DALY averted is greater than 3 times the country's GDP per capita (WHO website). Marseille et al (1998, 1999) and Maclean et al, (2005), both reported ratios meeting this benchmark with the regimens been even more cost-effectiveness in scenarios with higher HIV prevalence. Sweat et al (2004) reported a range cost per DALY from about 58 to 310 from among the 8 countries under their review.

***4.6.3. Cost per infant HIV infection averted*:** There was a wide range in the cost per neonatal HIV infection averted. Estimates ranged from $138 to $86,420 per infant infection averted. Cost effectiveness of the same regimen(s) or interventions also varied in ratios from one study to the next. This can be attributed to the differences in settings, in epidemiological and cost parameters, in study population, in year of study, and to differences in methodological assumptions and model structure. Interventions including NVP in different combinations cost typically between $138 to close to $977 per infant infection averted. Interventions with ZDV under various scenarios cost from $1109 to $5806 per infant infection averted and formula feeding interventions registered a cost effectiveness ratio ranging from a close to $3600 to around $20,052.

Table 5: Cost-effectiveness of interventions to reduce mother to child transmission (MTCT) of HIV

Study	Cost (US$) per infant HIV infection averted	Cost (US$) per life year gained	Cost (US$) per QALY or DALY gained
(Mansergh, Haddix et al. 1996)	(1) CDC Thai regimen (healthcare perspective): 3748 (2) CDC Thai regimen (societal perspective): 1115	n/a	n/a
(Marseille, Kahn et al. 1998)	(1) PETRA - A: 5134 (2) PETRA - B: 2680 (3) PETRA - C: 1129	n/a	(1) PETRA - A: 274 (2) PETRA - B: 143 (3) PETRA - C: 60 Cost per DALY (US$)
(Wilkinson, Floyd et al. 1998)	(1) ACTG 076 with breastfeeding, delivered within current infrastructure: 5806 (2) ACTG 076 without breastfeeding delivered through enhanced infrastructure: 5591 (3) PETRA - A delivered through enhanced infrastructure: 2492 These are not incremental costs. Incremental costs ranged from 828-5468 per infection averted.	(1) ACTG 076 with breastfeeding, delivered within current infrastructure: (205, 356) (2) ACTG 076 without breastfeeding delivered through enhanced infrastructure: (198, 343) (3) PETRA - A delivered through enhanced infrastructure: (88, 153) (All expressed as 3% discount rate, 6% discount rate). Not incremental costs.	n/a
(Marseille, Kahn et al. 1999)	(1) HIVNET 012 (targeted): 298 (2) HIVNET 012 (universal): 138 (3) PETRA - A: 2781 (4) PETRA - B: 1265 (5) CDC Thai (targeted):1109	n/a	(1) HIVNET 012 (targeted): 11.29 (2) HIVNET 012 (universal): 5.25 (3) PETRA-A: 105.31 (4) PETRA-B: 47.92 (5) CDC Thai (targeted): 41.76 Cost per DALY (US$)

Study	Cost (US$) per infant HIV infection averted	Cost (US$) per life year gained	Cost (US$) per QALY or DALY gained
(Soderlund, Zwi et al. 1999)	**Total Deaths Averted)** (1) FF recommended from birth: 3600 (2) FF recommended from 4 months only: 4700 (3) FF recommended from 7 months only: 20,052 (4) FF recommended and supplied: 5967 (5) ACTG076 regimen: 2441 (6) PETRA-B regimen: 252 (7) CDC Thai regimen: Cost Saving (CS) (8) CDC Thai regimen + FF recommended: CS (9) CDC Thai regimen + FF supplied: 669	(1) FF recommended from birth: 200 (2) FF recommended from 4 months only: 258 (3) FF recommended from 7 months only: 1111 (4) FF recommended and supplied: 331 (5) ACTG076 regimen:134 (6) PETRA -B regimen: 14 (7) CDC Thai regimen: CS[1] (8) CDC Thai regimen + formula recommended: CS (9) CDC Thai regimen + formula supplied: 37	n/a
(Stringer, Rouse et al. 2000)	(1) Early HIVNET 012 (targeted): 853 (2) Early HIVNET 012 (universal): 834 (3) Labour and delivery maternal NVP (Universal): 977 (4) Universal Infant-only therapy = no maternal dose, but immediate postpartum treatment of all infants: 834	From $4-$115 for the strategies evaluated	n/a

