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MOTHER-TO-CHILD-TRANSMISSION Of HIV

A Guide for Health Workers and HIV/AIDS Trainers

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Note:
A paper on the cost effectiveness of MTCT Prevention can be obtained from Nathan Geffen, or downloaded from http://www.tac.org.za/mtctcost.rtf

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Abbreviations used in this Guide:

MTCT	Mother-to-Child-Transmission
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
STI	Sexually Transmitted Infections
STD	Sexually Transmitted Disease
VCT	Voluntary Counselling and Testing
ART	Anti-retroviral Treatments
ARV	Anti-retrovirals

Useful Terms:

CD4+	The CD4 count roughly reflects the state of the human immune system
DNA	*Deoxyribonucleic acid* - molecules that encode genetic information.
RNA	*Ribonucleic acid* - molecules that encode genetic material
in utero	Foetus inside the mother's womb
post partum	after birth
Prophylaxis	Medication that prevents illness from developing
3TC	*Lamivudine* – an anti-retroviral medicine
AZT	*Zidovudine* – an anti-retroviral medicine
Nevirapine (NVP)	Anti-retroviral medicine
Vertical Transmission	HIV infection from mother to her infant
Micronutrient	Essential vitamins
Serostatus	A person's HIV status
Prevalence	The total number of people infected with HIV
Incidence	The rate of new infections
Epidemiology	The study of the spread of an epidemic

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INTRODUCTION

Did you know that…..

- HIV infection has become the most common pregnancy complication in a number of countries including SA?
- Over 90% of all HIV infections in children result from mother-to-child transmission?[i]
- At current estimates, nearly 600,000 children are infected by mother-to-child transmission of HIV every year
- Over 70 000 children will be infected by MTCT in SA in 2001

It is clear that MTCT poses an important and dangerous threat to the well being of women, their children, their families and to society as a whole. Yet, it is important to note that this threat can be limited and contained. A number of methods and approaches to the prevention of vertical transmission have been developed and have been used successfully in various parts of the world. This guide contains the most convincing studies and best practices of prevention.

A guide to mother-to-child transmission of HIV brings together the latest scientific and medical facts on MTCT. It presents the central concerns of the factors impacting on vertical transmission, while setting out various strategies of prevention with demonstrated experiments and trials. This guide then makes recommendations on suitable prevention programmes for South Africa. It also contains procedures of implementation and the projected costs associated with such programmes.

EPIDEMIOLOGY

In South Africa the prevalence of HIV in women attending antenatal clinics has risen from 1% in 1990 to 23% in 1998. The ante-natal survey conducted in October 2000 and released by the Department of Health in February 2001 show a 24.5% (1999 = 22.4%) national prevalence rate among women attending antenatal clinics in the public health services in South Africa. This survey projects that there are approximately 4.68 million (1999 = 4.2 million) people in South Africa living with HIV/AIDS.[ii]

One in every three children whose mothers have HIV will also become infected with the virus.[iii] In order to understand the complexities involved in typical prevention strategies, one has to become familiar with the epidemiology of HIV and what influences the spread of the virus from mother to infant.

MOTHER TO CHILD TRANSMISSION

There are three ways in which mother-to-child transmission of HIV can occur:

- in utero (in the womb)
- during labour and delivery
- post partum (after birth), particularly via breast milk

Ways in which HIV is not spread to the baby

- Not with sperm during conception
- Not with sperm during pregnancy

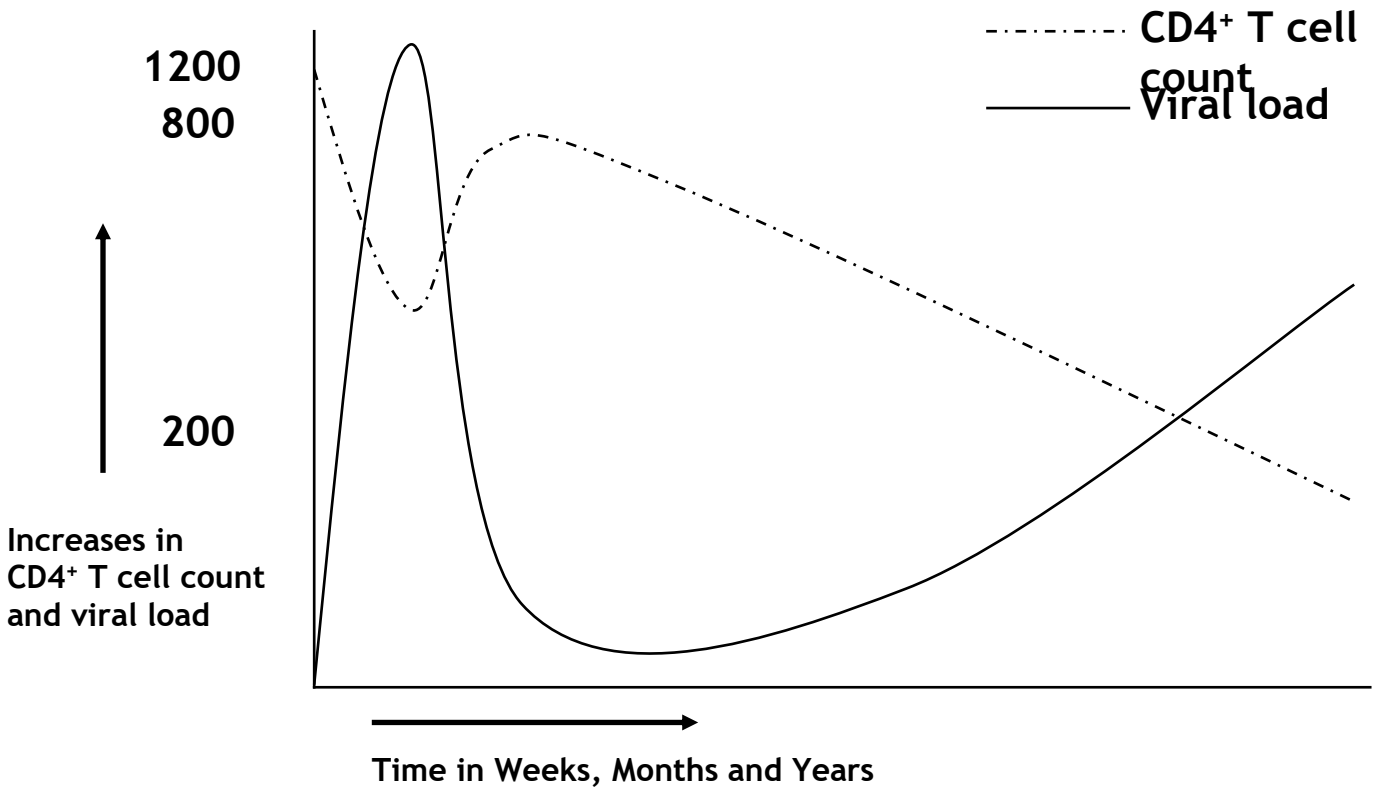
- There is no direct contact of the mother's blood with the foetuses/babies blood. Although the foetus in the womb gets its nutrition from the mother's blood, its blood and the mother's blood actually never mix.

Only a small minority of children actually get HIV in the womb. The foetus is surrounded by an amniotic bag which protects it against HIV. Only when this bag breaks during labour (the "water breaks") or when the afterbirth starts tearing from the womb is the baby at increased risk.

The majority of infants are infected late in pregnancy, during or immediately after delivery.

The length of time that a mother has carried the virus also has an impact on MTCT. When a mother has recently been infected with HIV, the risk of transmission through breastfeeding may be twice as high (29%) as the risk posed by a woman with an established infection (15%). This is probably due the high viral load associated with recent infection.

The following figure shows the high viral load in the early stage of HIV infection which may increase the chance of verticle transmisson.