Study	Cost (US$) per infant HIV infection averted	Cost (US$) per life year gained	Cost (US$) per QALY or DALY gained
(Wilkinson, Floyd et al. 2000)	Cost per infant infection averted: US$1460* ..... *This was converted from 1997 South African Rands (6724) to 1997 US$.	n/a	Cost per DALY: US$ 14* *This was converted from 1997 South African Rands (213) to 1997 US$.
(Wood, Braitstein et al. 2000)	n/a	(1) 25% HIV+ pregnant women and infants would receive ART:19 (2) 75% HIV+ pregnant women and infants would receive ART:19 (3) 100% ART provided to all pregnant women (HIV+ve and HIV-ve):133 (4) Triple-combination antiretroviral treatment of 25% of non-pregnant HIV-1-positive adults:15000	n/a
(Rely, Bertozzi et al. 2003)	(1) 4% VCT to pregnant women + ACTG 076 or HIVNET012: $67,089 or NVP: $86,420 (2) 85% VCT to pregnant women + ACTG 076 or HIVNET012: $62,900 or NVP: $86,323 (3) 30% VCT to pregnant women at highest risk + ACTG 076 or HIVNET012: $39,220 or NVP: $53,267. (4) VCT to HIV+ pregnant women + ACTG 076 or HIVNET012: $41,758 or NVP: $56,262. (5) VCT to HIV+ pregnant women and to 15% of late presenters + ACTG 076 or HIVNET012: $42,516 or NVP:$57,132	n/a	n/a

Study	Cost (US$) per infant HIV infection averted	Cost (US$) per life year gained	Cost (US$) per QALY or DALY gained
(Sweat, O'Reilly et al. 2004)	Botswana: 1808 Ivory Coast: 9258 Kenya: 4292 Rwanda: 1868 Tanzania: 2284 Uganda: 4857 Zambia: 2566 Zimbabwe: 3573	n/a	Botswana: 58 Ivory Coast: 310 Kenya: 140 Rwanda: 66 Tanzania: 77 Uganda: 168 Zambia: 86 Zimbabwe: 115 Cost per DALY
(Maclean and Stringer 2005)	n/a	n/a	(1) UC[8] + BF for 6 months: 1.81 (most cost effective) (2) UC + BF for 12 months: 1.83 (3) UC + BF for 6 months + daily infant NVP: 3.01 (4) VCT + Maternal 3-drug ART during pregnancy + 3-drug ART during 6 months of BF: 2.76 (5) Same as (5), but only for women with CD4<=200: 2.28 (6) UC + FF for 12 months: 3.33 Cost per QALY

Study	Cost (US$) per infant HIV infection averted	Cost (US$) per life year gained	Cost (US$) per QALY or DALY gained
(Teerawattananon, Vos et al. 2005)	(1) 1 or 2 VCT + ACTG 076: 716 & 1740 (2) 1 or 2 VCT + HIVNET 012: 851 & 1776 (3) 1 or 2 VCT + ACTG 076 (early ANC attenders) or HIVNET 012 (late ANC arrivals): 570 & 1381 (4) 1 or 2 VCT + ACTG 076 + HIVNET 012: 556 & 1266	n/a	n/a
(Manoj, Stephen et al. 2006)	(1)Universal screening in all states +HIVNET 012: Rs.25,787* (2)Universal screening in the six highest prevalence + HIVNET 012: Rs.12,091* * Reported in Indian Rupees	(1)Universal screening in all states +HIVNET 012: Rs.1935* (2)Universal screening in the six highest prevalence + HIVNET 012: Rs.907* (Cost per year reduction in PYLLs)	n/a
(Reynolds, Janowitz et al. 2006)	(1) Family planning programs(contraceptive use): 663,47 (2) VCT + HIVNET 012 (15% coverage): 856.66	n/a	n/a