FACTORS INFLUENCING VERTICAL TRANSMISSION

The factors that influence transmission rates will be discussed under five headings. A list of what these factors entail and a brief elaboration of the relevant key points, follows:[iv]

Viral

- viral load
- viral genotype and phenotype
- viral resistance

Viral load is the most important factor. Chances of transmission are increased when the mother has a high viral load.

One study shows that women with a measurable viral load were six times more likely to transmit the virus to their infants than women who had undetectable virus levels.[v]

There may also be changes in disease progression according to the viral strain transmitted from mother to child. Possible viral resistance to certain anti-retroviral treatment administered during pregnancy may result in higher transmission rates amongst women who have subsequent children.[vi]

Maternal

- immunological status
- nutritional status
- clinical status
- behavioural factors
- anti-retroviral treatment
- breast infections[vii]

While a decreased *immune status* of the mother does not directly influence the rate of HIV transmisson, it does ussually indicate advanced disease progression and this again often goes together with a high viral load, which is the main factor influencing vertical transmission.

Nutritional factors also play a factor: low vitamin A levels suggest the likelihood of higher transmission between mother and child, as well as an increased viral load count in breast milk. *Anti-retroviral treatments* and *breast infections* will be discussed at greater length below.

Obstetrical

- prolonged rupture of membranes
- mode of delivery
- intrapartum haemorrhage (internal bleeding during birth)

- obstetrical procedures
- invasive foetal monitoring

Prolonged rupture of membranes (over 4 hours) has been associated with increased risk of transmission, whilst in some studies Caesarean section delivery has been associated with a reduction in transmission rates.[viii] Invasive diagnostic procedures before birth should be avoided, as should any procedure during birth that breaks the baby's skin or increases contact with the mother's blood. Vasectomies should be avoided by all means. If assisted labour is necessary a forceps assisted delivery is better than a vacuum. Obstetrical factors as well as the mode of delivery are further elaborated later in this document under strategies for preventing MTCT.

Foetal

- prematurity
- genetic
- multiple pregnancies

Premature infants have higher reported rates of infection. If twins are delivered vaginally the first-born has a higher infection rate than the second. Women with low CD4+ counts are also more likely to have preterm deliveries.

Infant

- breastfeeding
- gastrointestinal tract factors
- immature immune system

The role of breastfeeding in MTCT has already been mentioned and will be discussed in more detail later on.[ix] With regards to breastmilk, decreased acidity, and the state of the mucus and lining of the newborn child's gastro-intestinal tract can also assist transmission.[x] The newborn child's immune system may also experience deficiencies in T-cell immune response, increasing the likelihood of infection.

2
STRATEGIES FOR PREVENTION OF MTCT OF HIV

Voluntary Counselling and Testing (VCT)

On 10 December 1999 the South African government released its 'National Policy on Testing for HIV'. It sets out the circumstances under which HIV testing may be conducted, the importance of informed consent and of pre- and post-test counselling.[xi] This policy states that voluntary testing and counselling should be available to all pregnant woman who request it and that all pregnant women should be made aware of this option.[xii] Counselling models also need to move beyond the individual to include the family and wider community. This will ensure that sustainable support for people with HIV-1 is developed and will decrease discrimination against people living with HIV/AIDS.[xiii]

In 1997 the AIDS Law Project drafted a 'Recommended Code of Best Practice on Pregnancy and HIV'. This document points out that *reproductive autonomy* is a precondition for women to realize other fundamental rights, such as equality, dignity, and privacy.

Women have the right to information that will help them make informed decisions about their reproductive lives, particularly on the issues of safer sex, nutrition, support networks, alternative or experimental therapies, termination

of pregnancy and medical interventions to reduce MTCT. This information should contain a clear explanation of the risks and advantages of breastfeeding as well as the facts on availability, efficacy, cost, and the risks involved in alternatives to breastfeeding.

Women have the right to refuse an HIV test for themselves and their infant(s). They can also refuse that any medical procedures be performed on their own bodies or those of their infant(s). Women have the right to pre- and post test counselling, as well as ongoing counselling. They also have the right to decide whether their partners may take part in this process.

It must be noted that a recent study in three developing countries found that the proportion of individuals and couples reporting unprotected intercourse decreased significantly for those actively involved in the processes of VCT. [xiv] Knowing their HIV status empowers individuals to plan and make important life decisions - decisions about care and support of themselves and others, reducing the risk of transmitting the virus to others, breastfeeding and family planning. The study concluded that VCT is as cost-effective a measure as enhancing STD services or universal provision of nevirapine for pregnant women in high prevalence areas. The study noted that a powerful impact could be made if governments were willing to allocate and distribute funds for these initiatives.

Termination of Pregnancy[xv]

Termination of pregnancy should be seen as an option elected by each individual woman, and *not* as a public health intervention for the prevention of transmission of HIV. Proper counselling should be provided to all pregnant women who are living with HIV, and they should be informed of all the options available to them. The offer of termination must never be coercive, as all

women, regardless of their HIV status, have the right to choose the extent of their reproductive life and to be fully informed about the implications.

Termination of pregnancy can be done on demand of the client until 13 weeks of pregnancy, however for medical reasons (including HIV) it can be done up to 18 weeks of pregnancy. After 13 weeks the procedure usually has to be done at a hospital and not at a clinic.

Therapeutic interventions

- Anti-retroviral therapy
  - AZT (alone or in combination, long or short regimen)
  - Nevirapine
- Vitamin A and other micronutrients
- Immunotherapy
- Treatment of Sexually Transmitted Infections (STIs)

Nutrition

In most developing countries, women have a general tendency toward micronutrient deficiencies. Within the context of pregnancy, a deficiency in the intake of Vitamin A is of particular concern. Vitamin A has significant effects on immune response[xvi] and mucosal tissue protection, both of which are vital issues throughout any term of pregnancy. Within this context, Vitamin A supplementation has been examined as a potential option in reducing MTCT through breast milk. This is because the absence of Vitamin A in the mother impairs her immune system and could therefore lead to an increase in her viral load. Vitamin A may also impair the integrity of the inner surfaces of the vagina, cervix and nipples - all of which may facilitate HIV transmission.[xvii]

A study of 338 pregnant women with HIV in Malawi found that the relative risk of transmitting HIV to infants increased with less serum Vitamin A.[xviii]

Vitamin A deficiencies were associated with a three to fourfold increased risk of MTCT. However, it should be stressed that subsequent studies have failed to show a similar effect of Vitamin A supplementation on MTCT. Nevertheless, a recent trial in Tanzania showed that multivitamin supplementation in pregnant women with HIV decreased the risk of low birth weight by 44%, severe preterm birth by 39% and a small size at birth by 43%. Vitamin A supplementation had no effect on these variables. Multivitamin supplementation, but not Vitamin A alone, resulted in increases in CD4+, CD8 and CD3 counts.[xix]

The South African Vitamin A Study Group compared placebo versus supplements in the third trimester of pregnancy. The results from 728 women showed no significant differences in HIV transmission or foetal or infant mortality rates. [xx] Women receiving Vitamin A supplements were however less likely to have preterm deliveries (11.4% vs. 17.4 % in placebo group) and among the early deliveries those assigned to the Vitamin A group were less likely to be infected (17.9% vs. 33.8%). It should also be noted that some studies suggest that Vitamin A could cause physical defects in the foetus.[xxi]

Obstetric Interventions and Mode of Delivery

- Avoidance of invasive tests
- Birth canal cleansing
- Caesarean section delivery

Vertical transmission of HIV often occurs during labour and delivery. Caesarean sections are a valuable and proven method in significantly reducing the risk of transmission. This is borne out by the fact that in South Africa, medical schemes are providing a programme of care for HIV infected mothers that allows them to choose Caesareans along with anti-retroviral therapy (ART). Women, who undergo elective Caesarean sections that take place in the pre-interpartum stages, benefit from a significant reduction in the risk of

transmission. *This reduction can be as much as 50%* after adjusting for ART, birth weight and the stage of HIV infection of the mother.[xxii]

The effectiveness of Caesarean sections is reduced if the operation is carried out after commencement of labour or after the rupture of membranes has already taken place. As a result, emergency Caesarean sections do not carry the same level of effectiveness in decreasing the risk of transmission.

The preponderance of studies concludes that combining elective Caesarean sections with drug therapy is the most effective method of reducing vertical transmission.[xxiii]

Whilst Caesarean sections (as surgical interventions) carry risks to the mother and infant, *elective* Caesarean sections reduce the latter risk.[xxiv] The benefit to the mother of conducting surgery has to be weighed against the risks generally associated with surgical interventions – risks that are significantly increased by a compromised immune system.

Modification of Infant Feeding Practice

- The choice to avoid breastfeeding
- Early cessation of breastfeeding
- Heat treatment of expressed breast milk
- Exclusive breast feeding rather than mixed feeding

Breastfeeding remains one of the most effective ways to improve the chance that a child will survive in unfavourable conditions. This is because breast milk provides for the infant's fluid and nutritional requirements, as well as growth factors and antibacterial and antiviral agents that protect the infant from disease. In poor, developing countries where hygiene and sanitation are often inadequate and access to health care is limited, infant mortality is primarily

due to infectious diseases such as diarrhoea and pneumonia. Under such conditions, artificial feeding can put infants at tremendous risk.

Breastfeeding accounts for 15% of MTCT of HIV, depending on the duration of breastfeeding after birth.[xxv]

Factors that may increase transmission of HIV through breast milk include:

- *recent infection* in the mother during either pregnancy or the breastfeeding period (this is itself a period that is associated with higher maternal viral load)[xxvi]
- *poor breastfeeding techniques* (which may result in fissured nipples)
- *damage to the child's mucous membranes* (caused by infection, such as oral thrush, or intestinal damage due to allergic reactions to cow's milk or complementary foods).[xxvii]

The lack of access to safe drinking water as well asa number of factors that make substituting breastfeeding difficult, are determining factors in deciding whether to recommend formula feed to mothers. [xxviii] Health workers need to be provided with counselling guidelines regarding the risks and benefits of available infant feeding methods and how to make the method chosen by the mother as safe as possible. Provision of ART to the infant, mother or both would also greatly help in preventing HIV infection during breastfeeding, whilst immunisation could assist in averting certain infections where formula feed is practised.[xxix] In the case of formula feeding, effective education on bottle cleaning should be provided.

In 1996, UNAIDS advised that HIV positive women in resource-poor areas be encouraged to make an informed choice about infant feeding, weighing both its relative risks and its potential benefits.[xxx] All women should be informed of the different dangers and advantages associated with formula feeding, breastfeeding and a combination of the two. Women should be put in a position in which they can make informed choices for themselves in a supportive environment.

A study of 401 mother-infant pairs in Kenya found that avoiding breast milk reduced MTCT by about 44%. At 24 months, there was a 36.7% cumulative probability of HIV-1 infection in the breastfeeding arm, while the formula-feed arm had a cumulative probability of 20.5%.[xxxi] Among the increased infections in the breastfeeding arm, almost half was specifically attributable to breastfeeding. At two years of age, the HIV-1 free survival rates were significantly lower in the breastfeeding arm than the formula arm. Breast milk avoidance was estimated to reduce MTCT by 44%.

An analysis of results by the South African Vitamin A Study Group compared transmission rates in infants who were exclusively breastfed, or exclusively formula-fed or who were mixed fed.[xxxii] The proportion of infants infected with HIV was significantly lower for those who were exclusively breastfed for three months, compared to those infants who received mixed feeding over three months. This is because mixed feeding could introduce contaminated fluids that might predispose the infant to gastrointestinal infections and inflammation. This could compromise the infant's gastrointestinal mucosal integrity and consequently facilitate HIV-1 transmission.[xxxiii] The results of this study are however inconclusive and need further research.

The working conditions many women face when working outside of their homes can also influence the decision of breast-feed exclusively. These constraints include demanding working hours, limted control over schedules, job

insecurity, fear of discrimination and harassment, lack of adequate maternity benefits, and lack of venues to breastfeed in the workplace.[xxxiv]

Thus far, formula feed (used exclusively) has been shown to be the most effective way to reduce the risk of MTCT after birth[xxxv]. This position is supported by Unicef, WHO and UNAIDS. In the event that formula feeding is difficult due to lack of resources such as formula feed or clean water, exclusive breastfeeding is recommended, as not to introduce other hazards that may affect the child immune system and susceptability to HIV.

Conclusion:

The government should bring down the high cost of formula feed by buying formula feed in bulk and providing it free-of-charge to HIV-positive mothers with infants. Other possibilities include campaigning for price reductions of milk formula. Another strategy is to promote production of alternatives to presently available formula feeds that should be cheaper and of a high quality.[xxxvi] In the meantime, various trials that assess the use of anti-retrovirals to decrease breast milk transmission are being planned in addition to methods to inactivate HIV in breast milk.

Anti-retroviral Therapy (ARV)

To understand the efficacy of anti-retroviral therapies (ARVs), the process of HIV reproduction needs to be described.

How the HIV virus spreads

The HIV retro virus replicates by using an enzyme called *reverse transcriptase* to convert its RNA (the form in which it stores its genetic material) into DNA.

Once HIV DNA enters the nucleus of the human CD4+ cell, it inserts itself into the cell's DNA and instructs the cell to make copies of the original virus. These new virus particles then leave the cell and proceed to infect other CD4+ cells. HIV mainly infects CD4+ cells causing a gradual drop in their number and a weakening of the immune system. An untreated person with HIV may have thousands or millions of HIV virusses in every millilitre of blood or bodily fluids.

The aim of anti-retroviral treatments is therefore to drastically reduce the level of HIV in the blood and thus reduces the rate of mother –to-child - transmission. But antiretrovirals can also be used for treatment of HIV.

Three main types of anti-retroviral drugs exist and each of these attack HIV in different ways. For a concerted attack on the virus, these different types of drugs should be used in combination. This then allows the infected human's immune system to recover and to fight infections.

The three types of ARVs are described in the following table:

Name	Action	Examples
1 Nucleoside analogue reverse transcriptase inhibitors (NRTIs).	These incorporate themselves into the DNA of the virus and prevent the building process of the virus. The result is an incomplete DNA that is unable to create new viruses.	The most common examples of NRTIs are AZT and 3TC. Also DDI, d4T, ABC.
2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	These bind directly onto the reverse transcriptase and prevent the conversion of HIV RNA to DNA.	Nevirapine (NVP) and Efavirenz
3		

Protease inhibitors (PIs)	These work at another stage of virus reproduction, by preventing the HIV virus from being successfully assembled and released from the infected CD4+ cell.	Nelfinavir, Ritonavir, Saquiavir, Indinavir and Amprenavir.

ARVs are used not only as medication for people already living with HIV/AIDS, but can also be utilised to prevent transmission. As a prophylaxis (preventative medication), ARVs can prevent HIV infection by obstructing the initial building process of the HIV virus in the first place. The medication has to be taken within a few hours after infection has occurred, as the virus must not have been able to convert to DNA and start the HIV production process yet. *AZT* is an example of a medication used to prevent HIV infection after needle stick injuries or rape.

Anti-retroviral drugs can be used both to treat HIV/AIDS but also to prevent HIV infection, in the case of mother to child transmisson, needle stick injuries and rape.

The Advantages of ARVs in preventing MTCT

1. ARVs will lower the viral load of the mother, thereby reducing the risk of transmission in the womb, during labour and during birth.[xxxvii] The duration of treatment would determine how low the viral load in the breast milk will

be and could therefore also reduce the risk of transmission through breastfeeding.