Study	Cost (US$) per infant HIV infection averted	Cost (US$) per life year gained	Cost (US$) per QALY or DALY gained
(Soorapanth, Sansom et al. 2006)	n/a	n/a	(1) VCT (at 20 and 28 weeks) + ACTG 076 (from 28 weeks) + plus HIVNET 012 with ART: CS (2) VCT (at 20 and 28 weeks) + ACTG 076 (from 28 weeks) + plus HIVNET 012 without ART: 62.25 (3) VCT (at 20 and 34 weeks) + ACTG 076 (from 34 weeks0 + HIVNET 012 with ART: CS (4) VCT (at 20 and 34 weeks) + ACTG 076 (from 34 weeks) + HIVNET 012 without ART: 0.5 (5) VCT (at 20 and 36 weeks) + HIVNET 012 with ART: CS (6) VCT (at 20 and 36 weeks) + HIVNET 012 without ART: 12.34 per QALY saved
(John, Farquhar et al. 2008)	Not given	n/a	(1) Couple VCT: 15.39 (2) Individual VCT: 15.34 per DALY saved

[1]CS = Cost saving

CHAPTER 5. DISCUSSION

The purpose of this review was to identify available evidence on pMTCT of HIV /AIDS in developing countries. With maternal HIV prevalence rates and vertical transmission rates reaching about 30% in some areas, coupled with the ever growing challenges of limited healthcare resources in low and middle income countries, cost effective pMTCT interventions represent a sustainable approach to identifying those strategies that represent value for money as we attempt to contain the epidemic.

Our review identified 16 full economic evaluations of pMTCT for HIV /AIDS studies in developing countries published between the years 1996 to 2008 with over 80% of these carried out in sub-Saharan Africa. Interest in carrying out analysis of cost and outcome of pMTCT strategies seemed to peak from 1996 to 2000 with nine of the studies published within this period. This can be attributed to the fact that globally, the spread of HIV appears to have peaked during the mid 1990s, generating more research interest.

5.1. Methodology.

By failing to clearly describe the context, the population, the economic model (s), the regimen etc, in detail, authors left room for interpretations and speculations on their methodology. There was a conspicuous absence in reporting of the model used for the economic analysis in most of the studies, and even in studies were the modelling approach was reported, its completeness was consistently questionable. A majority of the authors omitting to clearly describe the methods used to estimate the input cost values or to justify the choice of computed assumptions, which has the effect that the studies are not reliably reproducible.

This can be attributed partly to the fact that peer reviewed journals impose space limitations for articles submitted for publication. A few articles (3) addressed this shortcoming by providing an external website or link that contains details of methodologies and various costs and effectiveness tables.

5.2. Cost Estimates and Effectiveness Parameters.

Most of the cost data presented did not reflect the perspective chosen, as the authors failed to measure all the relevant costs in relation to the viewpoint from which they were analysed. These omissions make it hard to assess the reliability and transparency of the cost data due to the fact that intervention costs may have been underestimated leading to an over-estimation of cost-effectiveness and vice-versa.

This review shows that different pMTCT interventions vary considerably in their costs, as well as in their effectiveness or utility. We found substantial heterogeneity in the value(s) of major cost(s) across the studies. There was a variation in the reported drug costs, in costs incurred for voluntary counselling and testing, and in costs of formula food. These variations in costs between different geographic locations suggest that generalising the results from one country or region to another maybe of concern since economic, epidemiological and behavioural factors vary from one region to another.