2. ARVs can by used as a post-exposure prophylaxis for an infant who has contracted the virus in the womb, during labour, during birth or to a limited extent through breastfeeding.[xxxviii]

A Survey of ARV trials

A number of trials have been conducted that prove the merits of the use of ARVs in preventing MTCT. What follows below is a summary of the findings of these trials:

AZT

United States

In 1994 a randomised, double blind placebo controlled clinical trial was conducted in the United States. This means that some of the patients received AZT and others did not, but that neither they nor their doctors knew which they were.

It demonstrated that AZT:

- administered orally
- five times a day
- to HIV positive pregnant women
- starting at 14 weeks gestation,
- intravenously during labour, and
- orally to their babies for six weeks

reduced the risk of HIV transmission by 67% in a non-breastfed population (PACTG076).[xxxix]

The drug was well tolerated and readily crossed the placenta. It provided exposure prophylaxis protection to the infant and also reduced the maternal viral load. The ACTG076 follow up of uninfected children born to women who participated in the trial, showed no indication of unexpected long-term side effects.[xl]

AZT, together with a combination of other ARVs, has become the standard of care during pregnancy in many developed countries such as France and the USA, with an accompanying decrease in reported transmission rates.[xli]

Thailand

In 1996, the Centers for Disease Control of the US sponsored a trial in Thailand. It consisted of a randomised, double blind placebo controlled trial. It indicated that short term antenatal AZT used from 36 weeks gestation, during labour and formula feeds (as replacement for breastfeeding) *reduced the risk of vertical transmission by 50%.*[xlii]

Burkina Faso and Cote D'Ivoire

A trial of 350 women was conducted in Burkina Faso where a placebo and AZT were compared. The women were provided with:

- a twice daily 300mg dose during 36-38 weeks of gestation,
- followed by a single dose of 600mg at onset of labour, and
- 300mg twice a day to the mother for seven days after delivery.[xliii]

85% of infants were breastfed for longer than three months and the efficacy of AZT was estimated at 38% when the infants were six months of age, and 30% when they were fifteen months old.[xliv] A similar study was done with 260 women in Cote d Ivoire where 95% of infants were breastfed.[xlv] A 37% reduction was estimated at three months of age.[xlvi]

The Perinatal HIV Prevention Trial (PHPT)

PHPT compared the efficacy of AZT by administering AZT at starting 28 weeks gestation, to starting at 35 weeks gestation. In both arms of the trial the infants received AZT six weeks after birth.[xlvii] *It was found that transmission in the womb of 1.8% for the regimen starting at 28 weeks was significantly lower than the 5% observed with the regimen starting at 35 weeks*. The authors of this trial concluded that while the AZT administered to infants six weeks after birth may not add benefit when the mothers had received the long antenatal treatment, it may prevent some infections when mothers receive only the shorter treatment.

PETRA study

The multicenter PETRA study[xlviii] commenced in July 1996 in South Africa, Tanzania and Uganda. Its aim was to evaluate AZT and 3TC in infants who were breastfed, while the study evaluated three regimens. The group receiving a combination of AZT and 3TC antenatally 36 weeks after gestation, during and after birth, *demonstrated a 50% reduction in transmission*.

Side Effects of AZT

The adverse effects of taking AZT include headache, gastrointestinal intolerance (nausea, anorexia and vomiting) and bone marrow toxicity (anaemia and granulocytopenia). [xlix] Bone marrow toxicity is the major dose-limiting toxic effect of AZT. In the context of MTCT prevention, anaemia seems to be related to how long therapy with AZT lasts. In the ACTG 076 trial the short-term side effects of the regimen were limited to mild, reversible anaemia in the infant that does not require treatment. The "short course" regimens therefore carry low risks. Despite this, pregnant women should only be offered AZT after correction of any pre-existing anaemia.

No particular pattern of foetal abnormality is attributable to AZT toxicity and clinical experience provides no evidence that AZT causes tumours.[l] There is also no direct evidence for a negative effect on the immune system. This is borne

out by the ACTG076 observational cohort. This study found no association between exposure to AZT perinatally and the more rapid disease progression among an HIV infected sub-group of children. This study also reported findings on AZT resistance. It found that the chances of developing resistance to the drugs by the time of delivery were low, provided that the mother had a well-preserved immune system (therefore a CD4+ count of more than 200/microL) and limited, or no, prior experience of AZT.

Conclusion:

A range of AZT regimens can significantly reduce MTCT of HIV. Each individual regimen has a variety of advantages and disadvantages with respect to potential toxicity. Regimens also differ in degrees of practicality and feasibility for implementation. On the question of toxicity it is important to note that the World Health Organization (WHO) considers AZT to have an acceptable clinical safety profile. For the prevention of MTCT, the WHO specifically places AZT on its essential drug list, as an indispensable drug that should be made available at all times, in adequate amounts and in the appropriate dosage formulations.[li]

Nevirapine

Nevirapine is a fast-acting and potent ARV, which takes a significant amount of time to be eliminated from the body. It is considered to be a valuable option in reducing the risk of MTCT, since it is absorbed quickly into the body and passed readily to the placenta. Only a limited dose is required for effectiveness, and it remains active in the body of both mother and infant for a period of time that would limit infection via breast milk.

What follows is a survey of recent studies into the application and efficacy of nevirapine.

ACTG 250

This study was performed in seven hospitals in the USA and Puerto Rico with the aim of defining the dosage regimen that maintains a serum concentration of nevirapine above 100ng/mL throughout the first week of the life of the infant.[lii] The dosing schedule that was established involved a single dose to the mother during labour, followed by a single dose to the infant between 48 and 72 hours after birth. No toxicity was noted in either infants or mothers.

HIVNET 006

This trial was conducted in Uganda and examined 21 women who each received a single 200mg dose of nevirapine during labour.[liii] Half of the infants received a single dose of nevirapine (2mg/Kg) 72 hours after birth, while the other half did not receive any nevirapine. Drug levels in breast milk remained >100ng/mL in most treated mothers in the trial throughout the first week after delivery. No serious adverse events related to nevirapine were observed, and only one of the infants was infected at birth. Two infants showed signs of infection at week six and another one was infected, possibly via breast milk, at six months.

These positive results of pharmacokinetic and safety studies of nevirapine has prompted subsequent and larger clinical trials to evaluate the efficacy of the drug in the prevention of MTCT:

PACTG 316

The PACTG 316 trial was a randomised blind study in USA and Europe where women received 200mg nevirapine or placebo during labour, and infants received 2mg/kg nevirapine or placebo during the first 48-72 hours of life.[liv] In addition, women could receive any combination of ART for their own health, except NNRTIs. No serious adverse reactions related to nevirapine-use have yet been observed, and the dosages have been tolerated.

HIVNET 012

The HIVNET 012 study was a randomised controlled trial conducted in Uganda.[lv] In this trial the following procedures were compared:

- the use of a maternal single 200mg oral dose of nevirapine during labour and an infant 2mg/kg dose of nevirapine within 72 hours of birth, with
- a maternal 600mg oral dose of AZT at onset of labour and 300mg orally every 3 hours during labour, with a 4mg/kg twice daily dose of AZT administered to the infant for 7 days after birth.

Data from 618 women and infants was examined. *At 6-8 weeks of age, 11,9% of infants in the nevirapine group were HIV infected, compared with 21,3% in the AZT group*. Similarly at 14-16 weeks of age, 13% of infants in the nevirapine group were infected, compared to 25% of infants in the AZT group. At 14 weeks of age, 95% of all infants were still breastfed. Results in the AZT arm are consistent with a reduction in transmission observed in other studies, although the regimen was shorter than those employed in previous studies. Participants in both arms reported mild side effects such as skin rashes and anemia in infants, which were equally distributed in both arms of the trial.

A preliminary study found that 3 of 15 women receiving a single-dose of nevirapine in the HIV012 study, had the K103N nevirapine resistance mutation identified at 6 weeks after birth. There is no evidence that nevirapine resistance accelerates progression of the HIV-1 disease, or that it increases transmissibility.[lvi] What this means is that a single dose of nevirapine may not completely stop HIV from replicating and could allow mutations to develop. These mutations will not affect the health of the woman. Yet they do present a problem where a woman is in a position to use combination ART, since the resistance means that it is possible that other drugs in the same class as nevirapine will not necessarily work effectively. To overcome this problem, the woman can simply avoid using nevirapine later since there are other drugs that can replace it. If a woman develops resistance to nevirapine, it can still be used in subsequent pregnancies, as the resistant virus loses its selective advantage within 2-3 months after stopping the drug.

Since the majority of women do not have access to longer-term anti-retroviral therapy, the impact of resistance is small and is outweighed by the positive results nevirapine has in preventing MTCT.

South African Intrapartum Nevirapine Trial (SAINT)

The SAINT programme saw the participation of 1306 HIV-infected women who were assigned to two arms of the trial. These arms compared the administration of 200mg of nevirapine during labour and one dose to mother and infant 24-48 hours after delivery; to multiple doses of AZT+3TC during labour and for one week after delivery to mother and infant. No significant differences between the two arms were observed and both regimens were viewed as effective and comparable to the results of nevirapine in the HIVNET 012 trial, and AZT+3TC in PETRA Arm B.[lvii]

Conclusion

The HIVNET 012 researchers see the following advantages of the use of Nevirapine as ARV:

- it is simple
- it costs little
- it has potential for widespread use.

Using US retail prices, our research estimates the nevirapine regimen at $4. This is seventy times cheaper than the short course AZT regimen, and 200 times cheaper than the long course AZT. Mother-infant pairs continue to confirm that nevirapine is safe and significantly reduces the rate of MTCT compared to the short course AZT regimen.[lviii]

3
IMPLEMENTATION

Costs

A number of studies have shown that it is cost-effective to provide MTCT interventions in developing countries.

Marseille and others investigated the cost effectiveness of the HIVNET 012 nevirapine regimen in sub-Saharan Africa.[lix] The nevirapine regimen was compared with other short course ARV regimens. A further comparison was made between targeted treatment (VCT before treatment) and universal treatment (nevirapine for all pregnant women without VCT). It was found that the HIVNET 012 regimen was cost effective under a wide range of parameters and would be particularly cost effective where HIV infection was widespread. HIVNET 012 regimen is as cost-effective as other public health interventions.[lx]

NEVIRAPINE: HIVNET 012	Universal treatment: 30% HIV prevalence	Universal treatment: 15% HIV prevalence	Targeted treatment: 30% prevalence
Cost	US$83 333	$83 333	$141 922
cases of HIV babies averted	603	302	476
cost of cases averted	$138	$276	$298

Söderlund *et al* made an analysis of the cost-effectiveness of the various options available to prevent MTCT.[lxi] After estimating cost effectiveness of four

feeding strategies and three ARV interventions, they concluded that *combined formula feeding and low-cost anti-retroviral intervention would avert the most deaths and would be cost-effective*.

Whilst ARV interventions were cost-effective over a wide range of settings, with or without formula feeding interventions, formula feedings were highly cost effective only in high seroprevalence situations with reasonable levels of child survival. The study costs the intervention as an add-on to existing antenatal care. The study did not factor in the problems created in terms of efficacy with short course ART where women delivered preterm or at home, and the extended costs of those delivering after term. However, it can be argued that new data on the effectiveness of nevirapine would counter these problems, since women can administer the dosage on their own (even at home) and only require the dosage at birth. The relatively low cost of the nevirapine regimen is also important in this regard.

According to the government-commissioned study done by the EU, it is clear that MTCT intervention is extremely cost-effective.[lxii] This study calculated that providing nevirapine to HIV-positive women could take place in South Africa at present levels of prevalence for a total cost to the health budget of R87.5m per year (including staff time). If AZT were used the cost would be R124,8m per year.

It is estimated that a nationwide nevirapine MTCT programme would save between 14 000 and 22 000 babies per year from HIV infection at a cost of R6 284 per life saved.

A similar AZT programme would save 12 000 babies' lives per year at a cost of R10 078 per life saved. The study argues that the government's national counselling and testing policy could readily be combined with MTCT intervention to ensure cost effectiveness and better access.[lxiii]

The Khayelitsha Example

This section offers a brief account of the implementation of an MTCT programme in Khayelitsha near Cape Town. It shows what initiatives took place and their relative successes and outcomes for future action. It also gives a short overview of the pilot programme on MTCT to be implemented by South Africa's Department of Health.

In January 1999, a mother-to-child HIV prevention pilot programme was implemented in Khayelitsha based on the Thai regimen.[lxiv] Its objective was to research a programme of implementation as well as the the Thai intervention regimen in the Khayelitsha district, with the intention of extending the programme throughout the entire province, if it proved to be feasible and effective. [lxv]

The following procedures were followed:

- All women who came to antenatal booking were offered voluntary confidential HIV counselling
- HIV Elisa testing was performed once the woman gave written consent
- HIV positive women received AZT from 36 weeks gestation at 300mg twice daily up to the onset of labour
- During labour the mother received 300mg AZT every three hours
- The infant was started on formula feeds as a replacement for breastfeeding
- The infant received Cotrimoxazole, a *Pneumocystis carinii* Pneumonia (PCP) prophylaxis, from 6 weeks of age to 18 months
- HIV testing on the infants was done at 9 and 18 months of age.

Since June 2000, HIV testing was performed using rapid tests instead of Elisa, and the AZT protocol was commenced at 34 weeks. A monitoring system tracked the screening and enrolment of all women present at the two maternal obstetric units (MOUs) in Khayelitsha.

Findings:

The programme has proved to be extremely beneficial to the Khayelitsha community. The uptake was 74% (women accepting HIV testing) with 16% of these women testing HIV positive in the first year, 20 % in the second and 24% in 2001. It is interesting to note that most women opted for HIV testing despite being aware of discrimination towards HIV positive women in the community.[lxvi] Post-test counselling rates were high for HIV positive and HIV negative women, and the many of the women disclosed their test results to their partners. Counselling was a crucial dimension of the process, and formed the backbone of the entire programme.

Partial adherence to AZT was high, while full dose adherence was low.
The main determinants of non-adherence from a service perspective were:[lxvii]

- late antenatal clinic booking,
- defaulting antenatal clinic attendance
- "missed opportunities" (attending antenatal clinic and arriving early in labour ward but not receiving AZT according to the regimen)
- arriving late in the labour ward
- deliveries before 36 weeks gestation
- the lack of any formal protocol for AZT use in Caesarean sections.[lxviii]

Many mothers received only one dose of AZT in labour. Minor as well as low cost modifications to the program could increase the level of adherence and thus the effectiveness of the programme.

Unplanned spin-offs of the programme were the improved integration of local health management, increased general awareness and knowledge of HIV/AIDS, reduced stigma and improved staff knowledge and attitudes.

Access to treatment in this community has also had social and individual benefits. [lxix] From people's experiences of HIV infection as an isolated, stigmatised and deeply personalised ordeal, such programmes created a renewed sense of community priority, and a movement away from stigmatisation, to openness and consciousness. The silence around HIV had been broken and the receptiveness to AIDS awareness increased. HIV positive mothers have become empowered and they were now able to make informed decisions about safer sex and future pregnancies. Where there had previously been no or little incentive to be tested, this study demonstrated that access to treatment is the key for prevention and awareness strategies.

In the Study the transmission rate of tested babies was 12% (with 4 % inaccuracy possible to either side thus between 8 and 16%) instead of a base rate of 25 – 30 %.