There was an acceptable homogeneity in the values reported for effectiveness parameters. This can be explained by the fact that the information sources from which these base case values were obtained were similar especially throughout sub-Saharan African studies. Similar values were presented for the following key parameters; maternal HIV prevalence, vertical transmission rates, percentage of women who breastfeed, life

expectancy, expected drug efficacy, acceptance of HIV testing, and adherence to treatment. However, in the majority of cases, the studies failed to explain the methods through which these input parameters were computed in order to obtain effectiveness outcomes in terms of number of infant HIV infections averted, QALY or DALY. This was particularly the case in cost-utility studies where the methods used to value the health states of participants were not clearly disclosed.

We recorded a mean HIV testing acceptance rate of around 75% overall. This can be attributed mainly to the fact that in developing countries, several women decline HIV testing as well as due to staffing and space limitations. Compounding this concern is the fact that of those women who did accept testing and had positive HIV results, only about half do return to clinics to receive ART. This demonstrated a need for community mobilization, educating and empowering women to mitigate attrition, as well as improving staffing conditions and personnel training to increase human resources availability.

The sources of the data used for modelling the analysis were primarily Randomized Controlled Trials (RCT) which represents the best source of unbiased efficacy data. However, one of the major limitations of RCT's is that the resources used, and the results obtained are not readily generalisable outside the trial settings into the local population due to the fact that monitoring of study, of resource utilization and of study subjects, coupled with close supervision in RCT's, takes away the reality in the outside world .

Also, it is recommended that economic evaluations should be carried out alongside clinical trials because is an efficient way of getting valid and reliable information with minimum assumptions made during data collection, and it presents timely information on

both the effectiveness and cost-effectiveness of alternative treatments to inform their evidence based practice (Jain and Arora 2000; Barrett and Byford 2009). In our identified economic analysis studies, none was reported to have been carried out alongside the pMTCT intervention(s) they were evaluating. This can be possibly explained by the fact that setting up and conducting an economic evaluation alongside an RCT is often time consuming and in the case developing countries, expensive and unaffordable.

5.3. Comparability of studies.

It was difficult for us to carry out a direct comparison across studies because they differed in their target populations, in the pMTCT strategy being analysed, and in the economic evaluation techniques utilized. Different authors vary in the models they use which have different structures and assumptions. They also vary in the outcomes parameters they chose to include or exclude in their analyses. Even in cases where the same regimen was analysed, these model-level differences led to different results and conclusions.

Due to its highly heterogeneous nature, it was impossible to standardize the cost data (cost year, discount rate, intervention unit and total costs, productivity costs etc) across the studies in order to make them comparable. Variations in the input costs and effectiveness parameters used in the base case analysis, variations in price structures between different settings, and reduction in drug prices through the 12 years (1996-2008) during which the selected studies were published, made it impossible to pool the data for comparison.

5.4. Cost-Effectiveness / Cost-Utility Interventions.

There are 2 established official guidelines for acceptable benchmarks in cost-effectiveness or cost-utility analysis in the context of developing nations. The 1993 World Development Report (World Bank 1993) recommended a willingness to pay of $50 per life-year gained as a reasonable benchmark for developing countries. For Disability Adjusted Life Years (DALY), we evaluated study results based on the World Health Organisation-CHOosing Interventions that are Cost-Effective (WHO-CHOICE) standards. CHOICE is a WHO tool developed to assist policy makers in determining which health interventions are cost-effective based on specific country settings. CHOICE uses the Gross Domestic Product (GDP) per capita as an indicator and it divides cost effectiveness into 3 categories; very cost effective if the DALY averted is less than the country's GDP per capita; cost-effective if the DALY averted is between 1-3 times the country's GDP per capita; and not cost effective if the DALY averted is greater than 3 times the country's GDP per capita (WHO website). Therefore interventions meeting these very cost-effective and cost-effective benchmarks should be given priority and implemented first before other less cost effectiveness strategies are considered.

In general regimens that met these benchmarks were: twice daily maternal zidovudine and lamivudine (intrapartum and postpartum), short course maternal zidovudine (ZDV), ZDV with formula recommended or supplied, universal or targeted single dose nevirapine (maternal and infant) and exclusive breast feeding for 6 months with provision of ART. Interventions targeting the intrapartum period were found to be most cost effective for two reasons: firstly because of the high proportion of pregnant women who present to

the delivery ward without prior antenatal care or ART and secondly because of the relatively high proportion of transmission that occurs during this period.