Current Policy of the Department of Health

At the time of writing this pamphlet, the Department of Health is in the process of implementing a MTCT pilot programme around certain sites around South Africa.[lxx] This programme will provide HIV testing, nevirapine, medical treatment and formula feed free of charge (although the latter, can be decided site by site and some sites do not envisage giving formula milk) to pregnant mothers to be treated at 18 selected public hospitals or clinics – one rural and one urban site per province.[lxxi] This programme is planned to run for two years and has been allocated a budget of approximately R23 million.[lxxii]

The aim is to expand current research on the prevention of MTCT and use of nevirapine, as well as to gather conclusive data on drug resistance and breastfeeding issues.[lxxiii] This will eventually lead to the formulation of a national policy on MTCT.[lxxiv]

However, this programme is thoroughly insufficient if the sheer magnitude of the number of HIV-infected pregnant mothers in South Africa is taken into account, as well as the number of trials already conducted on the safety and efficacy of nevirapine. The scope of the pilot programme is estimated to reach 90 000 women only, while in fact 1.2 million women give birth each year.[lxxv] It is therefore imperative that a nation-wide plan on MTCT is implemented without any further delay. This plan should place all women in a position where important treatment and information can readily be accessed – not only the few who are admitted to 18 selected sites.

Conclusion

It is clear that MTCT is one of the most crucial issues in the current struggle against HIV infection.

This statement holds particularly true for South Africa – a country facing an AIDS crisis of immense proportions. Yet there are many courses of action that can be undertaken to prevent the spread of HIV and provide quality of life to people already living with HIV/AIDS. In this paper we have shown that a drastic reduction in the rate of MTCT can be achieved through sustained funding and implementation of anti-retroviral therapy, nutritional status, changed approaches towards breastfeeding, and programmes of voluntary testing and counselling, as well as obstetric practices, including modes of delivery. As

outlined in a previous section, state funding of these strategies would prove, in the language of the government's own study of MTCT, to be "cost-effective".

In the area of anti-retroviral therapy, a range of programmes has shown the extent to which such therapy can radically reduce rates of MTCT. One such success story is Thailand, where the Royal Ministry of Health successfully initiated a pilot short-course AZT programme. This programme was eventually extended to a national policy offering universal VCT, provision of short course AZT and formula feed to pregnant women with HIV.

Another example is that of the Botswana 'Prevention of MTCT of HIV Programme'. It was launched in Gaborone and Francistown in April 1999 and was later extended nationally. This programme offered VCT, oral AZT at both 34 weeks and during labour, and AZT syrup to infants. In January 2000, the WHO, UNAIDS and others participated in a review of the Botswana project. They felt that scaling up was advisable and that the use of nevirapine should be considered. The reviewers concluded that most of the programme's problems were associated with inadequate counselling.

The Botswana example demonstrates that an effective MTCT prevention strategy necessitates the combination of two essential elements: treatment and educational programmes. Treatment like anti-retroviral therapy should be made available to all, while education programmes aimed at changing people's lifestyles and everyday practices should be developed and widely disseminated. It is only when this two-tier strategy is successfully in place that one would be able to conclude that a coherent and comprehensive response to MTCT has been formulated.

References and Notes

[i] UNAIDS, WHO HIV in *Pregnancy: A Review* Occasional paper 2 prepared by James McIntyre, Perinatal HIV Research Unit, University of the Witwatersrand, 1999.

[ii] Department of Health – 14 February 2001

[iii] McIntyre J "Preventing mtct of HIV:African solutions for an African crisis" Southern African Journal of HIV Medicine, July 2000

[iv] This list is based on the factors enumerated in McIntyre (1999) *op cit*. Please refer to this document for a comprehensive discussion of each of these factors.

[v] McIntyre (1999) *op cit*. p.11 cites the trial conducted by Thea DM *et al* and the New York Perinatal HIV Transmission Collaborative Group in "The Effect of maternal viral load on the risk of perinatal transmission of HIV-1" *AIDS*, 1997, 11:437-444.

[vi] McIntyre (1999) *op cit*. p.12. He also writes the following: "Since the risk of resistance emergence increases with the duration of treatment and since resistance to AZT usually emerges after 3-4 months of treatment, the emergence of resistance with a short-regimen of zidovudine (1 month) is very low and less likely compared to long regimen of zidovudine."

[vii] Breast abscesses, mastitis, nipple cracks and other factors can affect the risk of HIV infection via breastfeeding. Women who choose to breastfeed should be counselled about this possibility and be given treatment for such problems when they occur. McIntyre (1999) *op cit*. p15. Also see the section on breastfeeding later on in this paper.

[viii] In France, women who receive long course ART in pregnancy and who have elective Caesarean sections had a transmission rate of less than 1%. McIntyre (1999) *op cit*. p.14.

[ix]It is important to note that the additional risk of transmission through breast-feeding is between 7 and 22%. In breast-feeding populations between 1/3 and 1/2 of MTCT occurs during breast-feeding. Rates are higher where the mother seroconverts during breast-feeding, where the estimated additional risk is around 30%. McIntyre (1999) *op cit*.p15.

[x] It is possible that MTCT happens via ingestion of the virus in the womb or at birth where the newborn child's gastro-intestinal tract has low acidity and mucus etc. Part of the effect of ART in pregnancy can be attributed to its post-exposure prophylaxis effect after birth. McIntyre (1999) *op cit*. p15.

[xi] *Government Gazette* Vol 414 No 20710.

[xii] McIntyre (1999) *op cit*. p.27. It is emphasised that testing of pregnant women without consent or without access to counselling is an unacceptable practice and that these disadvantages may negate any benefit obtained from knowing one's HIV status. It is further emphasised that unless people have real choices for action once they have their results, there is no good reason to take a test (e.g. access to affordable services such as MTCT programmes, care and support). The contents of pre- and post- test counselling, particularly in the case of

pregnant women, are set out in more detail. See also "Tools for evaluating HIV voluntary counselling and testing" *UNAIDS*, May 2000.

[xiii] Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol 355, June 2000. WA32.

[xiv] Coates TJ *et al*. "The Voluntary HIV-1 counselling and testing Efficacy study: A randomised controlled trial in three developing countries" Prevention No 1, June 2000.

[xv] This section draws on McIntyre (1999) *op cit*. p16, 31.

[xvi] Patrick L "Nutrients and HIV: Part 2 - Vitamins A and E, Zinc, B-Vitamins and Magnesium" *Alternative Medical Review*, February 2000, 5(1):39-51. Abstract. There is a direct relationship between certain nutrient deficiencies and decreasing CD4+ counts. Certain deficiencies appear to influence vertical transmission (Vitamin A) and may affect progression from HIV to AIDS (Vitamins A, B12 and Zinc).

[xvii] Hoppenbrouwer J "Preventing mother-to-child transmission of HIV: Setting the right priorities" *HIV/AIDS in the Commonwealth* 2000/01, Kensington Publications, 2000, p33-7.

[xviii] Semba RD *et al*. "Maternal Vitamin A Deficiency and Mother to child transmission of HIV-1" *Lancet* 343:1593-7, June 1994.

[xix] McIntyre (1999) p.24. From Fawzi *et al*. for the Tanzania Vitamin and HIV infection Trial Team "Randomised trial effects if vitamin supplements on pregnancy outcomes and T cell counts in HIV-1 infected women in Tanzania" *Lancet* 1998 351:1477-1478. See also Castetbon "Lack of association between maternal Vitamin A status and MTCT of HIV in West Africa" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:112.

[xx] Coutsoudis A *et al*. "Randomized Trial Testing the effect of Vitamin A supplementation on Pregnancy outcomes and early Mother-to-child transmission in Durban, South Africa" *AIDS*, August 1999, 13(2):1517-24. Abstract.

[xxi] Burger H *et al*. "Maternal Serum Vitamin A Levels are not associated with MTCT of HIV-1 in the United States" ***Journal of AIDS Human Retroviral***, April 1997, 14(4):321-6. The study recommends that pregnant women living in nations where Vitamin A deficiency is not a public health problem, should not be advised to take such supplements. "Nutrition: National AIDS Manual", UK, June 2000. It is suggested that pregnant women should not take supplements containing Vitamin A without consulting their doctors as high intakes may harm foetuses.