In the case of single dose NVP to the mother and child, studies noted that due to the low cost of this drug, it is the VCT component that renders pMTCT strategies unaffordable in certain settings. This leads to suggestions that in high prevalence settings like sub-Saharan Africa, eliminating the VCT component altogether and providing NVP to all willing pregnant women can potentially increase cost-effectiveness. On the flip side, universal provision of ART (mass therapy) without testing was found to be non cost-effective because of poor adherence to treatment if the woman is unaware of her HIV status. In any case, provision of universal NVP should be recommended only if its long term safety and issues related to drug resistance are established, which is still a topic of debate.

In the same vein, universal counseling and testing if found to be affordable should be promoted as it is more likely to be widely accepted because less stigma will be associated when all pregnant women are been offered testing. Unlike in a targeted testing program, a universal program if offered to all pregnant women can help avoid problems of discrimination, partner abuse, and desertion. Also counseling and testing the mother and her partner together (couple counseling) can have the benefits that in couples where the mother is HIV negative, acute acquisition of HIV during late pregnancy or breastfeeding can be prevented. At the same time, sexual behavior may be modified in couples finding out that they are both HIV negative.

In order to minimize the total cost of the interventions in low prevalence settings like Mexico, India and Thailand, studies reported that VCT costs rather than drug costs should be the focus of analysis, and it was suggested that programs should explore less costly ways to implement VCT.

Infected women aware of their HIV status had a much higher chance to bottle feed their infants than those who are unaware. So when alternatives to breastfeeding were included as an element of these strategies, this resulted in a greater effectiveness, but a lower cost-effectiveness due to costs, and duration of formula feeding. Almost all mothers breastfeed in developing countries, breast milk has a protective effect against other infant infections and a high proportion of mothers will acquire HIV during breastfeeding. Our review found that various breast feeding strategies with provision of ART to lactating mothers in developing countries recorded cost-utility values in terms of maternal and infant QALY that fall within acceptable benchmarks.

Providing ART to these HIV-infected breastfeeding mothers is very expensive and unaffordable under developing country budgets, therefore a substantial decrease in drug prices or ART donation by manufacturers was suggested as a feasible alternative. Additionally, leaving the cost of formula feeding at the expense of the mother will substantially reduce program costs. However, program effectiveness will also be compromised due to families being unable to sustain provision of formula feed, thereby resorting to breastfeeding with its associated risk of transmission.

Despite the growing amount of literature on mode of delivery and MTCT of HIV, there is no consensus on the effects of elective as compared to emergency cesarean section on vertical transmission. Cesarean section, though recommended as a practice to avoid vertical transmission of HIV, has had a widespread usage mainly in developed countries but is a very limited practice in developing countries. Of all the studies, only the one carried out in Mexico mentioned cesarean section as a strategy but the results did not present it as a cost effective strategy. Other difficulties in providing emergency cesarean section in developing countries can be linked to lack of trained personnel, coupled with the fact that most women deliver away from healthcare facilities.

The studies did not include in their analysis any external benefits derived from the pMTCT interventions like prevention of adult- to- adult transmission, improved maternal health or decreased cost of orphan care associated with increased maternal longevity. It is stated that prolonging the life of the children born to HIV infected women requires lengthening the survival of their mothers (Nduati, Richardson et al. 2001; Kurewa, Gumbo et al. 2009).

It was in line with this view that in 2001, as a direct response to the Declaration of Commitment on HIV/AIDS by the United Nations General Assembly, a new program called MTCT-plus was conceived. The objective of MTCT-plus was to provide lifelong care and treatment to every family member infected or affected by HIV/AIDS in resource-limited settings. Recognizing the important role that women and mothers play within their communities; it was intended to build on and modify the existing pMTCT strategies that until then did not focus on providing lifelong care and treatment to pregnant women and mothers.