[xxii] McIntyre (1999) *op cit*, p.25. Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol 355, June 2000. WA30. They quote results from an individual patient meta-analysis in 1999. This analysis showed that Caesarean delivery performed before labour and the rupture of membranes reduced MTCT by 50-87% in women receiving no ART or AZT prophylaxis.

[xxiii] Butler M "Costs and benefits of a vertical transmission prevention programme in the Dominican Republic" *13th International AIDS conference*, South Africa, 9-14 April 2000. Abstract WEOrC616. The study shows the cost effectiveness of an MTCT programme that includes nevirapine with Caesarean sections. McIntyre (1999) *op cit*. p.21. They quote a French study with an MTCT rate of 0.8% where women received long course AZT and elective Caesarean sections, compared with 6,6% with vaginal delivery. Fiscus S "Elective C-section may provide additional benefit in conjunction with maternal combination ART to reduce perinatal HIV transmission" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:112. See also Pesaresi "Hemostatic Caesarean Section A New Surgical Technique in HIV + pregnant women" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract,

Vol1:81. It was indicated in a study in Argentina that elective Caesarean with technical modification, used in all patients with ART and where breastfeeding is prohibited, decreased MTCT to less than 2%.

[xxiv] Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol 355, June 2000. WA27. They emphasize that there is a substantial risk involved in operative delivery in HIV- infected women in less- developed countries.

[xxv] McIntyre (2000) *op cit*. p.31. The additional risk of transmission via breastfeeding is estimated between 7-22%. The additional risk of transmission for women who became infected during the breastfeeding period is close to 30%.

[xxvi] Also see Richardson B "Breast milk infectivity of HIV-1 infected mothers" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:101. This study found that HIV-1 infectivity per day of breastfeeding is 1.6 times higher for infants under 4 months than for those over 4 months. Also that the volume of milk ingested and the length of exposure are both important factors in breast milk transmission. In addition, higher maternal plasma RNA levels were associated with higher breast milk infectivity. See also Sapalya R "Correlation of cell-free HIV-1 plasma, colostrum and breast milk" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:367. The findings suggested that a plasma viral load of more than 41,000 virions/ml may be a surrogate marker of potential MTCT through breast milk. It was suggested that where a high plasma viral load exists, breast-feeding should be discouraged and formula feed should be provided, or that the viral load must be reduced through the use of ART given to lactating mothers.

[xxvii] Hoppenbrouwer J "Preventing mother-to-child transmission of HIV: Setting the right priorities" *HIV/AIDS in the Commonwealth 2000/01*, Kensington Publications, 2000, p33-7.

[xxviii] Premixed formula feed is one option of dealing with unsafe drinking water. Also see Angoran Benie MA "Implications of household water storage practices on replacement feeding of children born to HIV infected women, Abidjan, Cote d'Ivoire" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:109. They argue that if formula feed is used, the risk of diarrhoeal disease for infants is increased. This danger could be reduced by safe water storage and in-house chlorination.

[xxix] Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol. 355, June 2000. WA31.

[xxx] "Effect of Breastfeeding and Formula Feeding on Transmission of HIV-1: A Randomised Clinical Trial" *JAMA* March 2000 Vol283 No 9: 1167-74.

[xxxi] "Effect of Breastfeeding and Formula Feeding on Transmission of HIV-1: A Randomised Clinical Trial" *JAMA* March 2000 Vol283 No 9: 1167-74. See also Mbori-Ngacha "Morbidity and mortality in breast-fed and formula fed infants of HIV-1 infected women: results of a randomised clinical trial" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:101.

[xxxii] Coutsoudis A, Coovadia HM *et al*. "Influence of infant feeding patterns on early mother to child transmission of HIV-1 in Durban, South Africa: A prospective cohort study" Volume 354, No9177, August 1999. See also Krasovec K, Soderlund N "Cost effectiveness of feeding interventions for preventing MTCT of HIV" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:108. It is suggested that in a developing country where mixed and supplementary feeding is common, child deaths and MTCT could be prevented cost-effectively. This could be done via interventions that increased the practice of exclusive breastfeeding, followed by abrupt weaning from 4 months onwards and combined with short course ART.

[xxxiii] Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol 355, June 2000. WA31. See also Taren D "Early introduction of mixed feedings and postnatal HIV transmission" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:72. It was suggested that mixed feedings were associated with increased risk of postnatal HIV transmission.

[xxxiv] Guttman N, Zimmerman DR "Low-income mothers' views on breastfeeding" *Social Science & Medicine* 50(2000): 1457-73. Also see Bland RM "Longitudinal infant feeding study: constraints due to exclusive *breastfeeding*" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:102.

[xxxv] For an interesting point see Paul D "Breastfeeding and HIV infection" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:261. It is argued that 'informed choice' has no meaning but passing the buck and compounding the confusion of HIV infected women about breast-feeding. It is emphasised that it must be a national government policy to discourage breast-feeding and to provide formula feed free of charge to babies born from HIV mothers. Proper implementation is however critical. This includes proper maintenance of hygiene, education, information-dissemination on the dangers of breast-feeding, providing formula feed as well as counselling sessions. It is further argued that more studies are needed on making cheaper breast milk alternatives. See also Nduati R "Impact of breastfeeding on maternal mortality among HIV-1 infected women: results of a randomized clinical trial" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:102. Here it was suggested that adverse consequences may also result from breast-feeding for both mother and child, and that breast-feeding is associated with the increased risk of maternal mortality.

[xxxvi] See also Ndagire L "Determinants of early cessation of beast feeding among HIV infected mothers in Kampala" *13th International AIDS Conference,* 9-14 July 2000, South Africa. Abstract, Vol2:402. It was concluded that the affordability of alternate feeds, rather than social factors or awareness, contributed to the early cessation of breastfeeding. The study was conducted in Uganda. A similar conclusion was reached in a South African context: See Sibiya N, Coovadia, Moodley "Factors that influence the choice of infant feeding practice by HIV infected women in KZN" SA *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:109.

[xxxvii] Also see Beckerman KP "Impact of combination ART on maternal health and pregnancy outcome" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:71. It is suggested that combination ART during pregnancy effectively suppresses maternal HIV-1 disease activity, and halts or reverses maternal immune system reduction. Vertical transmission is also mainly confined to mothers with no ART, or only AZT, or no/limited prenatal care. Munoz-Fernandez MA "Spanish report on maternal and neonatal effects of potent ART during pregnancy" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:56. Combination ART during pregnancy with more than 1 NA or more than 1 NA+PI was well tolerated by mothers overall. No relevant toxicities or side effects were noted. Also no severe short-term adverse effects in newborns with intra utero and perinatal HIV exposure to ART during the 6 months follow up were found.

[xxxviii] At this point it should be noted that where children are infected with HIV perinatally, their survival would be significantly improved if they have access to combined ART. See de Martino M "Population based effectiveness of ART on survival of perinatally HIV-1 infected children" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:73.

[xxxix] Connor EM *et al.* "Reduction of maternal-infant transmission of HIV-1 with zidovudine treatment" Paediatric AIDS Clinical Trials Group Protocol 076 Study Group *New England Journal of Medicine* 1994; 331:1173-1180.

[xl] Culnane MS *et al*. "Lack of Long-term Effects of In Utero Exposure to Zidovudine Among Uninfected Children Born to HIV-infected Women" *JAMA*, 1999 Vol281 No.2, p.151.

[xli] McIntyre (1999) *op cit*. p20. The regimen is less applicable to developing countries due to its high cost, implementation problems and the fact that women in resource-poor settings do not attend antenatal care at an early stage etc. See also McIntyre J "Preventing MTCT of HIV: African solutions for an African crisis" *Southern African Journal of HIV Medicine*, July 2000, p30.