The MTCT-plus model was initially implemented in 14 clinical sites throughout sub-Saharan Africa and Asia. Its fundamental elements are to provide integrate services in clinical care and prevention, accessibility to ART, nutrition, family planning, education and counseling, prevention of opportunistic infections, early management of complications, as well as other essential forms of supportive care. By 2007, MTCT-plus had provided over 13,000 adults and children with life saving care and treatment and rendered tremendous contributions to preserving families (ICAP ; Mitka 2002; Rabkin 2003). This model program for family based care is basically an upgraded version of pMTCT programs which includes strategies aimed at increasing the life years gained and improving the quality of life of HIV positive mothers.

However all the studies that we reviewed analyzed the benefits of pMTCT interventions conceived uniquely in baby-centric terms. PMTCT is a complex intervention with more far-reaching effects not only for the child but for the mother as well. It would have been interesting to include as a component in their studies, a holistic analysis of the costs and effects of improving maternal health and quality of life of mothers.

Some cost effective regimens found to represent value for money elsewhere, when applied to other contexts were not found to meet acceptable contextualized thresholds. This may be due to different national Gross Domestic Product (GDP), health expenditure budgets, HIV prevalence, local drug costs and needs to enhance infrastructure for implementation in these other settings. These contextual variations can clearly be illustrated by the studies carried out by Sweat et al (2004) where the same regimens were analysed in

8 different countries in sub-Saharan Africa, but found to meet an acceptable benchmark in only 4 of these nations.

5.5. Quality of studies.

By using an established instrument, the British Medical Journal's (BMJ) guidelines for Economic Evaluations in Healthcare to evaluate the quality of the retained studies, we highlighted lack of uniformity in analysis, poor design and inadequate technical quality in a majority of the studies. This paucity in high quality studies, suggests that the economic evaluations analyzed in this review did not follow appropriate guidelines in their analysis like those set out by the Canadian Agency for Drugs and Technologies in Health (CADTH), the BMJ and elsewhere.

However, it is interesting to note that the BMJ checklist did not allow us to record some important aspects of study quality, such as whether there were mistakes in the studies, or to document the quality of sensitivity analyses. Also, the BMJ checklist does not have a weighted point value that permits one criteria to carry more weight over another. However, it seems that some criteria, such as whether a model was clearly described, are of central importance and should carry more weight. This would have provided a quantitative overall quality score for the identified studies to allow them to be appraised in a more reliable fashion and better judge their relative quality.

5.6. Strengths and weaknesses of our review.

All through the conduct of this review, we applied consistent and validated methods for undertaking systematic reviews in healthcare (Cochrane Collaboration and NHS - Centre for Reviews and Dissemination) and subjected the identified studies through a rigorous quality assessment.

On a bi-monthly basis and throughout writing this review up until its submission, we ran a current search of all relevant databases using appropriate search strategies to ensure that recent publications were retrieved and included.

One of the strengths of our review was that we initiated contact with some of the authors to clarify some study details, unclear methodologies or results. An associated weakness here is the fact that not all of the authors replied to address our inquiries.

We excluded all studies not published in English and searched only English language databases. This is a limitation which could be the reason why we only retained 15 articles; with Asia having 2 articles, and Latin America having only 1 article. Even though we carried out an exhaustive English language search, as per systematic review guidelines set out by the Cochrane Collaboration, chances that we missed out on some relevant article(s) cannot be overlooked.

We did not perform a meta-analysis of the studies or pool them for their relative comparability. Due to the heterogeneity of the data that we had, our systematic review was analyzed as a narrative synthesis of evidence. The quality assessment revealed important methodological flaws for some studies. In light of our taking a narrative approach to data synthesis and the fact that only a small number of studies exist on this topic, we chose not

to exclude methodologically weaker studies from consideration and to review them on an equal footing with other studies. However, in principle, we should have less confidence in their findings.

With the difficulty and cost to carry out economic evaluations in developing countries, input parameters used in the studies to estimate costs and effectiveness data were generally pooled from previous studies carried out within different contexts with different populations. Even though this data should be interpreted with caution, all the authors carried out a sensitivity analysis and varied the parameters over a range of values in order to address this shortcoming.

CHAPTER 6. CONCLUSIONS

It is interesting to note that pMTCT interventions usually apply to mothers who deliver within healthcare facilities. None of the studies selected for this review took into consideration women who deliver under other practices like at home for example or with a traditional healer. Future studies in developing countries should be culturally sensitive and incorporate this proportion of women in their analysis.

Since cost-effectiveness is a relative term, absolute statements that one intervention is more cost effective than another, should be viewed with caution. The results of economic evaluations analyzed in this review varied based on the following factors: HIV prevalence, country income classification, available resources and staff costs especially for counseling and testing, program setting (urban or rural), and ultimately costs of the interventions, especially drug prices. Drug costs were an important source of variation in differing conclusions among the studies and represented the major cost item.

Considering that drug prices have significantly dropped since the publication of these studies, considering that treatment options have significantly evolved, and also due to the fact that adherence to testing and treatment has improved as antiretroviral become readily available, further research in economic evaluations is required in order to draw appropriate up-to-date conclusions. Although clinical studies on pMTCT of HIV are constantly evolving, there is a dearth in corresponding economic evaluations to these studies. This makes it difficult for decision makers who rely in part on the results of these

clinical studies and the outcome of the economic evaluations in order to propose an up-to date cost-effective option.

We found that interventions that are effective and enhance health benefits, especially in regions where HIV prevalence is high, are those in which: attendance rate of Ante Natal Care (ANC) and screening programs is high, begins early on in pregnancy, mothers adhere to testing and are compliant to therapy. One should consider the advantages of early ANC such as: provision of VCT services early on, early detection and identification of pregnant women who need ART, and counseling for infant feeding options.

Some of the studies stated that the largest expense to scale up pMTCT interventions is costs to enhance the health system especially as health systems in developing countries are severely limited in their capacity to provide VCT, ART and other administrative functions. The costs to improve infrastructure and facility capacity should be taken into account when attempting to scale up interventions. In some developing countries like South Africa, there is an acceptable capacity and infrastructure available to carry out VCT and ART interventions. However, an efficient implementation of these pMTCT strategies in the vast majority of developing countries require substantial extra effort in health system expenditure and enhancement in order to provide a reasonable service.

Designing pMTCT interventions should allocate additional resources for babies saved from HIV infection, as they eventually become orphans in impoverished families. Unlike children born to HIV uninfected parents, these children will not thrive and survive under relatively similar conditions. Allocating resources to sustain the long term benefits of

the pMTCT should be a component of the interventions, but so far there has been no recorded data. This expansion in health expenditure was not found to be feasible in developing countries considering widespread national budgetary constraints; suggesting the need for external funding to be acquired. These costs can be offset by productivity gains to the society from infants born free of HIV. The long term economic, social and health system benefits, as well as infant care avoided as a result of successful pMTCT interventions have not yet been quantified in developing country settings.

Benchmarks for favorable cost-effectiveness ratios are context-specific, and these thresholds and willingness to pay, serve as guidelines when choosing among alternative interventions. However, they vary worldwide based on numerous situation-specific factors such as available resources, competing interests, and issue priority. In the case of HIV prevention in general and pMTCT in particular, other factors are equally vital during decision making such as human rights, health equity, socio-cultural and religious matters.

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APPENDIX A

MeSH used on Pubmed:

"Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Program Evaluation"[Mesh] "Cost Effectiveness"[Title] OR "Cost utility"[Title] OR "Health Care Economics and Organizations"[Mesh]) AND "HIV Seropositivity"[Mesh] OR "HIV"[title] OR "HIV"[Mesh] OR "Acquired Immunodeficiency Syndrome"[Mesh] AND "Disease Transmission, Vertical"[Mesh] OR "pmtct"[Mesh] OR "PMTCT"[Title].