[xlii]Shaffer N *et al*. "Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomized controlled trial" *Lancet* 1999;353:733-80.

[xliii] McIntyre (1999) *op cit*., p21. From Dabis F. *et al*. DITRAME Study Group "6 month efficacy, tolerance, and acceptability of a short regimen of oral AZT to reduce vertical transmission of HIV in breastfed children in Core d'Ivoire and Burkina Faso: a double blind placebo controlled multicentre trial" *Lancet* 1999, 353:786-92.

[xliv] McIntyre (2000) *op cit*, p.30

[xlv] McIntyre (1999) *op cit*. p21. From Wiktor *et al*. "Short course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomized trial" *Lancet* 1999, 353:781-785.

[xlvi] McIntyre (2000) *op cit*. p.30

[xlvii] Lallemant M, Le Coeur S, Kim S *et al*. "Perinatal HIV Prevention Trial (PHPT), Thailand: Simplified and shortened zidovudine prophylaxis regimens as efficacious as PACTG076", Abstract LbOr3, *13th International AIDS Conference*, Durban, South Africa, 9-14 July 2000.

[xlviii] Saba J on behalf of PETRA Trial Study Team. "Interim Analysis of Early efficacy of Three Short ZDV/3TC combination regimens to prevent mother to child transmission of HIV-1. The PETRA trial." Abstract S7 *6th Conference on Retroviruses and Opportunistic Infections*, Chicago, January 31-February 4 1999.

[xlix] Safety and Tolerability of Zidovudine - A Review of the Literature, WHO

[l] Also see Galli L "Combined ART, but not ZDV monotherapy in gestation may damage biliary epithelium in infants" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:370. This damage due to combined ART is however likely to be transient.

[li] See also Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol 355, June 2000. WA29.

[lii] Viramune Product Monograph, Boehringer Ingelheim International GmbH, p.70. From Mirochnik M *et al*. "Pharmacokinetics of nevirapine in HIV-1 infected pregnant women and their neonates" PACTG Protocol 250 Team. *Journal of Infectious Diseases* 1998; 178: 368-374.

[liii] Viramune Product Monograph, Boehringer Ingelheim International GmbH, p70. From Musoke, P. *et al*. "A Phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1 infected pregnant Ugandan women and their neonates" HIVNET006, *AIDS* 1999;13:479-486.

[liv] Viramune Product Monograph, Boehringer Ingelheim International GmbH, p71. From Dorenbum-Kracer A *et al*. "Anti-retroviral use in pregnancy in PACTG 316: a phase III randomized, blinded study of single-dose intrapartum/neonatal nevirapine to reduce mother to infant HIV transmission" *12th World AIDS conference* Geneva, 1998. Abstract 23281.

[lv] Viramune Product Monograph, Boehringer Ingelheim International GmbH, p72. See also Jackson B *et al*. "A phase IIB randomized, controlled trial to evaluate the safety, tolerance and HIV vertical transmission rates associated with short course nevirapine vs. short course zidovudine in HIV infected pregnant women and their infants in Uganda" 1999 Available: http://www.niaid.nih.gov/newsroom/simple/exec.html Guay L "Intrapartum and neonatal single dose nevirapine compared with zidovudine for prevention of mother to child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial" *Lancet* 1999; 354:795-802.

[lvi] Mofenson LM, McIntyre JA "Advances and research directions in the prevention of mother to child HIV-1 transmission" *Lancet* Vol 355, June 2000. WA27. See also Jackson B. *et al*. "Selection of NVP resistance mutations in Ugandan women and infants receiving NVP prophylaxis to prevent HIV-1 vertical transmission (HIVNET 012)" *13th International AIDS Conference*, 9-14 July, South Africa, Abstract LbOr13.

[lvii] Moodley D "The SAINT Trial: Nevirapine versus zidovudine (ZDV) + Lamivudine (3TC) in prevention of peripartum HIV transmission" *13th International AIDS Conference*, Durban South Africa, 9-14 July 2000, Abstract LbOr2. Also see McIntyre J "Evaluation of safety of 2 simple regimens for prevention of MTCT, NVP vs. ZDV/3TC used in randomised clinical trial (SAINT study)" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:329. Looking at the sample of 528 mothers, there were no maternal deaths and both treatment arms were deemed safe.

[lviii] Owor M "The one year safety and efficacy data of the HIVNET 012 trial" *13th International AIDS Conference*, Durban South Africa 9-14 July 2000. Abstract LbOr1. See also Mmiro F "Association of maternal HIV viral load and perinatal transmission in the HIVNET 012 trial" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol1:338. It is suggested that nevirapine substantially reduced maternal viral load by day 7 after dosing, whereas AZT did not. After 6 weeks the maternal HIV RNA levels were slightly higher than baseline in both arms.

[lix] Marseille E *et al*. "Cost effectiveness of single dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa" *Lancet* Vol 354, September 1999.

[lx] Also see Stringer J "Cost effectiveness of 2 novel strategies of perinatal NVP administration for women who deliver preterm or lack prenatal care" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:108 and Stringer J "For women in prenatal care, choice of the optimal perinatal NVP strategy hinges critically upon patient adherence" *13th International AIDS Conference* 9-14 July 2000, South Africa. Abstract, Vol2:387.

[lxi] Söderlund N, Zwi K, Kinghorn A, Gray G "Prevention of vertical transmission of HIV: analysis of cost effectiveness of options available in South Africa" *BMJ* 1999; 318: 1651-1656 (19 June).

[lxii] By Martin Hensher, EU Consultant in Health Economics, 19 April 2000.

[lxiii] Hensher points out that providing VCT without MTCT intervention "could leave the government in an exposed and logically inconsistent position".

[lxiv] The average HIV prevalence of women attending antenatal clinics in the Western Cape was 5.2% in 1998, and 12.97% in Khayelitsha.

[lxv] Abdullah F "Using Anti-retrovirals to Reduce MTCT in Khayelitsha", *MSF/TAC satellite conference, 13th International AIDS conference*, 9-14 July 2000, South Africa. See also Kariem S *et al*. "Lessons and challenges of the MTCT programme in Khayelitsha, Western Cape, South Africa".

[lxvi] Etibet MA *et al*. "Pregnant women opt for participation in district service based interventions to reduce perinatal HIV transmission in Khayelitsha, Cape Town" *13th International AIDS conference*, 9-14 July 2000, South Africa. Abstract ThPpC1447.

[lxvii] Young T *et al*. "Monitoring and evaluating the MTCT pilot project in Khayelitsha, South Africa" *13th International AIDS conference*, 9-14 July 2000, South Africa.

[lxviii] See also Anude C *et al*. "Obstetrical factors that may influence the implementation of short-course ART for the prevention of perinatal HIV transmission" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:114. Also see Majeke S, Abdool Karim, MRC "Provider acceptability of 2 dose NVP policy for reducing MTCT of HIV: Experiences from an urban primary health care clinic in AS" *13th International AIDS Conference*, 9-14 July 2000, South Africa. Abstract, Vol2:390. It is concluded that it is important to establish provider-knowledge and preparedness prior to implementation.

[lxix] Goemare E, MSF "Thinking outside the box: How access to treatment makes prevention realistic" *MSF/TAC satellite conference, 13th International AIDS conference*, 9-14 July 2000, South Africa.

[lxx] Smith, C. "Free Treatment for HIV+ moms" *Mail & Guardian* , 26 January 2001.
[lxxi] Interview with Ms. C. Serenata, Deputy Director: HIV/AIDS and STDs, Department of Health, Pretoria, 26/02/2001
[lxxii] ibid.
[lxxiii] ibid.
[lxxiv] ibid.
[lxxv] Mark Heywood as quoted by Kerry Cullinan "MTCT programme to launch on 1 April", 20/02/2001 Available: http://www.health-e.org.za/view.php3?id=20010214 Accessed: 26/02/2001